Clinical Study Protocol

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A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

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AstraZeneca

PROTOCOL SYNOPSIS

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

International Co-ordinating Investigator

PPD

Study centre(s) and number of patients planned

Approximately 228 patients with newly diagnosed differentiated thyroid cancer at high risk of primary treatment failure will be recruited from approximately 50 sites in Europe, South and/or North America.

Objectives

Primary objectives

To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in the overall study population. Complete remission is defined in Section 6.4.1.

To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

Secondary objectives

To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the overall study population. Clinical remission is defined in Section 6.4.6.

To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

Exploratory objectives

To explore subsequent thyroid cancer therapy given to patients who receive selumetinib with RAI, or placebo with RAI.

To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters.

To collect tumour, plasma and serum samples for potential future research on biomarkers relevant to DTC and response and resistance to study treatments.

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib or RAI and/or susceptibility to cancer.

Study design

This is a double-blind, randomised, placebo-controlled study comparing the efficacy of a short course (approximately 5 weeks) of selumetinib (75 mg, orally twice daily) with adjuvant RAI, to placebo with RAI.

Following recovery from surgery (1 or 2-stage total thyroidectomy), and screening to determine study eligibility, patients will be randomised and will take their assigned study treatment (selumetinib or placebo) twice daily for a period of approximately 5 weeks. Study treatment will begin approximately 4 weeks prior to the planned day of single dose RAI therapy, and will be continuous until 5 days following RAI therapy. Patients will be required to adhere to a standardised low iodine diet prior to their RAI therapy. For each of the 2 days immediately prior to their planned RAI therapy, patients will receive a 0.9 mg intramuscular (IM) recombinant human TSH injection (rhTSH, Thyrogen), in order to stimulate iodide uptake (patients or clinicians choosing to prepare for RAI ablation by withdrawal of thyroid hormone treatment will be ineligible for this study). Following the 2 consecutive days of rhTSH injections, patients will receive their planned RAI therapy as a fixed single 100 mCi (3.7 GBq) dose of ^{131}I the immediate next day. Study treatment will be taken as normal on the day of RAI therapy, and will be discontinued 5 days following the patient's RAI therapy.

Following RAI therapy, each patient will be followed up for a period of 18 months until the primary endpoint assessment of complete remission. The biochemical analysis contributing to the 18 month primary endpoint of complete remission will be performed by standardised central methodology, and the radiological imaging for structural disease at the primary endpoint will be subject to a blinded independent central review. Additional thyroid cancer therapy (eg, surgery or RAI treatment) must only be given during the 18 month primary endpoint follow up period according to the pre-specified study re-treatment criteria (refer to Section 5.9). Patients who do receive re-treatment in the 18 months following their initial RAI

therapy, will not have any 18 month primary endpoint assessments performed; they will remain in the study and enter standard of care follow up according to local practice.

Following the primary endpoint assessments (or re-treatment), all randomised patients will be further followed-up at 3 years after their initial RAI treatment, in order to further assess both the clinical status of patients, and the safety profile of selumetinib and RAI beyond the primary analysis (refer to Section 6.4.8).

Target patient population

Patients with histologically or cytologically confirmed follicular cell derived differentiated thyroid cancer (including papillary thyroid cancer and all variants, follicular thyroid cancer and all variants, and poorly differentiated thyroid cancer), who are determined to be at high risk of primary treatment failure, as defined by any one of the following staging categories post-surgery:

- Primary tumour greater than 4 cm
- Primary tumour of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)
- N1a or N1b disease with at least 1 lymph node ≥ 1 cm
- N1a or N1b disease involving 5 or more lymph nodes (of any size)

Patients with known distant metastatic disease will be excluded from this study.

Investigational product, dosage and mode of administration

Selumetinib Hyd-Sulfate (75 mg) will be administered orally twice daily as capsules (blue). The Hyd Sulfate formulation will be used in this study, and unless otherwise specified is the formulation referenced throughout this document.

Comparator, dosage and mode of administration

Placebo (to match selumetinib) will be administered orally twice daily.

Duration of treatment

The duration of study treatment (selumetinib/placebo) will be approximately 5 weeks in total (Day 36 will typically be the last day of study treatment, but this may be extended to a maximum of 43 days to allow the planned RAI to be postponed by up to 1 week if absolutely necessary).

Outcome variable(s):

Efficacy

The primary outcome variable for this study is the rate of complete remission at 18 months post-RAI treatment. Patients will be defined to be in complete remission if all of the following criteria can be demonstrated:

1. Serum thyroglobulin (Tg) levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer[a] by neck US, as assessed by investigator site review.

3. No confirmed radiological evidence of thyroid cancer[a], as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

[a]Confirmation of evidence of structural DTC will be either histopathological (from a biopsy/FNA; as criterion 4 above), or RAI-avid disease (refer to Section 6.4.4.2). In this disease setting, structural abnormalities that are not RAI-avid and do not have confirmed histopathology consistent with DTC (ie are not biopsy proven) are considered benign in the absence of biochemical DTC.

A secondary outcome variable will be the rate of clinical remission at 18 months post-RAI treatment, where clinical remission is defined on the basis of Tg, US and WBS assessments alone, without the additional radiological data.

Safety

AEs/SAEs, physical examination results, lab values, ECG, vital signs.

All randomised patients will be followed for safety monitoring for 3 years following their RAI adjuvant treatment, in order to monitor for selumetinib and RAI-associated side effects.

PK

Where sample collection and PK analysis allow, derived PK parameters for selumetinib and N-desmethyl selumetinib will be produced which may include, but not be restricted to, C_{max} and AUC. Exploratory variables will be analysed outside the clinical study report (CSR).

Statistical methods

Approximately 228 patients will be randomised in a 2:1 ratio in this study. The primary analysis will be performed when patients have been followed for 18 months following their RAI treatment. There will be two primary analysis populations: the first will comprise all randomised patients (overall population); the second will comprise the sub-group of randomised patients with tumours known to be mutation positive for *BRAF* or *NRAS*. The primary endpoint of complete remission rate will be analyzed using a logistic regression model with covariates histology status (papillary, follicular, poorly differentiated), mutation status (overall population only, *BRAF/NRAS* positive, *BRAF/NRAS* negative) and age, provided there are enough data points for a meaningful analysis. There will be two primary analysis populations: the first will comprise all randomised patients; the second will comprise the sub-group of randomised patients with tumours known to be mutation positive for *BRAF* or *NRAS*. To control the type I error rate for the study and account for the correlation between the two primary endpoints, the Dunnett and Tamhane step-up procedure will be used. The correlation between the primary endpoint comparisons will be calculated as $\sqrt{w}$, where w is the proportion of the overall population who are in the mutation positive sub-group. The associated significance level for declaring statistical significance in the mutation positive sub-group adjusting for this correlation to maintain an overall 5% type I error rate whilst assigning 4% to the overall population will then be derived.

Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumetinib-containing arms, respectively, the study will have 80% power to demonstrate a statistically significant difference at the 4% (2-sided) significance level.

Assuming the true complete remission rates in the mutation-positive sub-group are 30% and 62% for the placebo and selumetinib-containing arms, respectively, the study will have 80% power to demonstrate a statistically significant difference at the 1% (2-sided) significance level.

All secondary endpoints will be analysed at the time of the primary analysis. Exploratory biomarker analysis may be analysed after the time of the primary analysis and reported separately to the CSR (apart from the somatic genetic data required for analysis of the second primary endpoint).

All randomised patients will continue to be followed until the final study visit (3 years after their RAI treatment). At this time, data on clinical status, incidence of re-treatment and long-term safety will be summarised.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
^{124}I	Iodine-124
^{131}I	Iodine-131 (radioactive iodine; RAI)
AE	Adverse event (see definition in Section 6.5.1)
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatise
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
AUC	Area under the plasma concentration-time curve from zero to infinity
BD	Twice daily (dosing)
bid	*bis in die* – twice a day
BNP	B-type natriuretic peptide
BP	Blood pressure
Bpm	Beats per minute
BRAF	v-raf murine sarcoma viral oncogene homolog B1
cm	centimetres
C_{max}	Maximum plasma concentration
CRF	Case report form (electronic/paper)
CR	Clinical remission
CR	Complete remission
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
DAE	Discontinuation of investigational product due to adverse event
DNA	Deoxyribonucleic acid
DTC	Differentiated thyroid cancer
D-TC-FCO	Differentiated thyroid carcinoma of follicular cell origin

Abbreviation or special term	Explanation
DUS	Disease under study
EBRT	External beam radiation therapy
EC	Ethics committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ERK	Extracellular signal-regulated kinases
ETA	European Thyroid Association
FDG-PET	2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography
FNA	Fine needle aspiration
FSH	Follicle stimulating hormone
FTC	Follicular thyroid cancer
G1	Gap 1 phase of the cell cycle
GCP	Good clinical practice
g/dL	grams per decilitre
GMP	Good manufacturing practice
hr	hour
I	Iodine
IATA	International Air Transport Association
IB	Investigator brochure
ICH	International Conference on Harmonisation
ICH M3	The European Medicines Agency's International Conference on Harmonisation Topic M3 – "Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals"
IM	Intramuscular
INR	International normalised ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational product
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravascular
IVRS	Interactive voice response system

Abbreviation or special term	Explanation
IWRS	Interactive web response system
kg	kilograms
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LH	Luteinizing hormone
LIMS	Laboratory information management system
LLOQ	Lower limit of quantification
LSLV	Last patient last visit
LT4	Synthetic levothyroxine
LV	Left ventricular
LVEF	Left ventricular ejection fraction
M0, M1, Mx	Distant metastasis status (TNM cancer staging system)
MAPK	Mitogen-activated protein kinase
mCi	millicuries
MedDRA	Medical dictionary for regulatory activities
MEK	MAPK/ERK kinase
MI	Myocardial infarction
µg/L	micrograms per litre
µm	micrometers
mIU/L	milli-International units per litre
mg	milligrams
mg/day	milligrams per day
mL	millilitres
mL/min	millilitres per minute
mm	millimetres
mm^3	cubic millimetres
ms	milliseconds
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
N0, N1, Nx etc	Lymph node disease stage (TNM cancer staging system)
N/A	Not applicable
ng/mL	nanograms per milliliter

Abbreviation or special term	Explanation
NIS	Sodium iodide symporter
NOEL	No observed effect level
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase, receptor, type 1
NYHA	New York Heart Association
OAE	Other significant adverse event (see definition in Section 6.5)
PDTC	Poorly differentiated thyroid carcinomas
PET	Positron emission tomography
PFS	Progression-free survival
PGx	Pharmacogenetic research
PI	Principal investigator
PK	Pharmacokinetics
PRO	Patient reported outcomes
PTC	Papillary thyroid cancer
RAI	Radioactive iodine (^{131}I)
RET	Ret proto-oncogene
Rb	Retinoblastoma protein
RECIST	Response Evaluation Criteria In Solid Tumours
rhTSH	Recombinant human thyroid stimulating hormone
SAE	Serious adverse event (see definition in Section 6.5.2).
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBE-CD	Sulphobutylether β-cyclodextrin
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standard uptake value
T0, T1, Tx etc	Primary tumour disease stage (TNM cancer staging system)
T4	Free thyroxine
Tg	Thyroglobulin
TgAb	Thyroglobulin antibody
TNM	Tumour, nodes, metastasis cancer staging system
TPGS	D-α tocopheryl polyethylene glycol 1000 succinate

Abbreviation or special term	Explanation
TPO	Thyroid peroxidase
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	Ultrasound
WBDC	Web based data capture
WBS	Whole body scintigraphy (also whole body scan)
WHO	World Health Organisation
Wk	Week

1. INTRODUCTION

1.1 Background

1.1.1 Thyroid Cancer

There are approximately 56,500 new cases of thyroid cancer diagnosed in the USA per year, and approximately 34,000 new cases diagnosed in Europe per year. Thyroid cancers are classified according to their histopathological characteristics into 4 main variants: papillary thyroid cancer (PTC, the most common), follicular thyroid cancer, medullary thyroid cancer and anaplastic (undifferentiated) thyroid cancer. The papillary and follicular types together can be classified as differentiated thyroid cancer (DTC), and make up approximately 95% of thyroid cancers. All DTC (including PTC) begins in the follicular cells of the thyroid gland and is termed "of follicular cell origin." Other, rarer variants of thyroid cancer of follicular cell origin include Hürthle cell carcinoma and poorly differentiated thyroid cancer (PDTC). DTC is generally indolent and has a natural history which is measured in decades if treated appropriately (up to 95% 10 year survival). However there are very limited options for patients who ultimately fail radioactive iodine therapy and develop distant refractory metastases, and most of these patients will succumb to their disease (Durante et al 2006).

1.1.2 Radioactive iodine treatment

In addition to primary thyroid surgery, radioactive iodine (RAI, ^{131}I) is the mainstay of therapy for patients with thyroid cancer of follicular origin. It is a targeted therapeutic approach that exploits the expression of the sodium iodide symporter (NIS) to deliver radiation selectively to thyroid cells, which is used as adjuvant therapy after thyroidectomy, and to treat recurrent and metastatic disease.

Most patients with thyroid cancer of follicular origin have differentiated carcinomas which retain at least to some extent the biological properties of normal thyroid cells, including expression of NIS. Presence of this transporter is required for iodine uptake (Riesco-Eizaguirre et al 2006).

Following diagnosis, surgical resection of the thyroid gland with or without removal of the local lymph nodes is performed. Following surgical resection, a set of clinical-pathologic data (such as age at diagnosis, specific histological type, size of the primary tumour, extent of lymph node metastases, presence of distant metastases, gross extrathyroidal extension and completeness of resection) can be used to estimate the risk of recurrence and the risk of disease specific mortality. After surgery, radioactive iodine can be used for the following purposes:

For diagnostic scanning to improve initial staging and extent of disease assessment.

For ablation of the normal thyroid remnant (usually less than 2-3% of normal tissue remains after total thyroidectomy). This treatment facilitates follow-up by achieving an undetectable level of serum thyroglobulin and a subsequent negative diagnostic whole body RAI scan.

As adjuvant therapy, in an attempt to destroy microscopic residual disease in patients at intermediate to high risk of recurrence.

As primary therapy in patients with unresectable RAI-avid loco-regional disease or distant metastases.

Uptake of RAI by tumour tissue is a prerequisite for administration of RAI treatment and for its efficacy. Once patients develop distant metastatic disease, RAI uptake is observed in only two thirds of cases and less frequently in patients with aggressive disease (Durante et al 2006, Mazzaferri and Kloos 2001, Nemec et al 1979, Samaan et al 1985). Patients with no uptake in metastatic foci are considered refractory to RAI, which is then no longer indicated.

1.1.3 Risk stratified remission rates following RAI treatment

Several different risk stratification systems have been published for DTC. The Union Internationale Contre le Cancer/American Joint Committee on Cancer (AJCC) staging system is the most commonly used, but it was developed to predict the risk of death rather than recurrence. To overcome this limitation, the American Thyroid Association (ATA) published guidelines to grade the risk of recurrence into 3 categories (low, intermediate, and high) based on tumour-related parameters (pathological tumour-node-metastasis and histological variant) integrated with other clinical features, including the result of the first post-therapy RAI whole-body scan and serum Tg measurement. Although the ATA risk stratification system has been shown to better predict short-term clinically relevant endpoints of persistent and recurrent disease than the AJCC system, it does not adequately predict longer-term outcomes because the risk of persistent or recurrent disease changes following initial therapy. In addition, the ATA intermediate risk category includes a wide variety of potential risk factors that can have a significant influence on both short term and long-term outcomes (any tumour size, N1a/N1b node status, vascular invasion, extrathyroidal extension, aggressive histology).

Recent evidence suggests that the likelihood of achieving remission varies depending on the size of the primary tumour, extent of invasion, or lymph node status as defined by number and size of affected nodes (refer to Table 1, Tuttle, unpublished sub-analysis of data from Tuttle et al 2010 and Vaisman et al 2012).

Table 1 Remission rates in 2 independent data sets of risk-categorised patients with differentiated thyroid cancer - based on tumour size and lymph node status

TNM status	Description	Remission rate[a] MSKCC[b] n=588 patients	Remission rate[a] Brazil[c] n=506 patients
T1	Tumour diameter 2 cm or smaller	40%	59%
T2	Tumour diameter 2 - 4 cm	47%	52%
T3	Tumour diameter > 4 cm or with minimal extrathyroidal extension	25%	37%
T4	Tumour of any size extending to invade subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia or encasing carotid artery or mediastinal vessels	13%	17%
N0	No metastatic nodes identified	62%	54%
N1a	Metastatic nodes in central neck (pretracheal, paratracheal, or prelaryngeal)	31%	30%
N1b	Metastatic nodes in lateral neck or superior mediastinum	16%	12%

[a] Remission rate within a 2 year follow up period
[b] unpublished sub-analysis of data from Tuttle et al 2010
[c] unpublished sub-analysis of data from Vaisman et al 2012

As can be seen patients with either T3 disease or N1a disease have remission rates that approximate 30%, while patients with T4 disease or N1b disease have remission rates that approximate 15%. From a clinical perspective, these findings are not surprising since T3 disease is very commonly associated with N1a disease, and T4 disease is often associated with N1b disease. Therefore, the similarity in remission rates in T3 and N1a disease, and in T4 and N1b disease, is consistent with observations in clinical practice.

It is important to note that in addition to the location of the lymph node metastases (N1a vs. N1b), the extent of lymph node metastases (size and number of involved nodes) is also a critical factor in assessing the risk of recurrence and risk of failing initial therapy (Randolph et al, 2012, Ricarte-Filho et al 2012). The complete remission rates from the MSKCC and Brazilian cohorts are based on patients with clinically significant, structurally evident N1a and/or N1b disease that required therapeutic neck dissections for clinically apparent metastatic disease (prophylactic neck dissections to remove sub-clinical disease were not performed in either the MSKCC or Brazilian cohorts). For example, in a MSKCC series of 246 papillary thyroid cancer patients who presented with lymph node metastases at the time of diagnosis, a median of 6 metastatic lymph nodes were identified with a median maximal diameter of 1.3 cm (Ricarte-Filho et al 2012). Furthermore, multiple studies have demonstrated that small volume lymph node metastases which are usually identified as incidental findings in the fibroadipose tissue surrounding the thyroid, or as a result of prophylactic central neck dissections, are associated with a low risk of recurrence (Randolph et al, 2012, Ricarte-Filho et al 2012), and these may not even require RAI adjuvant therapy (and therefore would not be

appropriate subjects for the proposed study). Therefore, to prevent patients with lower risk N1a or N1b small volume metastatic disease from enrolling into this study, a requirement is that subjects must have N1a or N1b disease involving 5 or more lymph nodes (of any size) or at least 1 lymph node ≥ 1 cm in the largest diameter.

Since only approximately 30% of patients presenting with any of the following features are expected to achieve clinical remission following total thyroidectomy and RAI remnant ablation, they are at high risk of failing their primary treatment:

- Primary tumour greater than 4 cm
- Primary tumours of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)
- N1a or N1b disease with at least 1 lymph node ≥ 1 cm
- N1a or N1b disease involving 5 or more lymph nodes (of any size)

Total thyroidectomy and RAI ablation is therefore very effective at inducing remission in low risk patients, however approximately 70% of patients with the above characteristics do not enter remission, and have an incomplete response to initial therapy with biochemical and/or structural evidence of persistent disease.

1.1.4 The benefits of achieving remission

Thyroid cancer deaths are exceedingly rare if remission is achieved, and studies have shown that nearly all deaths ultimately occur in the group of patients who do not achieve remission. For example, two recent studies reported disease-specific deaths in 6% and 8% of the patients who did not achieve remission compared to 0% in patients who achieved remission with median follow-up times of 7 and 10 years respectively (Tuttle RM, unpublished sub-analysis of data from Tuttle et al 2010, Vaisman et al 2012). This mortality rate continues to rise with longer periods of follow up with nearly all deaths from thyroid cancer being seen in the cohort of patients that failed to achieve remission.

The importance of a successful initial therapy is demonstrated by the excellent prognosis that even high-risk patients have if therapy results in negative imaging and negative thyroglobulin levels after stimulation by TSH. The majority of patients who achieve remission do not relapse; recurrence rates are typically 1% to 4% over median follow-up periods of 5 to 10 years for patients who achieve remission (Castagna et al 2011, Tuttle et al 2010, Vaisman et al 2012).

In patients that achieve remission, there are important clinical and psychological benefits. Patients that achieve remission are re-classified as low risk patients and require much less frequent follow-up. Thyroglobulin testing and imaging assessments are reduced in frequency, and less aggressive TSH suppressive therapy is required. This in turn reduces the longer-term risks of osteoporosis and atrial fibrillation that are known complications of supra-

physiological dosing of levothyroxine, and reduces the anxiousness and fatigue that can result from the mildly hyperthyroid state caused by TSH suppression.

If remission is not achieved with initial therapy, many patients will be subjected to additional therapies (eg, more RAI, surgery, external beam irradiation), in an effort to control disease progression and achieve a cure. Therapeutic RAI is associated with a cumulative dose-related risk of early and late-onset complications such as salivary gland damage, dental caries, nasolacrimal duct obstruction, and decreased fertility (Cooper et al 2009). Furthermore, a dose-dependent relationship is also seen between cumulative administered RAI activity and the subsequent occurrence of secondary malignancies (Rubino et al 2003, Sawka et al 2009). All of these risks and symptoms constitute significant quality of life issues for the patient. The inconvenience of repeating a low iodine diet, the associated radiation safety precautions and missed days of work are additional factors the patient must consider. Additional surgery carries associated risks related to anesthesia, nerve damage (resulting in hoarseness, permanent tracheotomy in rare occasions, drooping eye lid, loss of control of shoulder muscles and loss of sensation in the neck), increased scarring in the neck (resulting in discomfort and difficulty swallowing), and damage to the parathyroid glands (resulting in hypocalcemia and a lifetime need for vitamin D and calcium supplementation and frequent blood tests). Thus avoidance of further therapy is beneficial to the patient.

Unfortunately, additional therapy is often less effective, particularly in patients with persistent structural disease (Vaisman et al, 2011). Further RAI can be given to patients that have persistent biochemical evidence of disease, and although repeat RAI is often less effective than the initial RAI treatment (especially for patients with persistent structural disease), it can be effective at driving some patients with persistent biochemical disease into remission. Thus, strategies designed to improve the tumouricidal effect of the initial RAI dose should result in higher remission and cure rates.

An intervention that enhances the effectiveness of initial therapeutic RAI in higher risk patients (the target population for this study), should result in higher remission rates and remove the need for further therapy, and would thus be of clear benefit to patients.

1.1.5 Selumetinib

Selumetinib is a potent, selective, noncompetitive inhibitor of MEK, licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma. Selumetinib was discovered by Array Biopharma and had the designation ARRY 142886. Other laboratory code names used during the development of this molecule are AR00142886 and AR-142886-X (where X refers to a sequential lot number). Array BioPharma was responsible for the first-into-human study; the remainder of the clinical development programme for oncology indications is the responsibility of AstraZeneca. AZD6244 has now been assigned the international non-proprietary name selumetinib.

1.1.5.1 MEK and NIS expression

Papillary thyroid cancer (PTC), which is the most common form of the disease, is characterised by a set of genetic alterations, all of which result in the activation of

RAF/MEK/ERK signalling. Of these genetic lesions the most common is the typical V600E mutant of *BRAF* also found in other cancers, most notably melanoma. The other genetic lesions occur in receptor tyrosine kinases (RET and NTRK1), and in *RAS* (*N* and *HRAS*). In total these mutations in effectors of ERK signalling account for approximately 70% of papillary thyroid cancer (Kimura et al 2003, Soares et al 2003). *BRAF* itself is seen in at least 38% of PTC, and is also found in poorly differentiated and anaplastic thyroid carcinomas with a prevalence of 12% and 50%, respectively (Nikiforova et al 2003, Ricarte-Filho et al 2009). These genetic mutations are mutually exclusive and suggest the importance of RAF/MEK/ERK signalling in papillary thyroid cancer.

With regard to the impact on efficacy of RAI therapy, one of the primary effects of activation of the RAF/MEK/ERK signalling pathway is a significant and sustained down regulation of the sodium iodide symporter (NIS) which is responsible for the uptake of iodine into thyroid cells and is required for the uptake of therapeutic ^{131}I into thyroid cancer cells. Studies have demonstrated that the expression of NIS (and other genes typical of differentiated thyroid cells) is suppressed by activation of RAF/MEK/ERK signalling in mouse models of the disease (Franco A et al. 2011). In mice engineered to express V600E *BRAF* in thyroid cells, expression of NIS and other thyroid differentiation markers is reduced (Knauf et al 2005). These mice develop papillary thyroid cancers with dedifferentiated features. Further data using a mouse model of thyroid-specific inducible expression of V600E *BRAF*, show that V600E *BRAF* activation suppresses expression of NIS, thyroid peroxidase (TPO) and thyroglobulin (Tg), and blocks ^{124}I uptake, all of which are re-established once expression of oncogenic *BRAF* is turned off. Treatment of mice expressing the induced V600E *BRAF* with a MEK inhibitor also re-established NIS expression and ^{124}I uptake in the poorly differentiated thyroid carcinomas (PDTC) (Chakravarty D et al 2011). Constitutive activation of MAPK signalling also inhibits the expression of thyroid peroxidase and thyroglobulin in BRAF-induced murine thyroid cancers. Genetic or pharmacological blockade of the pathway restores their expression, and consequently the ability to incorporate iodine into tyrosine (iodine organification), which is associated with greater retention time of ^{131}I in cancer cells (Chakravarty D et al 2011). Other MAPK activating alterations common to thyroid cancer can also cause de-differentiation. Over-expression of either the G12V *HRAS* mutant or *RET/PTC* in thyroid cancer cells suppresses NIS, thyroglobulin and thyroid peroxidase expression, which is restored with MEK inhibitor treatment (Knauf et al 2003, De Vita et al, 2005). These experiments provide a pre-clinical proof of concept that inhibition of ERK signalling by MEK inhibitors can reverse the suppression of NIS, TG and TPO expression and re-establish iodine incorporation into PTC.

NIS expression in clinical thyroid cancer samples

Analysis of clinical tumour samples for NIS expression indicates a relative loss of NIS expression (and the expression of other thyroid specific genes) relative to normal thyroid tissue (Durante et al 2007; Espadinha et al 2009). Furthermore, NIS expression is lower in *BRAF* mutant tumours than in those without *BRAF* mutation (Durante et al 2007; Morai et al 2011; Romei et al 2008). In a well differentiated rat thyroid cell line model, expression of RET/PTC, mutant HRAS, or constitutively active MEK1, blocked TSH-induced expression of Tg and NIS; an effect that was reversed by MEK inhibition. These data are consistent with

the hypothesis that activation of MEK, regardless of the upstream activating mutation is a key factor in the loss of thyroid differentiation specific gene expression including NIS (Knauf et al 2003).

In summary, this data predicts that both an unselected and genetically selected population may benefit from treatment with a MEK inhibitor and RAI. This study will thus assess two populations for the primary endpoint of complete remission rate at 18 months; the genetic 'all comer' population, and also a population of patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that other patients may also benefit.

1.1.5.2 Clinical data in thyroid cancer

The preclinical data generated to date suggests the clinical hypothesis that MAPK pathway inhibition in patients with RAI-refractory tumours will result in reacquisition of RAI uptake and renewed susceptibility to therapeutic ^{131}I. To test this hypothesis, an investigator-sponsored selumetinib pilot study has been performed at MSKCC for patients with RAI-refractory recurrent or metastatic differentiated thyroid carcinoma of follicular cell origin entitled, "Reacquisition Of RAI Uptake Of RAI-Refractory Metastatic Thyroid Cancers By Pre-treatment With The Selective MEK Inhibitor Selumetinib: A Pilot Study" (Ho et al 2012). In this study, the RAI avidity of thyroid tumours was quantified by lesional dosimetry with ^{124}I PET imaging in patients, before and after 4 weeks of treatment with selumetinib. For patients whose tumours reacquired the ability to take up RAI, ^{131}I treatment was administered, and tumour response was assessed both radiographically and with measurement of the serum tumour marker thyroglobulin (Tg).

20 patients were treated with selumetinib in this pilot study. Of the 20 patients, 9 patients had tumours with the V600E *BRAF* mutation, 5 patients had tumours with *NRAS* mutations at codon 61, 3 patients had tumours with *RET/PTC* rearrangements, and the remaining 3 patients were wild-type for these alterations. Twelve of the 20 patients in the study demonstrated increased tumoural ^{124}I uptake, and 8 of these 12 patients achieved sufficient iodine reuptake to warrant treatment with ^{131}I. Interestingly, 5 of these patients were found to have *NRAS* mutations, one a *BRAF* mutation, one a *RET/PTC* rearrangement and one patient was wild-type. Further genotyping and cytogenetic analysis is ongoing to discover other potential oncogenic drivers that may have promoted susceptibility to this therapeutic strategy. The increased iodine incorporation as quantified on the ^{124}I scans translated to clinical efficacy with RAI therapy. Reduction in tumour size by RECIST criteria was achieved in all RAI-treated patients, with 5 confirmed partial responses and 3 patients with stable disease. Substantial decreases in serum thyroglobulin following RAI therapy were achieved in all 8 RAI-treated patients. The mean percent reduction in serum thyroglobulin achieved "post-RAI" (2 months after RAI treatment) compared to "pre-RAI" (within 3 weeks before RAI treatment) was 89%.

Data from the pilot study also suggests that pre-treatment with selumetinib selectively increased RAI uptake in tumoural lesions compared to non-thyroidal tissue (salivary gland).

This pilot study demonstrates that MAPK pathway inhibition can modulate RAI uptake in the most difficult clinical scenario: patients with resistance to RAI therapy. Most patients in the pilot clinical study described above had many metastatic lesions, some of which were refractory to RAI at baseline, and some of which were partially RAI avid at baseline. Importantly, selumetinib not only restored RAI uptake in previously refractory lesions, but also increased RAI uptake in most partially-avid lesions (typically by more than 100% compared to the baseline value; 3 to 7 fold increases in maximum SUVs in such lesions were consistently observed). This provides a strong rationale to develop this strategy in the adjuvant setting for RAI naïve patients, with the goal of further enhancing what is more likely to be RAI-susceptible disease for patients at high risk of primary treatment failure.

In addition to the pilot study described above, a phase II study of 100 mg bid selumetinib (previous mix-and-drink formulation) in 39 patients with RAI-refractory differentiated metastatic thyroid cancer has also been completed (Hayes et al 2012). This study involved continuous monotherapy dosing of selumetinib and no RAI treatment. The results demonstrated few clinical responses (one partial response in 32 evaluable patients), but demonstrated a 66% stable disease rate; median PFS in this poor-prognosis cohort was 33 weeks in patients with mutations in *BRAF* V600E, and 32 weeks in all-comers. Although this study was conducted with the mix and drink formulation (from which selumetinib exposure may be lower), the efficacy of selumetinib as monotherapy in this population was disappointing.

Taken together, these data suggest a strong rationale for investigating selumetinib with RAI in patients with DTC. Given the known prevalence of MEK pathway activation in patients with DTC, and both the pre-clinical and clinical data seen when selumetinib is added to RAI, increasing iodine uptake, specifically with respect to selumetinib's ability to upregulate NIS expression, adding selumetinib to standard of care RAI treatment has the potential to provide important clinical benefit. This benefit may extend to all patients regardless of their genotype, or it may be greater in those patients with tumours driven by mutations in the MEK pathway. This study will allow these hypotheses to be tested.

1.1.5.3 Safety profile of selumetinib

Array BioPharma was responsible for the first study of selumetinib into patients. The remainder of the oncology clinical development programme is the responsibility of AstraZeneca. Selumetinib is currently in phase II development, and has been used as both monotherapy and in combination with other anti-cancer agents, in a variety of adult solid tumour settings (eg, pancreatic cancer, colorectal cancer, melanoma and NSCLC), and paediatric cancer patients.

The formulation taken into the phase I clinical programme by Array Biopharma was an extemporaneous preparation of an oral suspension of selumetinib as the free-base in an aqueous solution of sulphobutylether β-cyclodextrin (SBE-CD, Captisol®), referred to as the free-base suspension formulation (mix and drink). The AstraZeneca phase II monotherapy

clinical programme also utilised this formulation. Subsequent formulation development resulted in a capsule formulation of selumetinib as the hydrogen sulphate salt (AZD6244 Hyd-Sulfate), which will be used in this study. The maximum tolerated dose (MTD) for the suspension formulation was determined to be 100 mg twice daily, whereas for the capsule, the MTD was determined to be 75 mg twice daily. The emerging safety and tolerability profile of the capsule formulation is broadly consistent with that of the suspension formulation, although a higher frequency of fatigue and nausea has been reported with the capsule formulation compared to the suspension formulation in the phase II monotherapy studies.

As of April 2012, over 1200 patients have received selumetinib as monotherapy or in combination with other anti-cancer agents in clinical studies (AstraZeneca and non AstraZeneca-sponsored studies, including investigator-sponsored studies).

Two phase I studies (D1532C00005, D1532C00020) were performed with the Hyd-Sulfate formulation. Comparison of the frequencies from Study D1532C00005 and the AZ-sponsored phase II monotherapy studies described below, shows that there are higher percentages of patients reporting the most frequent AEs such as fatigue, dermatitis acneiform, diarrhoea, nausea and peripheral oedema with the Hyd-Sulfate formulation. This may be due to the higher plasma exposures achieved with the capsule formulation, but may also be in part as a consequence of the more heavily pre-treated patient population in study D1532C00005 having lower tolerances to developing toxicity.

- The frequencies of common AEs observed in Study D1532C00020 were generally more similar to that of Study D1532C00003 (free-base suspension formulation in a phase II population), which may mean that some of the differences in frequencies observed just reflect variations in the study population as the selumetinib safety profile is established.

Two hundred and sixty nine (269) patients received selumetinib free base suspension 100 mg twice daily in 4 completed phase II monotherapy studies (D1532C00003, D1532C00008, D1532C00011, and D1532C00012).

- Rashes (including the preferred terms dermatitis acneiform, rash, rash maculopapular, rash macular, rash papular, acne, and folliculitis) were reported in approximately 70% of patients receiving treatment with selumetinib, and dermatitis acneiform was the most common AE term overall (54%). Other commonly reported AEs were diarrhoea (49%), nausea (33%) and vomiting (24%). Adverse events of peripheral oedema, periorbital oedema, and facial oedema were reported in 31%, 9%, and 4% of patients, respectively. The AEs of fatigue or asthenia were reported in approximately 30% of patients in this phase II population. Dyspnoea exertional or dyspnoea was reported in 13% of patients and, in individual studies, dyspnoea exertional was reported at a higher incidence in the selumetinib groups than in the comparator chemotherapy groups.

- Serious AEs were reported in 24% of patients receiving selumetinib monotherapy. The most frequently reported serious AEs were vomiting (1.5%), diarrhoea,

erysipelas, and pulmonary embolism (in 1.1% patients each). Serious AEs of infections (bacterial sepsis, sepsis, infection, and bacterial arthritis) were reported in 2.2% of patients. The most frequently related reported treatment-related SAE was vomiting (3 patients).

- In Study D1532C00003, small increases in blood pressure were observed after 1 week on selumetinib, with mean increases of 7.4 mmHg (systolic, SBP) and 5.3 mmHg (diastolic, DBP) at Week 8, compared with mean increases of 1.1 mmHg (SBP) and 0.5 mmHg (DBP) in the temozolomide comparator arm. The AE of hypertension was reported in 18 patients (6.7%) receiving selumetinib in phase II monotherapy studies; 6 of these patients had hypertension at entry to the study, and a further 5 patients had documented risk factors for hypertension.

- Reversible asymptomatic reduction in left ventricular ejection fraction (LVEF) to below 55% has been reported in a small proportion of patients with advanced cancers in the monotherapy and randomised placebo controlled studies in combination with standard chemotherapies, with both formulations of selumetinib. In both placebo controlled studies no patient treated with selumetinib had severe LVEF impairment (< 35%) or symptomatic heart failure. Evidence of reversibility on continuing treatment with selumetinib has been demonstrated in some patients. LVEF scheduled assessments were only included in one phase II study (D1532C00003) and in the selumetinib group to evaluate a possible cardiac aetiology of the peripheral oedema reported in earlier studies. The median change in LVEF at Week 4 was 1.2 percentage points, and the individual change from baseline ranged from –20 to +19 percentage points. Adverse events of ejection fraction decreased, left ventricular dysfunction, or ventricular dysfunction were reported in a total of 5 patients (3.3%) receiving selumetinib (including 1 patient who had switched from temozolomide treatment after disease progression) versus 1 patient (1%) in the comparator group.

- Review of clinical laboratory parameters in phase II monotherapy studies identified a trend toward increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels after starting treatment with selumetinib. An increase in serum phosphate was observed in some patients after initiation of selumetinib, compared with patients randomised to comparator treatments.There was a trend toward a small mean decrease in albumin relative to the comparator. No other reports of selumetinib-related changes in laboratory parameters were considered to be of clinical relevance at this time. There was no evidence of myelosuppression or renal impairment.

- Adverse events related to visual function have been reported across the programme with selumetinib. Most often there were no specific clinical findings reported from patients that underwent ophthalmological evaluation after reporting the AE of visual disturbance. AEs consistent with central serous retinopathy have been reported in a

small number of patients receiving treatment with selumetinib, generally in combination with other anti-cancer agents.

- There have been reports of pneumonitis-type events in a small number of patients receiving treatment with selumetinib. An association with selumetinib has not been established. An algorithm for investigation of dyspneoa is provided in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

- Weakness of neck extensor muscles in conjunction with creatine phosphokinase (CPK) increases (reversible on treatment interruption) have been reported in 3 out of 54 patients with uveal melanoma receiving selumetinib 75 mg twice daily in one non-AstraZeneca sponsored study. Increases in CPK levels have been recorded in a small number of patients receiving treatment with selumetinib. CPK elevations are present in some patients with muscle symptoms, although asymptomatic elevations have also been reported. A relationship between selumetinib and elevated CPK levels or myopathy has not been established.

In the DTC pilot study described in Section 1.1.5.2 (Ho et al 2012), where 20 metastatic thyroid cancer patients were treated with a 4 week course of selumetinib 75 mg twice daily, all events attributed to selumetinib were Grade 1 or 2, and included fatigue (80%), maculo-papular rash (70%), acneiform rash (25%), elevation in AST (70%; all Grade 1), elevation in ALT (45%; all Grade 1), diarrhea (45%), nausea (40%), limb edema (30%), oral mucositis (35%), constipation (20%), hypoalbuminemia (15%), decreased white blood cell count (15%), face edema (10%), scalp pain (10%), decreased platelet count (1 patient; Grade 1), eye disorder (1 patient; Grade 1 consisting of visual halos and slight blurriness that resolved after therapy stopped), hypertension (1 patient; Grade 1), periorbital edema (1 patient; Grade 1), and vomiting (1 patient, Grade 1). One patient who was treated with RAI was subsequently diagnosed with myelodysplastic syndrome 51 weeks after RAI administration which subsequently evolved into acute leukaemia (this was determined to be unrelated to selumetinib and likely related to cumulative RAI toxicity as well as previous external beam radiation therapy). All adverse events were readily managed with supportive mediations and were reversible upon discontinuation of selumetinib. None of the 20 patients required dose delays or reductions due to selumetinib toxicity.

In the only other study to specifically investigate selumetinib in differentiated thyroid cancer patients (the phase II study of 100 mg bid selumetinib, previous mix-and-drink formulation) in 39 patients with RAI-refractory differentiated metastatic thyroid cancer (Hayes et al 2012). In these patients with RAI-refractory disease, common drug-related AEs included rash (77%), fatigue (49%), diarrhea (49%), and peripheral oedema (36%). Grade 3 and 4 AEs were consistent with those across the selumetinib program and also included rash (18%), fatigue (8%), diarrhea (5%) and peripheral oedema (5%). Twelve patients required dose reductions for reported AEs across the length of the study (the duration of treatment was greater than 16 weeks for 69% of patients). Six patients (15%) discontinued treatment due to adverse events.

A study of selumetinib in combination with radiation in patients with non-small cell lung cancer has recently been opened but no safety or efficacy results are yet available from this study.

Selumetinib is not mutagenic or clastogenic in vitro but produced increases in micronucleated immature erythrocytes in mouse bone marrow micronucleus studies. Investigatory studies show that this is predominantly via an aneugenic mechanism which is consistent with disruption of normal spindle function as a consequence of the known pharmacological action of a MEK inhibitor. With selumetinib Hyd-Sulfate, a NOEL of 24 mg/kg/day (for 2 days) was established for induction of micronuclei, with plasma exposures significantly above those observed in cancer patients at the maximum tolerated dose of 75 mg twice daily. This suggests that selumetinib will have little potential to cause aneugenicity in dividing cell populations in patients at the proposed clinical dose. Thus, any additional aueugenic risk from a 5 week course (maximum 43 days) of twice daily 75 mg selumetinib dosing in this potentially curative patient setting, is considered to be negligible in comparison with the known and more substantial risk from radiation exposure following a therapeutic dose of ^{131}I (100 mCi) that patients will receive as part of standard of care.

In summary, selumetinib has been shown to have an acceptable profile of side effects, in an extensive safety database for a compound at this stage of development.

Further details regarding the safety profile of selumetinib can be found in the Investigator Brochure.

1.2 Research hypothesis

Pre-treatment with selumetinib enhances the uptake of radioactive iodine in differentiated thyroid cancer, resulting in a greater incidence of complete remission after adjuvant RAI therapy in patients at high risk of primary treatment failure.

1.3 Rationale for conducting this study

Unfortunately a significant proportion of thyroid cancer patients are not cured by their initial surgery and RAI therapy. This is often due to the inability of their cancer cells to adequately incorporate RAI (due to reduced expression of NIS). In such cases, repeated administration of RAI may be given (for RAI avid disease) with the aim of inducing remission and curing their disease. This outcome however is not guaranteed, and patients who subsequently develop refractory metastatic disease have a much poorer prognosis and may eventually succumb to their disease; at least one third of patients who develop metastatic disease have no or very low uptake and are thus not amenable to further RAI treatment. There is thus an urgent need for a medicine that can enhance the effectiveness of initial RAI treatment and increase the probability of achieving remission, thereby preventing more patients from developing distant metastatic disease.

1.4 Benefit/risk and ethical assessment

It is clear from the Investigator-sponsored study (Ho et al 2012), that a short course of selumetinib prior to RAI therapy, is effective in enhancing RAI uptake, reducing tumour marker (Tg) levels, and reducing tumour size in heavily pre-treated patients with documented RAI-refractory disease. Most patients in the pilot clinical study had numerous metastatic lesions, some of which were refractory to RAI at baseline and some of which were partially RAI avid at baseline. Importantly, selumetinib pre-treatment not only restored RAI uptake in previously refractory lesions, but also increased RAI uptake in the majority of partially avid lesions (typically by more than 100% compared to the baseline value; 3- to 7-fold increases in maximum SUVs in such lesions were consistently observed). This pilot data not only supports the preclinical hypothesis that inhibiting the MAPK pathway can convert non-RAI avid lesions to RAI avid tumours, but also demonstrates that iodine uptake in previously iodine sensitive lesions can be significantly increased with selumetinib. This observation broadens the potential clinical applicability of this approach beyond just RAI-refractory thyroid cancer, to the use of selumetinib and RAI as part of upfront adjuvant treatment of RAI-naïve and susceptible DTC.

The potential benefit to patients in this study is therefore high, with an increased chance of complete remission. The toxicity risk from a short course (approximately 5 weeks) of selumetinib treatment has been carefully considered for this potentially curative population; the side effect profile of selumetinib in the short timeframe (maximum 6 weeks of exposure) is considered to be predictable, manageable and reversible (mainly rash and fatigue). The long term risk of secondary malignancies associated with RAI is considered low from a single 100 mCi dose, as these are rare and more typically develop following cumulative RAI treatments and exposure. Patients under the age of 18 years will be excluded to minimise any risk of increased radioactivity exposure in a younger population. The side effect profile of both selumetinib and RAI will be monitored over the entire 3 year study duration for each patient.

2. STUDY OBJECTIVES

2.1 Primary objectives

- To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in the overall study population. Complete remission is defined in Section 6.4.1.

- To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

2.2 Secondary objectives

1. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the overall study population. Clinical remission is defined in Section 6.4.6.

2. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

3. To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

4. To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

2.3 Exploratory objectives

1. To explore subsequent thyroid cancer therapy given to patients who receive selumetinib with RAI, or placebo with RAI.

2. To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters.

3. To collect tumour, plasma and serum samples for potential future research on biomarkers relevant to DTC and response and resistance to study treatments.

4. To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib or RAI and/or susceptibility to cancer.

The exploratory analysis will be reported separately from the CSR.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a double-blind, randomised, placebo-controlled study to assess the efficacy and safety of a short course (approximately 5 weeks) of selumetinib (75 mg, orally twice daily) in combination with adjuvant RAI therapy compared to placebo and adjuvant RAI therapy, in patients with differentiated thyroid cancer at high risk of primary treatment failure.

Approximately 228 patients will be randomised 2:1 selumetinib to placebo.

This will be a multi-centre, international study; it is anticipated that approximately 50 centres will recruit patients in South and/or North America and Europe.

3.1.1 Treatment Plan

Following randomisation, patients will take their assigned study treatment (selumetinib or placebo) for a period of approximately 5 weeks, twice daily. Study treatment will begin approximately 4 weeks prior to the planned day of RAI therapy. Refer to Table 2 for an example study treatment plan. The following treatment criteria must be adhered to:

1. Day 1 of study treatment must occur:
   - no earlier than 6 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy), and
   - no later than 16 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).
2. It is essential that patients remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator until the patient has been on study treatment for a minimum of 7 consecutive days beforehand.
3. Study treatment with selumetinib or placebo will typically last for 36 days, but must be for no longer than 43 days (this allows the planned RAI to be postponed by up to 1 week if absolutely necessary).
4. Patients will be required to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI treatment. Refer to Section 5.1.1 and the example diet in Appendix F for further details.
5. For each of the 2 days immediately prior to their planned RAI therapy, patients will receive a recombinant human TSH injection (rhTSH, Thyrogen), in order to stimulate iodine uptake (refer to Section 5.5.4 for details).
6. Following the 2 days of rhTSH injections, patients will receive their planned RAI therapy the immediate next day (refer to Section 5.5.4 for further RAI dosing information).
7. Twice daily dosing of selumetinib/placebo will continue for 5 days following RAI therapy (Day 36 will typically be the last day of study treatment, but this can extend to Day 43 if necessary).

Table 2 Example study treatment plan

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Day 1 X	Day 2 X	Day3 X	Day 4 X	Day 5 X	Day 6 X	Day 7 X
Day 8 X	Day 9 X	Day 10 X	Day 11 X	Day 12 X	Day 13 X	Day 14 X
Day 15 X	Day 16 X	Day 17 X	Day 18 X	Day 19 X	Day 20 X	Day 21 X
Day 22 X	Day 23 X	Day 24 X Low I diet	Day 25 X Low I diet	Day 26 X Low I diet	Day 27 X Low I diet	Day 28 X Low I diet
Day 29 X Low I diet **Thyrogen**	Day 30 X Low I diet **Thyrogen**	Day 31 X Low I diet **RAI**	Day 32 X Low I diet	Day 33 X	Day 34 X	Day 35 X
Day 36 X **last day of study treatment**		Day 38 (Day 36-41) WBS scan (3-10 days after RAI dose)				

X: Study treatment administration (selumetinib or placebo, twice daily)
RAI: radioactive iodine therapy (^{131}I) refer to Section 5.5.4.2 for details
This suggested treatment plan is an example only. The treatments may be planned for different days as long as all criteria in Section 3.1.1 are met.

3.1.2 Follow-up plan

Following completion of RAI therapy and planned discontinuation of study treatment (randomised selumetinib or placebo); patients will be followed up as follows:

1. 3-10 days after RAI therapy, patients will undergo a post-therapy whole body RAI (^{131}I) nuclear medicine scan to determine where the RAI has localized in the body (refer to Section 6.4.4.2 for further detail).

2. Patients will be monitored for TSH and thyroxine (T4) levels as per local standard of care (refer to Section 6.4.3.3 for further detail). Note that T4 levels will not be collected in the study database.

3. At 9 months (±3 months) following RAI treatment, patients will be assessed for:

   (a) TSH-suppressed Tg and Tg antibody levels (TgAb). Refer to Section 5.9.1.1 for further details.

(b) Neck ultrasound (US). Refer to Section 5.9.1.2 for further details.

It is important that these assessments are not performed earlier than 6 months after RAI treatment.

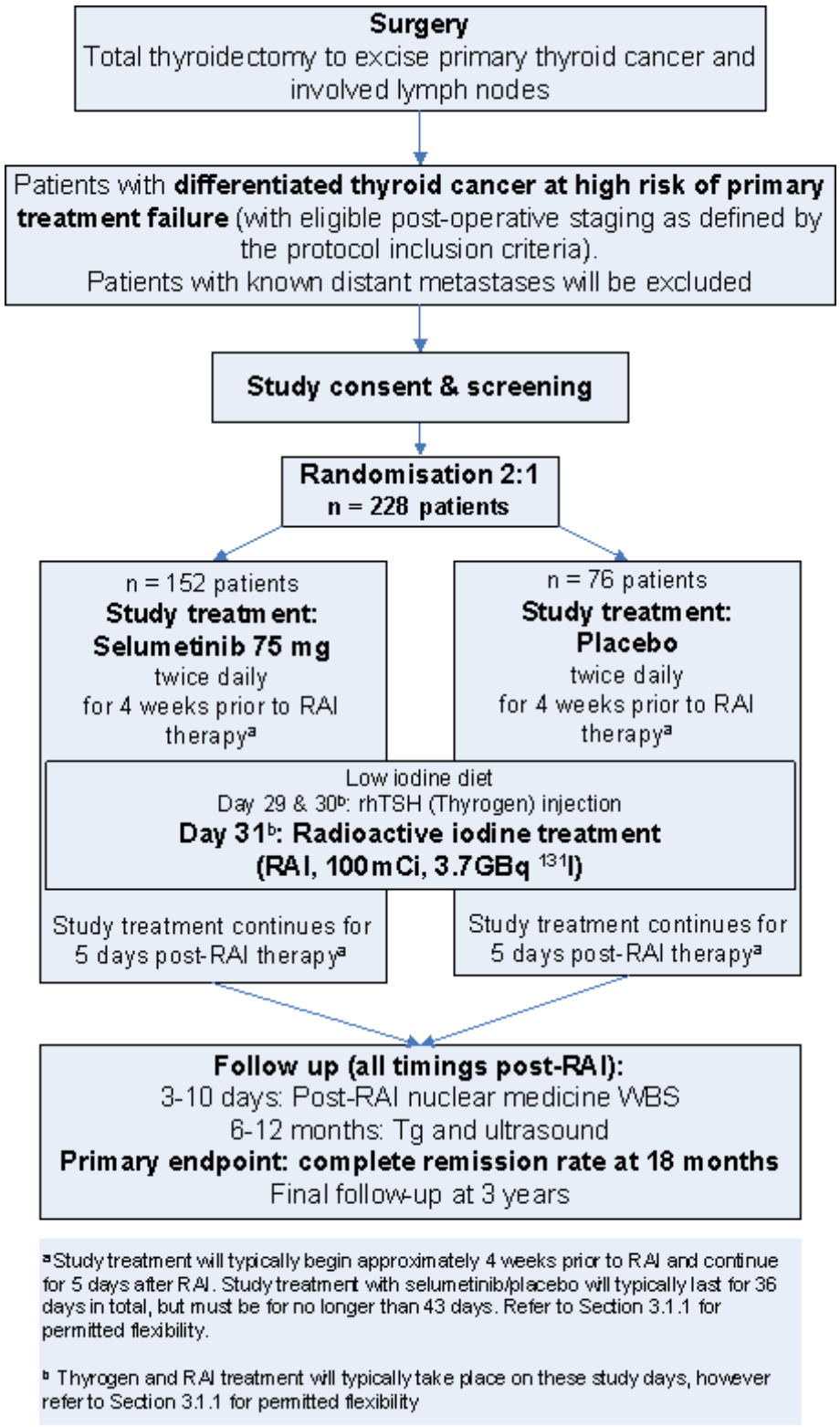
4. Patients will be assessed for their complete remission status at the primary endpoint 18 months following their RAI treatment. A staged approach to the primary endpoint assessments will be used in this study in order to determine remission status (presence or absence of thyroid cancer), such that each patient may not require all assessments. Refer to Section 6.4, Table 4 and Figure 3 for further details. The primary endpoint assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within an 8 week period.

   Further thyroid cancer therapy (eg, additional surgery, RAI re-treatment, external beam radiotherapy or systemic therapy) should only be given during the initial 18 month follow-up period according to the re-treatment criteria in Section 5.9. Any patient that is re-treated in the 18 month period following their RAI therapy will not require any primary endpoint assessments performing (they will be determined not to be in complete remission for the purpose of the study and will enter standard of care follow up, remaining in the study until the 3 year follow up).

5. Following the primary endpoint assessments (or re-treatment), all randomised patients will be further followed-up at 3 years following their RAI treatment. It is the responsibility of the study investigator to ensure they conduct follow-up as described in this protocol if patients transfer to non-study hospitals, or if patients are discharged for routine follow up at other institutions (eg, family doctor or local non-specialist hospital).

Assessments planned at each visit are detailed in Table 3, Table 4 and Section 6.

Figure 1 Study flow chart



[a] Study treatment will typically begin approximately 4 weeks prior to RAI and continue for 5 days after RAI. Study treatment with selumetinib/placebo will typically last for 36 days in total, but must be for no longer than 43 days. Refer to Section 3.1.1 for permitted flexibility.

[b] Thyrogen and RAI treatment will typically take place on these study days, however refer to Section 3.1.1 for permitted flexibility

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Informed consent	X												
Physical examination	X		X				X						6.5.6
Additional screening procedures	X												6.2
Provision of archival tumour[b]		X											6.10.1.1
Plasma/serum sample for exploratory analysis[b]		X											6.10.2
Pregnancy test	X				X					X[a]			6.5.9.1
Optional genetic consent & sample (whole blood)		X											6.9
Adverse events[c]	X	→	→	→	→	→	→	→	→	→	→	→	6.5.3
Concomitant medications	X	→	→	→	→	→	→	→	→	→	→	→	5.6
Telephone follow up for safety[d]								X			X		6.5.3

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Vital signs (including height at screening), weight	X	X					X						6.5.8
Clinical chemistry	X		X				X						6.5.5
Haematology	X		X				X			X		X	6.5.5
Urinalysis	X		X				X						6.5.5
ECG[e]	X	X		X			X						6.5.7.2
ECHO/MUGA[f]	X												6.5.7.1
Ophthalmologic examination[f]	X												6.5.9.2
Selumetinib/placebo dosing[g] twice daily		→	→	→	→	→							5.5.2
PK blood samples[h]		X		X									6.7
Low iodine diet[i]				X	X					X[a]			5.1.1
Thyrogen injection				Xx2						Xx2[a]			5.5.4.1

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
^{131}I (RAI) treatment single 100 mCi dose					X								5.5.4.2
^{131}I 5 diagnostic dose for WBS single 5 mCi dose										X[a]			5.5.4.2
^{131}I nuclear medicine WBS scan						X[j]				X[a]			6.4.4.2
Re-treatment assessment[k]									X	X		X	5.9
Blood sample for TSH									X	X			6.4.3.3
Blood sample for suppressed Tg									X[n]	X			6.4.3.1
Blood sample for TgAb	X								X	X			6.4.3.4
Blood sample for rhTSH-stimulated Tg										X[a]			6.4.3.2
Neck ultrasound	X[l]								X	X			6.4.4.1
Neck MRI	X[l]									X[a]			6.4.4.3

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to Table 4	± 2 months	± 1 month	
Chest CT without contrast	X[l]									X[a]			6.4.4.4
Final follow-up assessment of clinical status												X	6.4.8
Biopsy/FNA for disease confirmation									X[m]	X[m]			6.4.4.5
Tumour biopsy on progression (optional)	Optional sample on disease progression (for example, if the patient is re-treated for persistent or recurrent thyroid cancer, or has further surgery)												6.10.3

Study Plan Table 3 Footnotes

[a] Refer to Table 4 and Section 6.4.2.

[b] Provision of these samples is mandatory in this study.

[c] All AEs/SAEs should be collected from the day of consent until 30 days following the last dose of study treatment. From then on, all SAEs (regardless of causality), and all AEs related to either RAI, or the combination of RAI and study treatment, should be collected until the last study visit 3 years following the patient's RAI dose. The same AE collection scheme applies for any re-treated patient.

[d] The Investigator (or delegate) is required to contact the patient by telephone to follow up for any safety information (according to the collection scheme detailed in Section 6.5). For re-treated patients, safety follow-up should continue according to the protocol-scheduled visits, but may be collected by telephone if necessary at each visit (refer to Section 5.9).

[e] Single ECG assessments 1-2 hours following the first dose on Day 1 and Day 29 or Day 30 of study treatment. A single ECG assessment is also required whenever an ECHO/MUGA is performed, on any cardiorespiratory AE, and for premature discontinuation.

[f] These assessments must be performed during the screening period, and then only on symptomatology according to the relevant protocol section.

[g] Study treatment must be initiated no earlier than 6 weeks after the patient's thyroid cancer surgery, and no later than 16 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).

[h] Each patient will be asked to contribute 8 PK blood samples, one from each of the four pre defined time windows on both Day 1 and Day 29 or Day 30. The Day 29 or Day 30 PK blood samples may be taken earlier, from Day 22 onwards of study treatment if preferred, but it is essential that all PK blood samples are collected before the RAI dose is administered. (a) Pre-dose (within 15 minutes of dosing), (b) between 15 minutes and 1 hour post-dose, (c) between 1.5 and 2.5 hours post-dose, and (d) between 3 and 8 hours post-dose.

[i] All patients must adhere to a low iodine diet (an example diet is provided in Appendix F).

[j] The post-RAI WBS may be performed any time from 3-10 days following the patient's RAI dose (thus it does not have to be on the same day as the last dose of study treatment).

[k] The re-treatment assessment will establish whether the patient has received any further treatment for thyroid cancer. Refer to Section 5.9 for the study criteria for re-treatment in the initial 18 months following the patient's RAI dose.

[l] The post-operative imaging assessments must be performed no sooner than 4 weeks post-surgery, and after all other screening assessments have been performed (ie, they should not be performed for any patient that is otherwise ineligible).

[m] Only if required (refer to Section 6.4.4.5)

[n] A repeat sample for suppressed Tg may be required 2-4 weeks later, refer to Section 5.9.1.1.

For imaging data that is required to be sent to the central imaging CRO at any point in the study refer to Section 6.4.4.5.

Table 4 Study Plan for the 18 month Primary Endpoint Assessments

A staged approach to the primary endpoint assessments will be used in this study in order to determine remission status (absence of thyroid cancer), such that each patient may not require all assessments. Full details are outlined in Section 6.4.2.

	Stage 1	**Stage 2**	**Stage 3**	Protocol Section
Time window	Stage 1 assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within an 8 week period.			6.4.2
Thyroid cancer re-treatment assessment[a]	X[a]			5.9
Suppressed Tg	X			6.4.3.1
TSH	X			6.4.3.3
TgAb[b]	X[b]	X[b]		6.4.3.4
Neck US[f]	X			6.4.4.1
Biopsy or FNA[d]	X[d]			6.4.4.5
Clinical chemistry/haematology	X			6.5.5
Low iodine diet[e]		X[e]		5.1.1
Thyrogen injection[c]		X x 2[c]		5.5.4.1
Stimulated Tg[c]		X[c]		6.4.3.2
Pregnancy test		X		6.5.9.1
Diagnostic 5mCi ^{131}I dose[c]		X[c]		5.5.4.2
WBS (nuclear medicine scan)[c, f]		X[c]		6.4.4.2
Neck MRI with contrast[f]			X	6.4.4.3
Chest CT without contrast[f]			X	6.4.4.4
Selumetinib/RAI-related AE/SAEs	———	———	———▶	6.5.3

Footnotes for Table 4: Study Plan for the 18 month Primary Endpoint Assessments

[a] Patients that have been re-treated for thyroid cancer between their initial RAI dose and the primary endpoint assessments 18 months later (refer to Section 5.9 for re-treatment criteria), will not have any primary endpoint assessments performed, they will remain in the study and enter standard of care follow up according to local practice. They should still be followed up for safety information at 18 m, 27 m and 3 years following their initial RAI dose.

[b] For decision making purposes at any time in the study, standardised central analysis results must be used. If the stage 1 blood sample is positive for TgAb, but the stage 2 blood sample is negative for TgAb, then a third blood sample 10 days later (± 3 days) is required to confirm absence of TgAb.

[c] Patients will receive 2 Thyrogen injections on consecutive days (day 1 and 2), followed by a diagnostic dose (5mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5.

[d] Only if required to prove absence of disease for suspicious lesions (refer to Section 6.4.4.5).

[e] Patients will be required to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI treatment. Refer to Section 5.1.1 and the example diet in Appendix F for further details.

[f] For imaging data that is required to be sent to the central imaging CRO refer to Section 6.4.4.5.

3.2 Rationale for study design, doses and control group

This study is designed to determine the efficacy of a 5-week course of selumetinib or placebo, and adjuvant RAI therapy, by assessing the rate of complete remission at 18 months post-RAI therapy.

The dose and duration of selumetinib treatment in this study (75 mg twice daily for 5 weeks) is selected to be consistent with the pilot study, which has previously demonstrated enhanced RAI uptake following selumetinib treatment, reduction in Tg levels, and reduced tumour size following RAI therapy, in patients with RAI-refractory metastatic thyroid cancer (Ho et al 2012). In addition to the effects of selumetinib on the sodium iodine transporter (refer to Section 1.1.5.1), selumetinib may also increase levels of thyroid peroxidase and thyroglobulin in any remaining thyroid cells. These proteins are required to organify and retain iodide in thyroid cells, thus facilitating greater retention of ^{131}I, and a higher dose of radiation to cancer cells. For this reason, patients will remain on selumetinib treatment for 5 days after receiving the therapeutic dose of RAI.

Since RAI is the standard of care for this patient population, the selumetinib/RAI treatment group will be compared to a placebo/RAI control group for all study endpoints.

The population who will participate in this study will be patients with differentiated thyroid cancer at high risk of primary treatment failure that would routinely require RAI adjuvant therapy as standard of care. This risk-stratified population has been selected because it is known that they are at an increased risk of failing to achieve remission following standard initial therapy, and therefore require more effective treatment strategies (refer to Section 1.1.3). This study is intended to be an adjuvant therapy trial for patients without known structural persistent disease; patients with known distant metastases at screening will be excluded in order to minimise heterogeneity of the efficacy recorded.

The second primary efficacy endpoint will be assessed in patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that these patients are not likely to be the only population to benefit. Incorporation of a genetically predefined study population enables this hypothesis to be examined (mutation analysis of samples to identify the genetically predefined study population will be performed post-randomisation, and prior to data base lock for the primary endpoint data analysis).

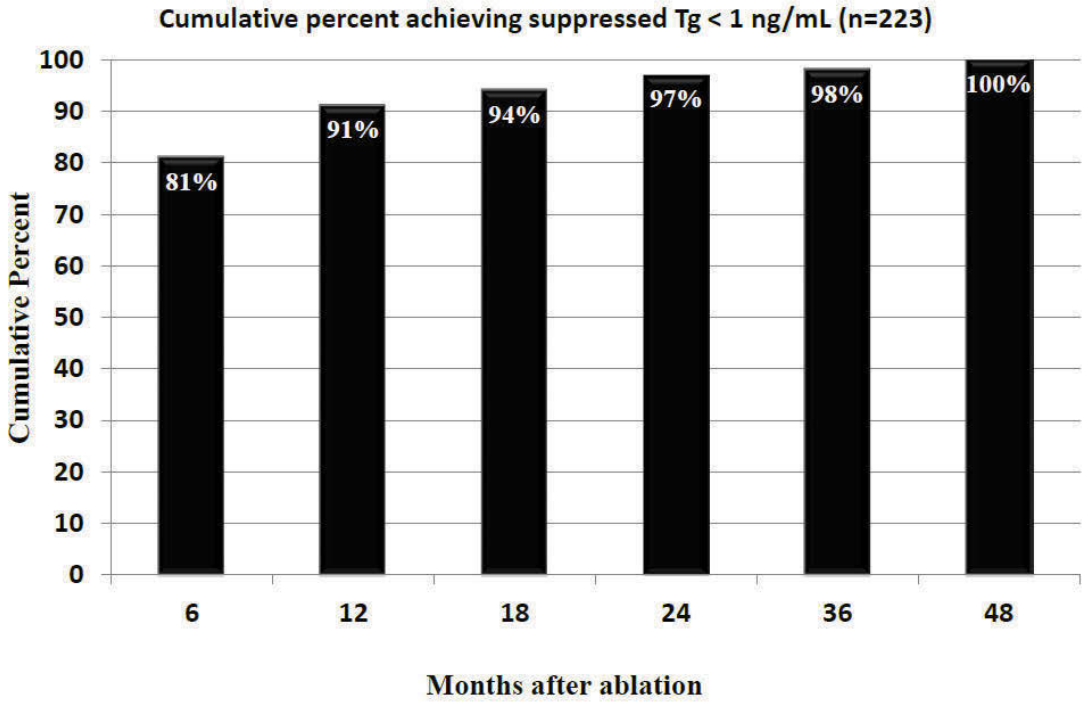
Enhancing RAI uptake into thyroid cancer cells has the potential to increase the incidence of complete remission following RAI treatment. It has been shown that the incidence of complete remission following initial RAI treatment correlates with long-term outcome, and if complete remission has not been achieved, further treatment is frequently administered (Castagna et al 2011, Tuttle et al 2010).

A study has retrospectively evaluated the time to nadir Tg in 299 patients who did not receive additional therapy after total thyroidectomy and RAI (Padovani et al 2012). This patient

population includes both patients with no evidence of disease (remission) and patients with low level disease who are being observed (median follow up time is 7 years). Figure 2 illustrates that 94% of the 223 patients with no evidence of disease achieved a suppressed Tg level of < 1 ng/mL (the biochemical component of remission) by 18 months after initial RAI therapy. Therefore, it is expected that most patients who are likely to achieve remission in both arms will have done so by this time (for the purpose of this study both biochemical and structural absence of disease will be assessed). Longer follow-up would not be expected to change the conclusions regarding an efficacy difference between the two study arms. In patients with similar characteristics to those planned in this study, a similar pattern and extent of Tg decline is also seen (Tuttle RM, unpublished sub-analysis of data from Padovani et al 2012). Previous studies have used time-points ranging from 8 to 24 months to assess remission rates after primary treatment of surgery and RAI (Castagna et al 2011, Tuttle et al 2010, Vaisman et al 2012).

Taking all the data into consideration, the incidence of complete remission at 18 months following initial RAI therapy has been selected as the primary endpoint for the proposed study. Each randomised patient will be followed beyond their 18 month primary endpoint assessment, until 3 years after their RAI treatment, in order to further assess both the clinical status of patients, and the safety profile of selumetinib and RAI beyond the primary analysis (refer to Section 6.4.8).

Figure 2 **Time course to achieving a suppressed Tg<1 ng/mL in patients receiving total thyroidectomy and RAI therapy**



4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, (eg, patient screening log), of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures. The main study consent will include mandatory consent to provide a sample of archival tumour material.

2. Males and females aged 18 years or above.

3. Patients with histologically or cytologically confirmed follicular cell derived differentiated thyroid cancer including papillary thyroid cancer and all variants, follicular thyroid cancer and all variants, and poorly differentiated thyroid cancer.

4. Note: Patients with a diagnosis of Hürthle cell carcinoma should be excluded. These are defined as having an invasive tumour composed of >75% of oncocytic (Hürthle) cells lacking the nuclear features of papillary carcinoma, tumor necrosis and marked mitotic activity. Patients with oncocytic (Hürthle cell variants) of papillary thyroid carcinoma defined as a tumour composed of a majority of oncocytic (Hürthle) cells having the nuclear features of papillary carcinoma are eligible to participate.

5. Patients presenting with any one of the following staging categories post-surgery:

   (a) Primary tumour greater than 4 cm

   (b) Primary tumour of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)

   (c) N1a or N1b disease with at least 1 lymph node ≥ 1 cm

   (d) N1a or N1b disease involving 5 or more lymph nodes (of any size)

   Note: Patients with known metastatic disease at screening will be ineligible for this study as per the exclusion criteria.

6. Patients must have had a one or two-stage total thyroidectomy with therapeutic neck dissection of any clinically apparent metastatic lymph nodes (levels I to VII of the lateral and central neck). All known tumour must have been resected.

Note, the optimal surgical procedure is based on the findings from preoperative ultrasound, to identify the extent of lymph node metastases and thereby facilitate compartment-oriented neck dissection for complete surgical removal of all gross disease. Prophylactic neck dissection is not required or encouraged, but may be performed at the discretion of the treating surgeon. As the surgical procedure(s) will have been performed before study consent, any patient for whom a total thyroidectomy cannot be verified must be excluded from the study (note that patients having undergone a robotic or endoscopic thyroidectomy, or any other novel or remote access surgical technique must also be excluded). For patients who have had a two-stage thyroidectomy, the second surgical procedure must have taken place no later than 12 weeks after the first procedure, otherwise the patient is not eligible.

7. Patients must have all of the following post-operative assessments performed no sooner than 4 weeks post-surgery (post their last surgery if it was a 2-stage thyroidectomy) and the results from each must verify the absence of macroscopic disease:

   (a) Neck US exam

   (b) Neck MRI with contrast

   (c) Chest CT without contrast

   Refer to Section 6.3 for further details. These assessments must be performed within the 28 day screening period (but ideally after all other screening assessments have been performed, ie, they should not be performed for any patient that is otherwise ineligible).

8. Patients must be suitable for radioactive iodine therapy.

9. Patients must be suitable for TSH suppression with a goal of ≤0.5 mIU/L TSH for the duration of the study (this may exclude some patients with cardiac conditions or osteoporosis).

10. Patients must be willing and able to start study treatment within 16 weeks of their thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy). Note that study treatment must not be initiated within 6 weeks of the patient's last surgery.

11. WHO or ECOG Performance Status 0 or 1.

12. Females must:

   (a) be using adequate contraceptive measures (refer to Section 5.1.2),

(b) not be breast feeding (breast feeding must be discontinued in order to participate in this study),

(c) have a negative pregnancy test prior to the start of dosing if they are of child-bearing potential,

(d) or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

(i) Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.

(ii) Women under 50 years old will be considered postmenopausal if they have been amenorrheic for at least 12 months following cessation of exogenous hormonal treatments, and with LH and FSH levels in the post-menopausal range for the institution.

(iii) Documentation of irreversible surgical sterilisation by hysterectomy and/orbilateral oophorectomy and/or bilateral salpingectomy but not tubal ligation.

13. Male patients with sexual partners who are pregnant or who could become pregnant (ie, women of child-bearing potential) must agree to use acceptable methods of contraception for 12 weeks after completing study therapy, or longer if required for standard RAI administration restrictions and in accordance with local labels, to avoid pregnancy and/or potential adverse effects.

14. Adequate organ function as defined by:

(a) ANC ≥ 1.5x109/L (1500 per mm3)

(b) Platelets ≥ 100 x 109/L (100,000 per mm3)

(c) Hemoglobin ≥ 9 g/dL

(d) ALT/SGOT and AST/SGPT < 2.5 X upper limit of normal (ULN).

(e) Bilirubin ≤ 1.5 X ULN (with the exception that patients with elevated unconjugated bilirubin due to a pre-existing diagnosis of Gilbert's syndrome are eligible for the study)

(f) Serum creatinine clearance > 50mL/min by either Cockcroft-Gault formula (see Appendix E) or 24hr urine collection analysis.

15. Patients must be able to swallow selumetinib/placebo capsules for the duration of the study treatment period. This may exclude some patients with swallowing

dysfunction due to the specific technique required for their thyroid surgery. Functional assessment of swallowing ability may be made by the treating Investigator.

4.1.1 Genetics research study (optional blood sample)

1. For inclusion in the optional genetics research study patients must provide optional genetics research informed consent.

2. If a patient declines to participate in the genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

4.1.2 Biomarkers research study on tumour progression biopsy

For inclusion in the optional progression tumour sample study, patients must provide optional consent for this sample to be obtained.

If a patient declines to provide consent to obtain optional tumour sample on progression, there will be no penalty or loss of benefit to the patient, and the patient will not be excluded from any other aspect of the main study.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Known distant metastatic disease at study entry. Investigators are not required to specifically screen patients for distant metastasis beyond their normal Standard of Care practices and the protocol-specific post-operative imaging assessments, but any patient with known distant metastatic disease at screening must be excluded.

2. Diagnosis of anaplastic thyroid cancer, medullary thyroid cancer, or Hürthle cell carcinoma (refer to inclusion criterion 3 for further details on Hürthle cell eligibility).

3. Presence of anti-Tg antibodies at screening (as determined by standardised central methodology, refer to Section 6.4.3.4).

4. Previous treatment with ^{131}I (RAI) or external beam radiation therapy (EBRT) at any time in the past.

5. Any unresolved toxicity ≥ CTCAE Grade 2 from previous anti-cancer therapy including the patient's recent thyroid cancer surgery.

6. Having received an investigational drug during the last 4 weeks prior to first dose of study treatment.

7. Recombinant human TSH (rhTSH, Thyrogen):

(a) Patients with known hypersensitivity to rhTSH will be excluded.

(b) Patients not willing to use rhTSH prior to their RAI treatment will also be excluded (ie, patients or clinicians choosing withdrawal of thyroid hormone treatment prior to their RAI treatment will be ineligible for this study).

8. Patients requiring medication with high content in iodide (amiodarone), or patients receiving IV iodine containing contrast as part of radiographic procedure within the last 3 months prior to the planned RAI treatment (unless a urine measurement demonstrates that urinary iodide level has returned to normal range earlier than 3 months following administration of a contrast agent).

9. Patients with clinically significant cardiovascular disease as defined by the following:

(a) Uncontrolled hypertension (BP ≥150/95 despite optimal therapy)

(b) LVEF < 55% measured by echocardiography (or MUGA)

(c) Symptomatic heart failure (NYHA grade II-IV), prior or current cardiomyopathy, or severe valvular heart disease

(d) Uncontrolled angina (Canadian Cardiovascular Society grade II-IV despite medical therapy)

(e) Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest

(f) Acute coronary syndrome within 6 months prior to starting treatment

(g) Mean QTc interval >470 ms

10. Patients with the following ophthalmological findings/conditions:

(a) Intraocular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intraocular pressure)

(b) Current or past history of central serous retinopathy or retinal vein occlusion

11. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to agents used in the study.

12. Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

13. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

14. Pregnant women will be ineligible (breast feeding should be discontinued if the mother is treated with study therapy).

15. Male or female patients of reproductive potential who are not employing an effective method of contraception (refer to Section 5.1.2).

16. Refractory nausea and vomiting, chronic gastrointestinal diseases, or significant bowel resection that in the Investigator's opinion would preclude adequate absorption of study therapy.

17. History of another primary malignancy within 5 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ and the disease under study.

18. Clinical judgement by the investigator that the patient should not participate in the study.

19. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

20. Previous treatment with any MEK or BRAF inhibitor.

21. Previous enrolment or treatment in the present study.

4.2.1 Genetics research study (optional blood sample)

1. Exclusion criteria for participation in the optional genetics research component of the study:

(a) Previous allogeneic bone marrow transplant

(b) Whole blood transfusion within 120 days of the date of genetic sample collection (except for leukocyte depleted blood transfusion, which is allowed)

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

5.1.1 Low-iodine diet

Published data and opinion regarding the necessity for a low iodine diet prior to RAI therapy or a diagnostic whole body scan is variable. For the purpose of this study a low iodine diet will be mandated in order to standardise patient care and study data as best as possible. Compliance to the low iodine diet will not be recorded or assessed, and all randomised patients will receive RAI treatment as planned. Refer to Table 2 and the Study Plan (Table 3) for further details. An example low iodine diet is provided as Appendix F to this protocol.

A low iodine diet is necessary at two occasions in the study:

Prior to RAI adjuvant treatment

All patients must be willing to adhere to the low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI therapy.

Prior to the primary endpoint Stage 2 assessments

All patients must be willing to adhere to the low iodine diet for a period of 1 week before the diagnostic ^{131}I dose used prior to the primary endpoint WBS assessment (^{131}I nuclear medicine scan), until the diagnostic WBS assessment is completed. This is only relevant for patients who pass Stage 1 primary endpoint assessments (refer to Section 6.4.2).

5.1.2 Other study restrictions

The following restrictions also apply while the patient is receiving selumetinib or placebo:

1. Female patients of child-bearing potential will be required to use reliable methods of contraception until 4 weeks after the last dose of selumetinib/placebo or longer if required for standard RAI administration restrictions and in accordance with local labels. Male patients will be required to use reliable methods of contraception until 12 weeks after the last dose of the last study treatment, or longer if required for standard RAI administration restrictions and in accordance with local labels. Reliable methods of contraception should be used consistently and correctly. Acceptable methods include implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception), some IUDs and vasectomised partner. Sexual abstinence is also an acceptable method of contraception according to ICHM3.

2. Fasting restrictions for the study are described in Section 5.5.2.

3. Patients should avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.

4. Patients should avoid large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study treatment period.

5. Selumetinib capsules contain D-α- Tocopheryl polyethylene glycol 1000 succinate (TPGS, a water-soluble form of vitamin E) as an excipient. Patients should not therefore take vitamin E supplements or multivitamin supplements which provide a total daily dose in excess of 100% of the recommended daily allowance for vitamin E. The maximum dose of vitamin E patients may receive from selumetinib is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided. High doses of vitamin E have been reported to potentiate the anticoagulant activity of coumadins such as warfarin. Patients who are taking coumadin anticoagulants should increase the frequency of assessment of anticoagulation, such as INR measurements, upon initiation of dosing with study treatment.

6. Permitted and excluded antiemetic medications in this study are described in Section 5.6.

7. Permitted and excluded medications for management of skin toxicities (eg, rash) are described in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib." All patients will be given prophylactic provision of emollient cream to take home and to start using when starting study treatment.

8. Unless patients require re-treatment, they should not be enrolled in other studies evaluating novel therapies for thyroid cancer for the entire study duration.

5.2 Patient enrolment, randomisation and initiation of investigational product

The Principal Investigator or delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 4.1 and 4.2

3. Call IVRS/IWRS to assign the eligible patient a unique enrolment number (beginning with 'E#'), and randomisation code (subject number). Randomisation codes will start at 001 and go up.

Randomisation codes will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for randomisation.

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused.

If a patient withdraws from the study after they have been enrolled or have received study treatment then they cannot re-enter the study.

5.2.1 Procedures for randomisation

Patients who satisfy all the entry criteria will be centrally assigned by the IVRS/IWRS, according to the randomisation scheme generated by the Biostatistics Group, AstraZeneca, to selumetinib or placebo in a ratio of 2:1.

Every effort should be made to minimise the time between randomisation and starting treatment. Patients must not be randomised unless all eligibility criteria have been met.

IVRS/IWRS will be used for allocation of enrolment number, allocation of randomisation number, study medication assignment, discontinuation from study treatment, emergency code breaks and study drug shipment confirmation.

5.3 Procedures for handling patients incorrectly enrolled, randomised or initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are incorrectly enrolled but are not yet randomised or initiated on treatment should be withdrawn from the study.

Where patients that do not meet the inclusion and/or exclusion criteria, are enrolled in error, or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the AstraZeneca Physician immediately.

The AstraZeneca Physician must ensure all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The active and placebo capsules will appear identical and presented in the same packaging to ensure blinding of the medication. Medication will be labelled using a unique material pack code which is linked to the randomisation scheme. IVRS/IWRS will allocate randomisation numbers sequentially when sites call IVRS/IWRS to randomise an eligible patient. IVRS/IWRS will allocate the medication pack code to be dispensed to the patient.

All patients must remain blinded until after the 18 month primary endpoint data analysis has been conducted for the study; most patients will thus remain blinded for longer periods of time than their initial 18 month follow up period. Any patient that is re-treated prior to the 18 month primary endpoint time-point (refer to guidelines in Section 5.9), must not be unblinded until after the primary analysis of 18 month primary endpoint data from all patients in the study.

The personnel analyzing the PK samples will be unblinded to treatment allocation in order to organise the appropriate sample analysis. The treatment allocation information will be kept in a secure location until the end of the study.

Once the 18 month primary endpoint data analysis has been conducted for the study, patients may be unblinded for the remaining study follow up.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Procedures for emergency unblinding will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Selumetinib	25 mg Hyd-Sulfate capsule	AstraZeneca
Placebo to match selumetinib	Capsule	AstraZeneca

5.5.2 Doses and treatment regimens

Patients will be randomised on a 2:1 basis, via IVRS/IWRS, to receive either selumetinib 75 mg twice daily, or matching placebo.

Patients will be instructed to take 3 capsules orally on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing), twice a day approximately 12 hours apart according to the Study Plan. Capsules should be taken with water only. On clinic days when PK samples are scheduled to be taken, dosing should be delayed until arrival at the clinic and until the pre-dose PK sample has been taken.

Selumetinib/placebo will be supplied in bottles of 60 capsules of 25 mg strength. At Randomization visit, selumetinib/placebo for the entire treatment period will be dispensed (5

bottles). Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Day 1 of study treatment must occur within 16 weeks of the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).

5.5.3 Management of study treatment related toxicity

The immediate management of any adverse event should be according to standard clinical practice for that event. Subsequent management of treatment related adverse events should be guided by the Investigators' assessment of causality.

5.5.3.1 Selumetinib dose interruption or reduction

It is essential that patients remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator until the patient has been on study treatment for a minimum of 7 consecutive days (as long as the total duration of study treatment does not exceed 43 days, this allows the planned RAI to be postponed by up to 1 week if absolutely necessary).

For all adverse events reported in this study that are considered at least partly causal to administration of selumetinib, the following dose modification guidance should be applied.

Study treatment with selumetinib/placebo should be temporarily interrupted if one of the following AEs are observed (and considered causal to study treatment), **despite optimal supportive care** (ie, supportive treatment may be given prior to withholding study treatment):

- Any intolerable adverse event regardless of Grade
- Any adverse events ≥ CTCAE Grade 3

On improvement of the adverse event to Grade 1 (Grade 2 for rash) or baseline, study treatment may be restarted at the original dose or may be reduced at the discretion of the investigator. One dose reduction of study treatment to 50 mg twice daily is permitted before permanent discontinuation.

- If a further episode of the same AE subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the AE.
- If a different AE subsequently requires dose interruption, selumetinib may be restarted at the same dose or at the next dose level down on improvement of the AE.
- Selumetinib should not be re-escalated to an earlier dose level on improvement of an AE.

- The schedule of assessments described in Table 3 should continue relative to Day 1 in the event of selumetinib dose interruption or reduction.

Therefore, the dose reduction/adjustment algorithm in the study allows for 2 steps only:

75 mg twice daily (initial dose)
↓
50 mg twice daily
↓
permanent discontinuation

All dose delays, reductions and adjustments will be recorded in the appropriate electronic Case Report Form (eCRF).

The guidance above should also be followed for dose interruptions or reductions for adverse events of rashes or diarrhoea. Guidance for interruption or reduction of treatment with selumetinib may be considered for particular events, as indicated in the algorithms provided as a separate study aid in the "Guidance for Management of Specific Adverse Events in Studies of Selumetinib" (refer to Section 5.5.3.2).

5.5.3.2 Management and investigation of specific selumetinib related AEs

Recommendations for the management or investigation of the following specific AEs is provided in Appendix G: Guidance for Management of Adverse Events in Studies of Selumetinib.

- Rash: early initiation of treatment for rash is strongly recommended to minimise the duration and severity of the adverse event. All patients should be given prophylactic provision of emollient cream to take home and to start using when starting study treatment as indicated in the algorithm for management and investigation of rash included in Appendix G.

- Visual disturbances: symptoms, including blurred vision, have been reported during treatment with selumetinib. Events consistent with central serous retinopathy have been reported in a small number of patients receiving treatment with selumetinib, generally in combination with other novel targeted anti-cancer agents. AEs of central serous retinopathy and retinal vein occlusion have been reported in studies of other MEK inhibitors (Lemech & Arkenau 2012). Investigation to determine the underlying cause of visual disturbance is recommended.

- Diarrhoea: early initiation of treatment for diarrhoea is strongly recommended to minimise the duration and severity of the adverse event. Treatment provision will be according to Investigator discretion according to local practice and regulations.

- Dyspnoea: new or worsening dyspnoea has been reported during treatment with selumetinib; investigation to determine the underlying cause is recommended.

5.5.4 Additional study drugs

5.5.4.1 Thyrogen (rhTSH, thyrotropin alfa for injection)

Thyrogen use prior to the RAI ablative dose

Effective use of RAI therapy requires stimulation by TSH in order to maximise RAI uptake by thyroid cells. Recombinant human TSH (rhTSH or Thyrogen) will be used to stimulate iodide uptake according to the manufacturer's recommendation (0.9 mg intra-muscular injection for 2 days immediately prior to the RAI treatment according to the Study Plan Table 3). rhTSH is approved for use in routine clinical care as a diagnostic tool to stimulated serum thyroglobulin and RAI uptake for diagnostic scanning and as an adjunct to RAI ablation in many countries. This allows patients to avoid the hypothyroidism state, since they can maintain their routine thyroid hormone supplementation. Patients or clinicians choosing withdrawal of thyroid hormone treatment for this purpose will be ineligible for this study. All randomised study patients will receive Thyrogen twice prior to their RAI treatment dose.

Thyrogen use for the primary endpoint assessments (18 months post-RAI)

For those patients that progress to Stage 2 of the primary endpoint assessments (refer to Section 6.4.2), Thyrogen will be used to stimulate iodide uptake immediately prior to administering the diagnostic ^{131}I dose for the primary endpoint WBS assessment. Patients will receive a 0.9 mg intra-muscular Thyrogen injection for two consecutive days. Refer to Section 6.4.2.2 for further details.

5.5.4.2 Radioactive iodine (RAI)

All RAI for the study will be locally provided at each site.

Therapeutic RAI dose (^{131}I)

A single oral RAI dose of 100 mCi (3.7 GBq) ^{131}I (+/- 10% at the time of administration) will be administered to all patients according to the Study Plan Table 3, according to standard practice at each site.

Diagnostic WBS dose (^{131}I)

For those patients that progress to Stage 2 of the primary endpoint assessments (refer to Section 6.4.2), a single oral RAI dose of 5 mCi (185 MBq) ^{131}I (+/- 10% at the time of administration) will be administered for the primary endpoint WBS (nuclear medicine scan) 18 months following the ablative treatment dose of RAI. Refer to the Study Plan Table 3, and Section 6.4.4.2 for further details.

5.5.4.3 Thyroid hormone supplementation (TSH suppression)

Routine thyroid hormone supplementation (levothyroxine, LT4) is required during the study as per standard clinical practice. The purpose of this is both to correct resulting hypothyroidism using a dosage appropriate to achieve normal blood levels of thyroid hormone, and to inhibit TSH-dependant growth of residual thyroid cancer cells. Thyroid

hormone supplementation will be adjusted in individual patients with the aim of achieving suppressed TSH levels of <0.5 mIU/L for the duration of the study.

5.5.5 Study drug labelling

Each bottle of selumetinib and matching placebo capsules will be labelled by Pharmaceutical Development Supply Chain, AstraZeneca or its designee.

All labels will comply with good manufacturing practice (GMP) regulations, and will state that the drug is for clinical use only or that it is the investigational drug and is to be used by qualified investigators only and should be kept out of reach of children. The labels will have blank spaces for the site personnel to complete the following at the time of drug dispensing: enrolment code, visit number and dispensing date.

Label text will be translated into local language.

Each bottle of selumetinib/placebo capsules will have a tear-off portion that will be removed at the time of dispensing and attached to the Drug Label Accountability Log.

5.5.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

5.6 Concomitant medications

The use of antiemetic medication for the prevention of nausea caused by administration of radioactive iodine is permitted in this study according to local clinical practice (with the exception of aprepitant which is an excluded medication in this study, due to the potential for modification of selumetinib exposure via CYP3A4). The administration of any antiemetic medication must be recorded in the appropriate sections of the Case Report Form.

All patients will be given prophylactic provision of emollient cream to take home and to start using when starting study treatment as indicated in the algorithm for management and investigation of rash included in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

The following treatments/drugs are restricted in this study:

- No other anti-cancer agents, or investigational drugs should be administered whilst patients are receiving study medication or are in follow-up in this study (unless the patient withdraws from the study, or meets the re-treatment criteria in Section 5.9).
- Patients who are taking coumarin anticoagulants should increase the frequency of assessment of anticoagulation, such as INR measurements, during the study treatment period with selumetinib/placebo.

- The maximum dose of vitamin E patients may receive from selumetinib is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided in patients receiving the capsule formulation.

- Throughout the study, patients should avoid changes to, or the addition of all other concomitant medications, in particular any that may affect the metabolism of selumetinib (eg, CYP1A2 or 3A4 inhibitors/inducers), unless considered clinically indicated.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

All concomitant medications will be recorded on the CRF until 30 days after the last dose of study treatment, and after this time a study-specific record must be kept of any further treatment for thyroid cancer (including surgery), or treatment for RAI-related AEs/SAEs until the last study visit for all patients (refer to Section 5.9).

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Where appropriate facilities and procedures for drug destruction exist, and prior approval from the site monitor has been received, site personnel will account for all unused drugs and for appropriate destruction.

Where such facilities do not exist study site personnel/study monitor will return all unused drugs to AstraZeneca or its designee according to country rules.

The AstraZeneca monitors will ensure that all drug-handling procedures at sites are appropriate, and that all certificates of delivery and return are completed and signed by the site, AstraZeneca, or its delegate, as appropriate. In addition, the monitor will check that the certificate of destruction has been signed by the site, if study drug destruction is performed at the site.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Risk to patients as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- A female patient becoming pregnant

5.8.1 Procedures for premature discontinuation of a patient from investigational product

A patient that decides to prematurely discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.5.3 and 6.5.4), and all study drugs should be returned by the patient. In this situation, a treatment discontinuation visit will be conducted as soon as possible after the patient received the last dose of study drug (selumetinb/placebo). A single 12-lead ECG is also required at premature discontinuation of treatment.

If a patient is withdrawn from the study (ie, withdraws consent for follow-up procedures), see Section 5.10.

Collection of all AEs/SAEs will continue until 30 days after the last dose of study drug (selumetinib/placebo) for prematurely withdrawn patients. As long as the patient does not withdraw consent, follow up in this study will continue as planned.

Any patient with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (±7days) after discontinuation.

5.9 Criteria for further thyroid cancer therapy during the study

5.9.1 Re-treatment prior to the 18 month primary endpoint assessments

It is acknowledged that there is variability in thyroid cancer re-treatment clinical practice. The study-specific criteria below are designed to standardise re-treatment prior to the primary endpoint assessments for the purpose of this study as best as possible. Thus, further thyroid cancer therapy (eg, additional surgery or RAI treatment) prior to the primary analysis of complete remission at 18 months post-RAI, must not be administered unless any of the following criteria are met.

Patients meeting the following re-treatment criteria do not have to be re-treated, they can instead be followed expectantly without re-treatment at the discretion of the treating Investigator.

5.9.1.1 Biochemical disease re-treatment criteria

The first scheduled post-RAI follow up for serum Tg will be assessed 9 months after the RAI dose (± 3 months). Tg assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (**but not before 6 months**).

All biochemical sample analysis for study re-treatment criteria must be performed by standardised central laboratory methodology (for further details refer to the Laboratory Manual).

Patients must not be re-treated for thyroid cancer unless any of the following biochemical criteria are met:

1. If a serum Tg level ≥ 5 ng/mL on central analysis is measured **during TSH suppression**, then a repeat Tg sample must be assessed by central analysis 2-4 weeks later. The patient must not be re-treated unless both centrally analysed samples demonstrate the suppressed Tg level to be 5 ng/mL or higher.

2. If a serum Tg level ≥ 10 ng/mL is measured **following TSH stimulation**, the patient may be re-treated (a repeat sample for confirmation is not necessary). Note, a stimulated Tg assessment is not part of the study-specific follow up plan for patients prior to the 18 month primary endpoint assessments (thus it is not recommended or required, and is not included in the Study Plan). However, if a stimulated Tg assessment is performed due to local practice, this re-treatment criterion applies.

3. If an increase (delta change) in serum Tg level of 3 ng/mL or more is determined between two Tg assessments taken 2-4 weeks apart (due to a repeat sample), the patient may be re-treated.

Thus, in the absence of structurally identifiable disease, patients in this study should have continued observation without additional thyroid cancer treatment (eg, additional RAI, surgery) until the study primary endpoint (18 months after RAI treatment), if the serum Tg level remains below 5 ng/mL during TSH suppression, below 10 ng/mL following TSH stimulation (if assessed), and is either stable/declining, or rising less than 3 ng/mL between samples 2-4 weeks apart.

Note: If a patient has Tg levels below the above re-treatment criteria, but TgAb are detected (ie, the patient is TgAb positive; refer to Section 6.4.3.4), the patient should not be re-treated unless new structural disease is detected according to Section 5.9.1.2 (ie, it is recommended that patients are not re-treated on the basis of new antibodies alone, in the absence of structural disease).

Unscheduled samples and local analysis

It is acknowledged that Investigators may wish to also perform their own local biochemical analysis according to local standard of care. In general, unscheduled samples that are taken

either outside of the visit window specified, or in addition to the scheduled study samples, should not be sent for standardised central analysis. Only if such unscheduled local analysis leads the Investigator to wish to administer further therapy for thyroid cancer, should a sample ideally be sent for central analysis and the above criteria applied before the patient is re-treated.

5.9.1.2 Structural disease re-treatment criteria

The first post-RAI ultrasound follow up will be assessed 9 months after the RAI dose (± 3 months). Ultrasound assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (but not before 6 months).

Patients must not be re-treated for thyroid cancer unless any of the following structural criteria are met:

1. In the absence of any biochemical evidence of thyroid cancer, structural DTC should be confirmed prior to re-treatment, by positive histology/cytology from a biopsy/FNA of ultrasonographically suspicious lesions or lymph nodes ≥ 5 mm in the smallest diameter (refer to Section 6.4.4.5).

2. Identification of new distant metastases (these do not need to be confirmed by biopsy). Assessment of potential distant metastases is not required, but may be performed if clinically indicated at the discretion of the treating Investigator.

5.9.1.3 Patient management on study (up to the primary analysis at 18 months post-RAI)

At the required follow up visits, the following questions should be answered for each subject:

1. Does the patient have a suppressed Tg ≥ 5 ng/mL, a TSH stimulated Tg ≥ 10 ng/mL or a rising Tg level (increase of 3 ng/mL or more) according to the guidelines in Section 5.9.1.1?

2. Does the patient have new loco-regional structural thyroid cancer according to the guidelines in Section 5.9.1.2?

3. Does the patient have new distant metastatic lesions according to the guidelines in Section 5.9.1.2?

If the answer is yes to any of the questions, the patient is unlikely to enter remission and may be re-treated for thyroid cancer (but does not have to be).

Full details of any thyroid cancer re-treatment must be recorded on the appropriate eCRF.

Any re-treated patients will remain in the study and should enter standard of care follow up according to local practice until 3 years after their initial RAI therapy (refer to Section 6.4.8). Patients who are re-treated prior to the primary endpoint at 18 months post-RAI do not require primary endpoint disease assessments performing, however these patients should continue to

follow all protocol-scheduled visits for safety (AE/SAE follow-up) as described in the Study Plan Table 3 and in Section 6.5. Patients do not need to attend these follow up visits in person (telephone contact is permitted), however when local follow-up visits coincide with protocol-specified visits, these should ideally be in person where possible.

If the answer is no to all questions, the patient should continue the study follow-up as per protocol without additional thyroid cancer re-treatment.

5.9.2 Re-treatment after the 18 month primary endpoint assessments

Following completion of all assessments for complete remission at the primary endpoint 18 months post-RAI, patients may receive re-treatment for thyroid cancer as per clinically indicated according to local standard of care. Any re-treated patients will remain in the study and should enter standard of care follow up according to local practice until 3 years after their initial RAI therapy (refer to Section 6.4.8).

Full details of any thyroid cancer re-treatment must be recorded on the appropriate eCRF.

5.10 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and follow-up assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.5.3 and 6.5.4); any remaining study drug should be returned by the patient.

5.11 Replacement of patients

There will be no replacement of randomised patients in this study for any reason.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

6.2 Data collection at enrolment

The following data will be collected & procedures performed for each patient:

1. Informed consent (to include consent for archival tumour sample provision)

2. Demography (date of birth, sex, race)

3. Histological/cytological confirmation of thyroid cancer, including post-operative disease staging

4. Medical and surgical history

5. Concomitant medications and previous anti-cancer therapy

6. Assessment of WHO or ECOG performance status (refer to Section 6.2.1)

7. Collection of AEs will start after signing the consent form

8. Physical examination

9. Vital signs (resting blood pressure (BP), pulse rate), weight and height

10. Single ECG

11. Blood samples for clinical chemistry and haematology

12. Blood sample for determination of interfering Tg antibodies (central standardised analysis)

13. Urinalysis (at sites where the local laboratory is able to determine the required parameters, see Section 6.5.5)

14. Pregnancy test for female pre-menopausal patients

15. Full ophthalmologic examination, including slit-lamp fundoscopy and intraocular pressure examination

16. ECHO or MUGA

17. The following imaging assessments must be performed within the 28 day screening period but only after all other screening procedures have confirmed eligibility status (refer to Section 6.3):

    (a) Neck ultrasound (US)

    (b) Neck MRI with contrast

    (c) Chest CT scan without contrast

18. Overall assessment of patient eligibility for the study

19. Upon confirmation of patients' eligibility, patients will be invited to attend the randomisation visit. Patients must not be randomised unless all eligibility criteria have been met.

20. Call interactive voice response system (IVRS)/interactive web response system (IWRS) to randomise the patient

6.2.1 Performance status definitions

Performance status will be assessed at screening according to either the WHO or ECOG criteria as follows:

0 = Fully active, able to carry out all pre-disease performance/activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

6.3 Post-operative imaging assessments for eligibility

The post-operative imaging assessments of US, neck MRI and chest CT are performed during screening to determine study eligibility. These assessments must determine the absence of macroscopic persistent disease post-surgery for a patient to be eligible prior to randomisation. The post-operative imaging assessments must be scheduled once all other screening assessments and eligibility criteria have been verified.

The screening chest CT procedure must be performed **without iodine containing contrast agent**.

Eligibility will be determined by the local investigational site.

Acquisition guidelines for the post-operative imaging assessments will be provided separately to this protocol.

In addition to information recorded on the eCRF for US, the post-operative images for chest CT and neck MRI must be collected and sent to the central imaging CRO.

6.4 Efficacy

6.4.1 Complete remission

The primary endpoint for this study is **complete remission rate at 18 months** (following RAI treatment).

Definition of complete remission:

Patients will be defined to be in complete remission if all of the following criteria can be demonstrated:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer[a] on neck US, as assessed by investigator site review.

3. No confirmed radiological evidence of thyroid cancer[a], as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

There are two main components to complete remission: biochemical remission and structural remission. Biochemical remission is measured by Tg and structural remission is assessed by the imaging assessments US, MRI, CT and WBS in conjunction with biopsy/FNA.

A staged approach will be taken for performing assessments contributing to the primary endpoint, to avoid unnecessary assessments for individual patients who received further therapy prior to the primary assessment, and for those patients not in biochemical remission (as determined by serum Tg levels in the absence of interfering Tg antibodies).

[a]Confirmation of evidence of structural DTC will be either histopathological (from a biopsy/FNA; as criterion 4 above), or RAI-avid disease (refer to Section 6.4.4.2). In this disease setting, structural abnormalities that are not RAI-avid and do not have confirmed histopathology consistent with DTC (ie are not biopsy proven) are considered benign in the absence of biochemical DTC.

6.4.2 Staged approach to primary endpoint assessments

Full details of the staged approach to the primary endpoint assessments are outlined below.

There will be 3 stages of assessments. Patients that have been re-treated for thyroid cancer will not have any primary endpoint assessments performed. All patients who have not been re-treated for thyroid cancer will have stage 1 assessments performed. The decision on whether to proceed to stage 2 and 3 assessments for patients that have not been re-treated will be based on centrally analysed biochemical data (Tg and TgAb data).

Sites will receive results from standardised central laboratory analysis of the biochemical data and make a decision to proceed based on these results. Patients identified as not in

biochemical remission will not be required to have all imaging assessments described in Section 6.4.1 performed.

For patients that have imaging assessments performed, the appropriate data will be sent to the imaging CRO for blinded independent central review to identify presence or absence of structural disease. Note: results from the central imaging review will not be reported to clinical sites.

Briefly:

In stage 1, suppressed Tg will be determined together with neck US assessment for all patients who did not require re-treatment for thyroid cancer during the first 18 months of follow up (refer to Section 6.4.2.1).

In stage 2, rhTSH stimulated Tg and diagnostic WBS will be performed (refer to Section6.4.2.2).

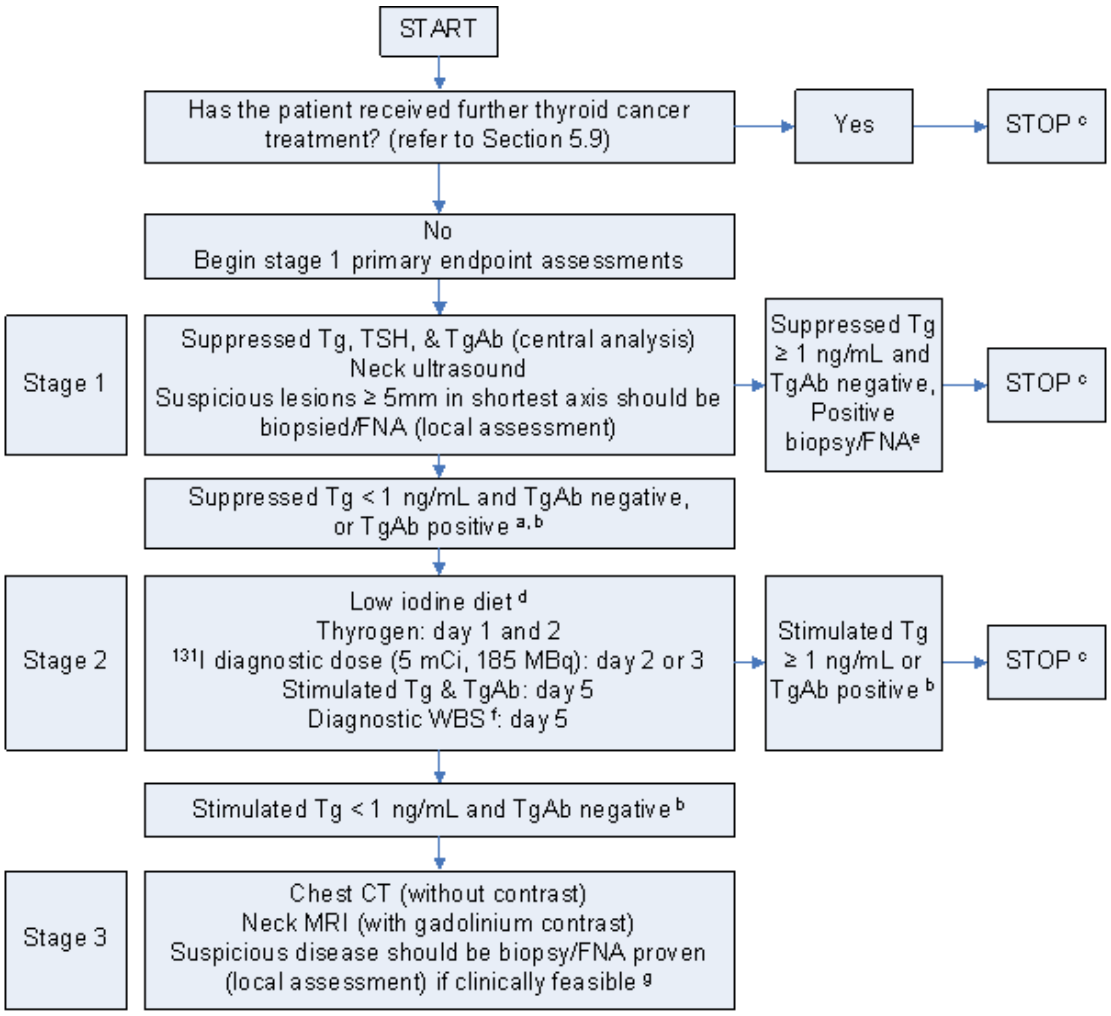
In stage 3, additional radiological imaging (chest CT and neck MRI) will be performed (refer to Section 6.4.2.3).

Stage 1 assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments (all 3 stages if required) must be completed within an 8 week period (refer also to Table 4).

Refer to the flowchart Figure 3 for a visual representation of the staged approach for primary endpoint assessments.

Refer to Section 6.4.5 for the process of determining complete remission from the primary endpoint assessment data.

Figure 3 Flow chart for staged primary endpoint assessments



[a] Patients should progress to stage 2 assessments based on biochemical data only (regardless of US results). Any TgAb positive patients should progress to stage 2 regardless of their suppressed Tg result.
[b] If both stage 1 and stage 2 blood samples are positive for TgAb, then the stimulated Tg result will be deemed to be uninterpretable, and for the purpose of this study the patient will be classified as not in complete remission. No further primary endpoint assessments are required. The patient will remain in the study for follow up until 3 years following their initial RAI treatment. If the stage 1 and stage 2 samples are discordant for TgAb status, then a third blood sample 10 days later (± 3 days) is required to confirm TgAb status.
[c] For the purpose of this study, patient will be classified as not in complete remission. The patient should remain in the study for follow up until the final study visit 3 years following their initial RAI treatment, and enter standard of care treatment/follow up according to local clinical practice.
[d] Low iodine diet is required from 1 week before the diagnostic dose of ^{131}I is administered, until completion of the WBS assessment. Refer to Appendix F.
[e] If a patient has a biopsy/FNA result available that confirms the presence of structural DTC then no further assessments are required. If a biopsy/FNA was taken, but the result is not yet available, then the patient should not delay moving to stage 2 assessments (even if the biopsy/FNA is subsequently confirmed to be positive for structural DTC).
[f] For study endpoint purposes the WBS will evaluated by blinded independent central review. Even if local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).
[g] For the size criteria for biopsy/FNA from MRI/CT assessments, refer to Sections 6.4.4.3 and 6.4.4.4 respectively.

6.4.2.1 Primary endpoint assessments Stage 1

Patients that have been re-treated for thyroid cancer between their initial RAI dose and the primary endpoint assessments 18 months later (refer to Section 5.9 for re-treatment criteria), will not have any primary endpoint assessments performed. For the purpose of the primary endpoint, such re-treated patients will be determined not to be in complete remission.

In stage 1, all patients that have not previously been re-treated for thyroid cancer will have:

- Suppressed Tg level determined by standardised central laboratory analysis.
- TSH and TgAb (using the same blood draw for suppressed Tg) determined by standardised central laboratory analysis. Refer to Section 6.4.3.
- Neck US assessment for structural disease to be assessed by investigator site review. Refer to Section 6.4.4.1.

Suspicious lesions identified by US ≥ 5 mm in the shortest diameter should be biopsied or aspirated by fine needle. All biopsy/FNA samples will be assessed locally at each site. Lesions identified by US < 5 mm in the shortest diameter do not require a biopsy.

All neck US and biopsy/FNA samples will be assessed locally at each site. The relevant US information with any biopsy findings will be provided to the imaging CRO as part of the blinded independent central review.

When to proceed to stage 2 assessments

All patients in the following situations should proceed to stage 2 assessments:

1. Patients with suppressed Tg < 1 ng/mL. These patients should proceed to stage 2 regardless of the TgAb or US results.
2. Patients who are TgAb positive in stage 1 (regardless of the suppressed Tg level, and US results).
3. Patients who fulfil either of the 2 above criteria, and have a biopsy/FNA result pending (ie, Investigators should not wait for the biopsy/FNA result before performing stage 2 assessments).

When not to proceed to stage 2 assessments

All patients in the following situations will be classified not in complete remission and should not proceed to stage 2 assessments:

1. Patients who have suppressed Tg level ≥ 1 ng/mL in the absence of TgAb (unequivocal biochemical disease).

2. Patients with a positive biopsy/FNA that confirms the presence of structural DTC. Note that if the biopsy/FNA results are not yet available, the patient should not delay proceeding to stage 2 assessments.

Patients who demonstrate presence of disease and do not proceed to stage 2 assessments will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, **and will continue to be followed in this study** until 3 years following their initial RAI dose (refer to Section 6.4.6).

6.4.2.2 Primary endpoint assessments Stage 2

In stage 2, patients will have:

- rhTSH stimulated Tg level determined by standardised central laboratory analysis.
- TgAb (from the same blood draw for rhTSH stimulated Tg) determined by standardised central laboratory analysis. TSH will not be analysed from this sample. A repeat (third) sample for TgAb analysis may be required 10 days ± 3 days later if the stage 1 and 2 TgAb status is discordant (refer to Table 5).
- Diagnostic nuclear medicine ^{131}I scan (WBS) to be evaluated by blinded independent central review.

These assessments will require the patient to follow a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose, until the diagnostic WBS assessment is completed (refer to Section 5.1.1 and Appendix F). Patients will also receive two Thyrogen injections (refer to Section 5.5.4.1) on consecutive days (day 1 and 2), followed by a diagnostic dose (5 mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5.

When to proceed to stage 3 assessments

Patients should proceed to stage 3 assessments in the absence of biochemical disease. Patients with stimulated Tg < 1 ng/mL and TgAb negative (for the definition of TgAb negativity refer to Section 6.4.3.4) should proceed to stage 3 **regardless of the WBS results**.

- Note that if the stage 1 and 2 blood samples are discordant for TgAb, a repeat (third) blood sample for central analysis is required 10 days (±3 days) later. Only if the third sample is negative for TgAb will the stimulated Tg level from stage 2 be considered to be interpretable and valid for decision making. Refer also to Table 5.
- Note also that for study purposes the WBS will evaluated by blinded independent central review, and even if local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).

When not to proceed to stage 3 assessments

All patients in the following situations will be classified not in complete remission and should not proceed to stage 3 assessments:

1. Patients who have stimulated Tg level ≥ 1 ng/mL in the absence of TgAb (unequivocal biochemical disease by standardised central laboratory analysis).

2. Patients confirmed to be TgAb positive (regardless of all other data):

   (a) When both the stage 1 and 2 blood samples are TgAb positive (refer to Section 6.4.3.4).

   (b) When the repeat (third) blood sample confirms positive TgAb following a discordant TgAb status from stage 1 and 2.

In these situations the stimulated Tg value will be deemed to be uninterpretable, and the patient will be deemed not to be in complete remission because absence of biochemical disease cannot be proven.

These patients will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, and will continue to be followed in this study until 3 years following their initial RAI dose (refer to Section 6.4.6).

Note that for study purposes the WBS will evaluated by blinded independent central review. If local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).

Table 5 Criteria for biochemical decision making (based on standardised central analysis results)

Scenario	Stage 1		Stage 2		Repeat 3rd TgAb sample[b]	Biochemical remission?
	Suppressed Tg	TgAb[a]	Stimulated Tg	TgAb[a]		
1	≥ 1ng/mL	Negative	Not required	Not required	Not required	No. Stop.[c]
2	< 1 ng/mL	Negative	< 1 ng/mL	negative	Not required	Yes. Proceed to stage 3
3	< 1 ng/mL	Negative	≥ 1 ng/mL	negative	Not required	No. Stop.[c]
4	Any	Positive	< 1 ng/mL	negative	negative	Yes. Proceed to stage 3
5	Any	Positive	< 1 ng/mL	negative	positive	No. Stop.[c]
6	< 1 ng/mL	Negative	< 1 ng/mL	positive[d]	negative	Yes. Proceed to stage 3
7	< 1 ng/mL	Negative	< 1 ng/mL	positive	positive	No. Stop.[c]
8	Any	Positive	Any	positive	Not required	No. Stop.[c]

[a] Standardised central methodology will be used to define TgAb negative/positive status, refer to Section 6.4.3.4.
[b] When the TgAb results from stage 1 and 2 are discordant, a repeat (third) blood sample for TgAb is required 10 days (± 3 days) after the stage 2 blood sample.
[c] For the purpose of the study, the patient will be deemed not to be in complete remission and no further stage 3 assessments are required. These patients will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, and will continue to be followed in this study until 3 years following their initial RAI dose (refer to Section 6.4.6).
[d] Although this stimulated Tg blood sample is positive for TgAb, the patient will be declared to be in biochemical remission if the other two TgAb samples are both negative by standardised central analysis. It is not feasible to repeat a second stimulated Tg assessment.

6.4.2.3 Primary endpoint assessments Stage 3

In stage 3, patients with biochemically-negative disease will have:

- Neck MRI with gadolinium contrast to be evaluated by blinded independent central review.
- Chest CT without contrast to be evaluated by blinded independent central review.
- If clinically indicated, a biopsy/FNA should be performed as follows:
  - For any suspicious lymph nodes on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter.
  - For any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter should be biopsied/FNA.

6.4.3 Blood sample assessments for efficacy

All protocol-scheduled samples for serum Tg (suppressed and stimulated), TSH and TgAb assessment, will be sent for central laboratory analysis using standardised methodology. All decision making for study purposes will be based on the standardised central analysis results; values obtained from different assay methods may be different and cannot be used interchangeably.

Full details of the sample collection, shipment and analytical methodology is provided in the Laboratory Manual.

Unscheduled samples and local analysis:

Investigators may also perform local biochemical analysis for these parameters as per standard site practice if desired, however this data will not be used for study-related decision making. If local analysis is performed, the data may be collected by eCRF for the clinical study database, and Investigators must ensure that the maximum permissible blood volumes for individual patients at their institutions are not exceeded.

In the case that an investigator performs additional assessment of Tg (and TSH, TgAb) outside of the protocol scheduled visits, such samples should not be sent for central laboratory analysis. Only if such unscheduled local analysis leads the Investigator to wish to administer further therapy for thyroid cancer, should an additional sample ideally be sent for central analysis and the protocol-specified re-treatment criteria applied (Section 5.9.1.1) before the patient is re-treated.

6.4.3.1 Suppressed Tg

Prior to the 18 month primary endpoint assessments:

A blood sample for TSH-suppressed serum Tg is required at 9 months after the RAI dose (± 3 months) in order to assess whether thyroid cancer re-treatment is clinically indicated; refer to the thyroid cancer re-treatment guidelines in Section 5.9.1.1. Tg assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (but not before 6 months). A second blood sample 2-4 weeks later may also be required to verify the biochemical re-treatment criteria (refer to Section 5.9).

Stage 1 primary endpoint assessments:

For all patients that have not been re-treated for thyroid cancer prior to the primary endpoint assessments 18 months following their RAI dose, a blood sample to centrally analyse the TSH-suppressed serum Tg level will be taken.

Anytime that a Tg blood sample is taken, the same sample will also be centrally analysed for TSH and TgAb (refer to Sections 6.4.3.3 and 6.4.3.4 respectively).

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

6.4.3.2 Stimulated Tg

Prior to the 18 month primary endpoint assessments:

Prior to the 18 month primary endpoint assessments, stimulated Tg levels are not recommended and not included as part of the patient follow up for this study.

Stage 2 primary endpoint assessments:

Serum Tg measured during TSH suppression is not sufficiently sensitive to confirm that a patient is free of thyroid cancer. For this reason, rhTSH (Thyrogen) stimulated serum Tg level will also be assessed at the primary endpoint, only for patients proceeding to stage 2 of the primary endpoint assessments.

For patients that require stimulated Tg assessment, 0.9 mg of rhTSH will be administered IM for 2 consecutive days (refer to Section 5.5.4.1), with the blood sample taken for stimulated Tg central analysis on day 5.

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

Each time that a blood sample is taken for central stimulated Tg analysis, the same sample will also be centrally analysed for TgAb (refer to Sections 6.4.3.4 respectively).

6.4.3.3 TSH

Thyroid hormone supplementation will be adjusted in individual patients with the aim of achieving suppressed TSH levels of 0.5 mIU/L or less for the duration of the study. Each time that a suppressed Tg sample is taken, TSH should also be assessed (by central standardised methodology).

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

6.4.3.4 Tg antibody (TgAb)

Each time that a blood sample is taken for central Tg analysis, the same sample will also be centrally analysed using standardised methodology for TgAb. Full details of the sample collection, shipment and analytical methodology to be used will be provided in the Laboratory Manual.

TgAb cut-off for decision making

For decision making purposes at any time in the study, standardised central analysis results must be used. The cut-off value for positive/negative TgAb status according to the standardised central methodology will be provided to sites prior to the start of recruitment.

At screening:

Patients with TgAbs present at screening will be ineligible for the study (refer to the exclusion criterion in Section 4.2, screening samples must be sent for standardised central analysis).

Prior to the 18 month primary endpoint assessments:

If TgAbs are detected in the follow-up Tg blood sample (at 9 months ±3 months), the patient should not be re-treated unless new structural disease is detected according to Section 5.9.1.2 (ie, it is strongly recommended that patients are not re-treated on the basis of new antibodies alone, in the absence of structural disease). Refer to Section 5.9.

Primary endpoint assessments (Stage 1 and 2)

The TgAb status of the stage 1 blood sample will not be taken into consideration alone. The following rules will apply (refer also to Table 5):

1. If both stage 1 and stage 2 blood samples are negative for TgAb, then the Tg results will be valid for decision making.

2. If both stage 1 and stage 2 blood samples are positive for TgAb, then the stimulated Tg result will be deemed to be uninterpretable, and for the purpose of this study the patient will be classified as not in complete remission. No further primary endpoint assessments are required.

3. If the stage 1 and 2 blood samples are discordant for TgAb status, then a repeat (third) blood sample is required 10 days later (± 3 days). Only if the repeat sample

is confirmed negative for TgAb, will the stimulated Tg level in stage 2 be considered to be interpretable and valid for decision making.

6.4.4 Imaging assessments for efficacy

6.4.4.1 Neck ultrasound (US)

Neck US assessments will take place at the times indicated in the Study Plan Table 3. Refer also to Section 6.4.2 and Table 4 for further details of US assessment at the primary endpoint.

Any suspicious lymph nodes or lesions in the neck ≥ 5 mm in the smallest diameter identified by US during the study should be biopsied/FNA.

Note: for a lesion to be suspicious it must be new or enlarged compared to the previously obtained imaging data, and be consistent with the biological characteristics of DTC.

Biopsy/FNA samples, where performed, will be assessed at each site. Needle washout may be analysed locally for Tg according to local standard practice. The totality of the information obtained from a biopsy/FNA (including washout Tg data where analysed), will be assessed locally to determine presence or absence of thyroid cancer in the sample.

US definition of structural DTC

Any soft tissue or lymph node lesions that are new or enlarged compared to previous ultrasound assessment (either post operatively and/or at 9 months) that are consistent with the biological characteristics of DTC and fulfil the following criteria will be considered as structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is subsequently shown to be RAI avid/positive on central review of WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on US that is non-RAI avid on the subsequent WBS, will be considered benign even in the absence of a biopsy.

The assessment of neck US and biopsy/FNA sample will be made by investigator site review.

The local ultrasound information will be recorded in the eCRF (with FNA/biopsy results if performed) and provided to the central imaging CRO if necessary as supporting clinical data (refer to Section 6.4.4.6).

Guidelines for standardised acquisition, defining suspicious lesions and reporting of US assessments required for this study will be provided to each study site.

6.4.4.2 Whole body diagnostic ^{131}I nuclear medicine scan (WBS)

Pre-RAI treatment

There is no pre-ablation WBS in this study. This is a fixed RAI dose study (100mCi, 3.7GBq) with Thyrogen stimulation. Study-specific post-operative imaging will be used to ensure that enrolled patients do not have overt macronodular disease remaining in the neck or distant metastatic disease in the lungs.

Post-RAI treatment

All randomised patients will have a WBS performed 3-10 days following their RAI treatment dose to assess where the administered ^{131}I has localised.

It is acknowledged that this assessment may identify a small number of patients with distant metastatic disease that was not previously identified (patients with known metastatic disease at study entry will be excluded). Such patients will continue in the study and should not be withdrawn; they will continue to be followed according to the protocol and will be included in both the Intention To Treat (ITT) efficacy and safety analysis sets for the study.

Primary endpoint (stage 2)

If required according to Section 6.4.2, the diagnostic WBS to assess the primary endpoint will be performed following a diagnostic dose of 5 mCi ^{131}I (refer to Section 5.5.4.2). Patients will receive 2 Thyrogen injections on consecutive days (day 1 and 2), followed by a diagnostic dose (5 mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5. Patients will be required to adhere to a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose, until the diagnostic WBS assessment is completed.

Standardised acquisition and submission guidelines for every WBS procedure will be provided separately to this protocol.

WBS definition of structural DTC

Any patient with increased ^{131}I uptake considered not to be anatomically normal (where normal includes uptake in the salivary glands, stomach, gastrointestinal, urinary tract and bladder), that is biologically consistent with DTC will be classified as not in complete remission for the primary endpoint of this study (due to having RAI-avid structural DTC).

For the thyroid bed, $< 0.1\%$ uptake on the region-of-interest method drawn over the thyroid bed will be considered normal/negative (no disease). If uptake in the thyroid bed is $\geq 0.1\%$ then these patients will be deemed not to be in remission due to the presence of RAI-avid disease.

Note that if an abnormality identified by US in stage 1, is subsequently shown to be RAI avid/positive on WBS in stage 2, the WBS data takes precedent over a negative biopsy/FNA from the same area.

The WBS evaluation will be made by blinded, independent central review.

6.4.4.3 Neck MRI

Post-operative (screening)

This baseline assessment is performed to determine study eligibility according to criterion 6 in Section 4.1). The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Primary endpoint (stage 3)

Neck MRI to define the primary endpoint will be performed in stage 3 of the assessments in patients deemed to be biochemically-negative for thyroid cancer. Refer to Section 6.4.2.3 and Figure 3.

The neck MRI must be performed using T1 weighted image sequences with and without gadolinium contrast agent, and T2 weighted image sequences.

If clinically indicated, any suspicious lymph nodes on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter, should be biopsied/aspirated by fine needle.

MRI definition of structural DTC

New lesions (nodal or non-nodal) or significantly enlarged lymph node lesions compared to previous post operative (screening) MRI which are consistent with the biological characteristics of DTC and fulfil either of the following criteria will be considered to represent structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is shown to be RAI avid/positive on WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on MRI that is non-RAI avid on the WBS, will be considered benign even in the absence of a biopsy.

This assessment will be made by blinded, independent central review.

6.4.4.4 Chest CT

In this study all chest CT procedures should be performed without iodine containing contrast agent.

Post-operative (screening)

This baseline assessment is performed to determine study eligibility according to criterion 6 in Section 4.1). The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Primary endpoint (stage 3)

Chest CT to define the primary endpoint will be performed in stage 3 of the assessments in patients deemed to be biochemically-negative for thyroid cancer. Refer to Section 6.4.2.3 and Figure 3.

If clinically indicated, any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter should be biopsied/FNA.

CT definition of structural DTC

New lesions (nodal or non-nodal) or significantly enlarged lymph node lesions compared to previous post operative (screening) CT which are consistent with the biological characteristics of DTC and fulfil either of the following criteria will be considered to represent structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is shown to be RAI avid/positive on WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on CT that is non-RAI avid on the WBS, will be considered benign even in the absence of a biopsy.

This assessment will be made by blinded, independent central review

6.4.4.5 Biopsy or fine needle aspirate (FNA)

A biopsy or FNA should be performed in the following situations:

- **US:** For any suspicious lymph nodes or lesions in the neck ≥ 5 mm in the smallest diameter identified by US during the study.
- **MRI:** If clinically indicated, for lymph nodes suspicious on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter.
- **CT**: If clinically indicated, for any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter.

Note: for a lesion to be suspicious it must be new or enlarged compared to the previously obtained imaging data, and be consistent with the biological characteristics of DTC.

All biopsy/FNA samples taken during the study will be assessed at each site according to local standard practice. Needle washout may be analysed locally for Tg according to local standard practice (this is not a mandatory requirement). The totality of the information obtained from a biopsy/FNA (including washout Tg data where analysed), will be assessed locally to determine presence or absence of thyroid cancer in the sample. This information will be provided to the central imaging CRO.

Refer to Section 6.10.3 for details regarding tumour sample acquisition on disease progression.

6.4.4.6 Information to be sent to the central imaging CRO

The following information will be sent to the central imaging CRO (further details are provided in the imaging charter/guidelines for this study).

1. Post-operative screening assessments (refer to Section 6.3): images for chest CT and neck MRI. This data must be sent for all patients as soon as possible after each patient is randomised.

2. Post-RAI WBS images taken 3-10 days after each patient's RAI dose. This data must be sent for all patients as soon as possible after each patient has their post-RAI WBS assessment.

3. Primary endpoints assessments stage 1: site ultrasound and biopsy information. The required data must be entered into the clinical database for each patient as soon as possible after completion of the assessment (NOTE: this information is not sent to the central imaging CRO, but instead must be entered into the database directly using eCRF).

4. Primary endpoint assessments stage 2: diagnostic WBS images. This data must be sent for all patients as soon as possible after completion of the assessment.

5. Primary endpoint assessments stage 3: chest CT and neck MRI images and biopsy information (if performed). This data must be sent for all patients as soon as possible after completion of the assessments. Biopsy data must be entered into the clinical database for each patient as soon as possible after completion of the assessment.

6.4.5 Derivation of primary endpoint of complete remission

The complete remission status of each patient will be determined programmatically by AstraZeneca, by incorporating data on re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, and structural disease assessment from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in complete remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer, all available imaging data will be sent to the imaging CRO. Determination of presence or absence of structural thyroid cancer will be made by the imaging CRO only for biochemically negative patients. A list of biochemically negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

The imaging CRO will assess the WBS, MRI and CT and also review the site assessment of neck US to provide an overall assessment: presence or absence of structural thyroid cancer, or not evaluable based on all of the available information. For the derivation of the complete remission endpoint, patients that are not evaluable for structural disease assessment will be considered as not achieving complete remission, regardless of the result of other assessments.

AstraZeneca will programmatically combine information on further therapy, biochemical data, and the determination of structural disease from the central imaging CRO, to determine the complete remission status of each patient as shown in Table 6.

The dates on which assessments were performed will be incorporated into the derivation of the primary endpoint to ensure patients are assessed within a time window around the scheduled 18 month post-RAI treatment. The first assessment must be started at 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within a 8 week period. If a patient has assessments/scans that fall outside of these time windows, the patient will be considered not to be in complete remission, regardless of the assessment of disease status.

Table 6 Programmatic derivation of complete remission status

Scenario	Further thyroid cancer therapy[a] (re-treatment)	Biochemical data[b]		Structural disease assessment[c]	Complete remission
		Stimulated Tg[b]	TgAb[b]		
1	Yes	N/A	N/A	N/A	No
2	No	< 1 ng/mL	Negative[d]	Absence of disease	Yes
3	No	≥ 1ng/mL	Any	Any	No
4	No	Any	Positive[d]	Any	No
5	No	Any	Any	Presence of disease	No
6	No	NE	Any	Any	No
7	No	Any	NE	Any	No
8	No	Any	Any	NE	No

[a] As assessed by investigator at site.
[b] As assessed by standardised central laboratory analysis.
[c] As assessed by blinded, independent central review.
[d] If the stage 1 and 2 blood samples are discordant for TgAb status, then a third blood sample 10 days later (± 3 days) is required. Only if the third sample is negative for TgAb will the overall TgAb result be considered negative for the primary endpoint assessments. Refer also to Table 5.
N/A primary endpoint assessments are not required for patients that have received further treatment for thyroid cancer in the previous 18 months.
NE Not evaluable (for example due to missing samples or assessments).

6.4.6 Clinical remission

The secondary efficacy endpoint for this study is **clinical remission rate at 18 months** (following RAI treatment). This is designed to more typically reflect clinical practice. As such, the definition of clinical remission will exclude the additional radiological assessments performed for the purpose of complete remission in this study.

Definition of clinical remission:

Patients will be defined to be in clinical remission if all of the following criteria can be demonstrated:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer on neck US, as assessed by investigator site review.

3. No evidence of thyroid cancer on diagnostic WBS, as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed to clarify equivocal US findings, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

6.4.7 Derivation of clinical remission status

The clinical remission status of each patient will be determined programmatically by AstraZeneca, by incorporating data on re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, structural disease assessment based on US by investigator site review and structural disease assessment based on WBS from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in clinical remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer:

A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the investigator based on US.

A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the central imaging CRO based on WBS for only biochemically negative patients. Information on US will not be reviewed as part of this assessment. A list of biochemically

negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

AstraZeneca will programmatically combine information on further therapy, biochemical data, determination of structural disease from the investigator site assessment of US and determination of structural disease from the central imaging CRO of WBS, to determine the clinical remission status of each patient.

Full details of the programmatic derivation of clinical remission will be provided in the SAP.

6.4.8 Final study follow up at 3 years

The final study follow-up will take place 3 years post-RAI for each patient, and will include:

1. The clinical status of each patient, for example: remission, persistent disease, recurrent disease, survival status.

2. The incidence of further therapy (re-treatment) for thyroid cancer, for example, additional RAI or surgery.

3. Final assessment of selumetinib or RAI-related AEs and SAEs.

Note, following the primary endpoint assessments until the final study visit at 3 years following each patient's initial RAI treatment, each patient will enter standard of care treatment or follow up according to local practice. No study-specific assessments will be performed, and locally performed assessments and data will not typically be collected as routine in the clinical study database (except for safety data, refer to Section 6.5.3). The patient's clinical status at the final study follow up will be collected (along with any relevant supporting local assessment data). For example, remission status will be defined by the Investigator on the eCRF based on the relevant local standard of care assessments (eg, locally assessed Tg and no evidence of thyroid cancer on locally assessed US).

6.5 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.5.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.5.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.5.3 Recording of adverse events

Time period for collection of adverse events

All AEs/SAEs will be collected from informed consent until 30 days following the last dose of study treatment (selumetinib or placebo).

After this time:

- all SAEs regardless of causality will be collected until the final study follow-up (3 years post-RAI for each patient, refer to Section 6.4.8)
- only AEs considered causal to RAI or the combination of RAI and study treatment will be collected until the final study follow-up (3 years post-RAI for each patient, refer to Section 6.4.8).

Follow-up of unresolved adverse events

Any AE or laboratory change occurring during the study treatment period should be followed up by the investigator for as long as medically indicated (resolution or stabilisation), and follow up information recorded in the eCRF.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no) and/or RAI (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study (yes or no)
- Treatments patient received for AE
- Outcome
- Whether event constitutes an SAE.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (if applicable)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.5.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke

that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The Investigator will assess causal relationship between Investigational Product and RAI and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication, study procedures and additional study drug (eg, RAI). Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient, or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation, will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs etc should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

After the 30 day follow up visit, AEs associated with RAI or the combination of study treatment and RAI, should continue to be collected by AE reporting, these would include abnormalities, for example, white blood cell count or Hb reductions.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law,' for further instructions. All patients with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (± 7 days) later for follow-up.

6.5.3.1 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.5.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.5.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (Table 3).

The following laboratory variables will be measured:

Table 7 Laboratory safety assessments

Clinical chemistry	Haematology	Urinalysis [a]
s-Albumin	Erythrocyte count	u-Albumin
s-ALT	Haemoglobin	u-Creatinine
s-AST	Platelet count	
s-ALP	Leucocyte cell count	
s-Total Calcium	Leucocyte differential count (absolute count):	
s-Creatinine	Neutrophils	
s-Gamma glutamyl transferase (γGT)	Eosinophils	
s-Glucose	Basophils	
s-Magnesium	Lymphocytes	
s-Phosphate	Monocytes	
s-Potassium		
s-Sodium		
s-Total protein		
s-Total bilirubin		
s-Urea nitrogen		
s-Creatine kinase		

[a] A single-spot urine specimen will be collected on the day of scheduled visit, at sites where the local laboratory is able to determine the concentration of urine albumin and urine creatinine from a single-spot urine specimen. Investigational sites unable to report these parameters will perform routine urinalysis according to the local standard of care.
s serum
u urine

All laboratory safety assessments will be analysed by the local laboratory.

Clinical chemistry, haematology and urinalysis testing will be repeated as clinically indicated as part of the routine management of the patient on the occurrence of AEs.

For blood volume see Table 9.

6.5.6 Physical examination

A complete physical examination will be performed at the times indicated in the Study Plan Table 3.

6.5.7 Cardiac monitoring

Note: troponin assessment in this study is only required for cardiac AE follow up as clinically indicated.

6.5.7.1 ECHO or MUGA

An ECHO or MUGA assessment (according to site preference) will be conducted at screening. A further assessment should be performed as part of the assessment package for any cardiorespiratory adverse event with no obvious diagnosis. Medical management of the event should follow local clinical practice. Selumetinib interruption should be considered until resolution of the event or until return to baseline.

LVEF can be measured in many different ways but echography is the preferred choice when possible. The same modality should be used as baseline for any ECHO/MUGA follow up. Recommendations include having complete high quality standardized 2-D with Doppler echocardiographic examinations performed by an experienced sonographer (preferably with the same operator performing all studies for a given patient), according to a specified protocol including evaluation of both systolic and diastolic left ventricular function. Ejection fraction determinations should be assessed quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.

6.5.7.2 Resting 12-lead ECG

ECGs will be analysed locally at each site. Patients should be supine and at rest 10 minutes prior to recording the ECG.

Parameters including heart rate, duration of QRS complex, PR and QT intervals will be collected. R-R interval and QTcF will be calculated by AstraZeneca from the data provided.

The investigator should review the paper copy of the ECGs on each study day and may refer to a local cardiologist if appropriate.

Any symptoms from the patient should be registered as a comment and if AE criteria are met, recorded as an AE.

At screening all patients will have a single 12-lead ECG performed. The screening ECG can be conducted up to 28 days prior to randomisation.

During the treatment phase of the study, patients will have single 12-lead ECGs assessments at the following timepoints:

- 1-2 hours after the first dose of study treatment on Day 1

- 1-2 hours after the first dose of study treatment on Day 29 or 30
- At the 30-day follow up visit following completion of study treatment
- Single ECGs must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event
- A single 12-lead ECG is also required at premature discontinuation of treatment

6.5.8 Vital signs

Resting blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size. Vital sign assessments, including weight, will be performed at the times indicated in the Study Plan Table 3. Pulse and blood pressure must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event. Height will be assessed at Visit 1 only.

Any changes in vital signs should be recorded as an AE if applicable.

6.5.9 Other safety assessments

6.5.9.1 Pregnancy test

A serum or urine pregnancy test (according to local practice) will be performed at the times indicated in the Study Plan Table 3. Following the RAI treatment, monitoring for pregnancy will be performed according to standard clinical practice at each centre.

6.5.9.2 Ophthalmologic examination

An ophthalmologic examination (best corrected visual acuity, intraocular pressure, slit lamp fundoscopy) should be performed at screening and if a patient experiences a visual symptoms (including blurring of vision) with additional tests if clinically indicated e.g. consider OCT scans.

Patients who have a retinal abnormality prior to discontinuation of selumetinib/placebo should have a follow up eye examination performed within 30 days after discontinuation of selumetinib/placebo in order to document reversibility.

An algorithm for management and investigation of visual symptoms is provided in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

6.6 Patient reported outcomes (PRO) – not applicable

Patient reported outcomes will not be collected in this study.

6.7 Pharmacokinetics

6.7.1 PK samples required

Blood samples (2 mL) for determination of plasma concentrations of selumetinib and N-desmethyl selumetinib will be collected from every patient according to the time points below. Other metabolites (eg, selumetinib amide) may also be determined in the PK analysis. Each patient will be asked to contribute 8 blood samples, one from each of the pre defined time windows below on both Day 1 and Day 29 or Day 30. The Day 29 or Day 30 PK blood samples may be taken earlier, from Day 22 onwards of study treatment if preferred, but it is essential that all PK blood samples are collected on a visit day **prior** to the RAI dose being administered.

- Pre-dose (within 15 minutes of dosing)
- Between 15 minutes and 1 hour post-dose
- Between 1.5 and 2.5 hours post-dose
- Between 3 and 8 hours post-dose

Depending on emerging data/information, the timings and number of the PK samples may be altered, but the maximum total blood volumes given in Table 9 will not be exceeded. The actual sample date and time of all PK samples must be recorded in the eCRF.

Samples will be collected, labelled, stored and shipped as detailed in Laboratory Manual.

6.7.2 Determination of drug concentration

Samples for determination of selumetinib and N-desmethyl selumetinib concentrations in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Other metabolites (eg, selumetinib amide) may also be determined in the PK analysis. Full details of the bioanalytical method used will be described in a separate bioanalytical report.

For each placebo patient, samples will only be analysed on a ‘for cause’ basis, for example, if no quantifiable concentrations were observed in a patient’s samples when the drug was expected to be present.

All samples still within the known stability of the analytes of interest (ie, selumetinib, N-desmethyl selumetinib and its metabolites) at the time of receipt by the bioanalytical laboratory will be analysed.

6.8 Pharmacodynamics – not applicable

Pharmacodynamic samples will not be taken during this study.

6.9 Pharmacogenetics

6.9.1 Genetic blood sample at study entry

An optional blood sample for genetic research will be obtained from eligible patients at Visit 1 or 2 ideally. If for any reason the sample is not drawn at Visit 1 or 2, it may be taken at any visit **before the RAI dose is administered** (radioactive samples for this purpose will not be accepted). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. Only one sample should be collected per patient for this purpose. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volumes see Section 7.1.

6.10 Biomarker analysis

6.10.1 *BRAF* and *NRAS* patient population

Archival tumour sample from every patient will be analysed for *BRAF* and *NRAS* mutational status centrally using standardised methodology. Full analytical methodology details will be provided in the CSR.

The genetic analysis of archival tumour samples to identify the *BRAF* and *NRAS* patient population will be performed retrospectively in the study (after randomisation but prior to the primary endpoint data analysis).

6.10.1.1 Archival tumour sample

All patients will be required to provide consent for AstraZeneca to collect and analyse samples of their previously obtained tumour material (ie, from their recent surgery) for analysis of biomarkers relevant to DTC. Archival tumour sample provision is mandatory in this study, and each Investigator should make every effort to collect a sample from all randomised patients. It is accepted that it may not be possible to obtain all samples prior to commencement of study treatment (which should continue as planned). However, it should be established during the screening period that sufficient sample exists and is available. Samples are expected to be made available as soon as possible. Note, no replacements will be made for patients where an archival tumour sample is not provided.

These samples will be analysed for the biomarkers necessary for the definition of the second primary objective patient population (*BRAF* and *NRAS* mutational status), and may also be used for exploratory analyses on residual material. Such analyses may include (but are not restricted to):

- Mutational status of *BRAF* and *NRAS* genes, *RET* rearrangements, and other known MAPK and PI3K effector oncogenes.

- Baseline expression of pathway and thyroid differentiation specific genes such as *NIS*, *Tg*, *TPO*, and *PAX8*.

- Comprehensive genetic analysis to ensure coverage of the major mutational events in DTC.

The exploratory analyses from tumour material may include but are not limited to mRNA expression profiling, microRNA expression profiling, gene copy number analysis and protein expression by immunohistochemistry for any markers relevant to DTC, either known at the time of analysis, or identified in the future.

For the tumour samples detailed below, each site will be asked to provide one of the following for each randomised patient:

– Formalin-fixed, paraffin-embedded tumour tissue block,

or

– 20 pre-cut sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides, including one stained with haematoxylin and eosin. Each section is to be 5 μm thick.

Sites should ship the tumour sample as soon as it is available. If mutational status cannot be adequately determined from the initial tumour biopsy sample, and histopathological review shows it to be a poor quality sample, a second sample should be submitted for re-testing.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

If requested, unused tumour samples will be repatriated. For further details see the Laboratory Manual.

6.10.2 Collection of plasma and serum for exploratory biomarker research

All randomised patients will be required to provide a blood sample at or before randomisation, and disease progression (for example, when the patient is re-treated for persistent or recurrent thyroid cancer) for exploratory biomarker research.

All patients will be required to provide:

– 1x 10ml blood sample for preparation of serum at randomisation (any time before the first dose of study treatment for eligible patients) and disease progression.

– 1x 10ml blood sample for preparation of plasma at randomisation (any time before the first dose of study treatment for eligible patients) and disease progression.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Residual material may be used for exploratory biomarker research.

6.10.3 Collection of disease progression tumour sample

Patients will be asked to provide a tumour sample removed during the study when the patient's cancer is deemed to have progressed (for example, when the patient is re-treated for persistent or recurrent thyroid cancer, or has had further surgery). This is an optional sample.

This will enable a comparison to be made of (for example) tumour genetics and relevant signal transduction pathways between the randomisation and the disease progression tumour sample and also the evolution of the tumour biology in response to treatment with selumetinib can be explored. Such changes may reflect an evolution in phenotype of the tumour, which ultimately may guide future treatment decisions post progression on selumetinib.

Samples can be of any type (such as FNA, or tumour sample taken from a surgical procedure performed as part of the patient’s disease management plan), and will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Table 8 Biomarker summary table

Biomarker sample	Time point	Protocol Section
Archival tumour for *NRAS* and *BRAF* analysis[a]	Randomisation	6.10.1.1
Plasma sample for exploratory biomarker analysis	Randomisation and disease progression	6.10.2
Serum sample for exploratory biomarker analysis	Randomisation and disease progression	6.10.2
Disease progression tumour biopsy (optional)	Disease progression	6.10.3
Blood sample for genetic analysis (optional)	Randomisation	6.9.1

[a] Residual tissue sample material will be stored for potential retrospective biomarker analysis, which will be performed in an AstraZeneca laboratory or AstraZeneca approved laboratory.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood (maximum) that will be drawn from each patient in this study is as follows:

Table 9 Volume of blood to be drawn from each patient

Assessment		Maximum sample volume [a] (mL)	Typical number of samples (over 18+ months)	Total volume (mL)
Safety	Clinical chemistry (local analysis)	5	3	15
	Haematology (local analysis)	3	5	15
Efficacy	Tg, TSH, TgAb (central analysis)	10	4	40
PK		2	8	16
Genetics at randomisation (optional)		10	1	10
Exploratory biomarkers at randomisation, serum		10	1	10
Exploratory biomarkers at randomisation, plasma		10	1	10
Exploratory biomarkers on progression, serum		10	1	10
Exploratory biomarkers on progression, plasma		10	1	10
	Total			136

[a] All volumes presented are maximums. The actual volume requirements will be detailed in the Laboratory Manual.

7.2 Handling, storage and destruction of biological samples

Biological samples for future research may be retained at or on behalf of AstraZeneca for a maximum of 25 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report or Scientific Publication.

7.2.1 Pharmacokinetic samples

Samples will be anonymised by pooling or will be disposed of after the Bioanalytical report finalisation or six months after issuance of the draft Bioanalytical report (whichever is earlier), unless requested for future analyses. Pooled, anonymised samples may be used for analytical method development and/or validation. Anonymised samples will be retained for no more than 5 years after the CSR is finalised. Samples may also be disposed of earlier, pending further notification.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical report.

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 25 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document.'

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of any optional donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central and bioanalytical laboratories holding the samples are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

In the USA the Principal Investigator is also responsible for providing the Ethics Committee with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of

AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study.' All patients in this study will be followed for 3 years following their RAI treatment.

The study is expected to start in 2013 and to end in 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with selumetinib.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the principal investigator has signed the eCRF electronically as per eCRF instructions, the subject's data will be locked.

Medical coding will be performed using the AstraZeneca Autocoder application. The Data Management Centre Coding Team will perform coding using agreed coding conventions. AEs and medical and surgical history will be coded using the standard dictionary – Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medication will be coded using the AstraZeneca Drug Dictionary.

SAEs will be entered into a global patient safety database for regulatory reporting purposes and be reconciled with the AEs in the clinical database.

Data associated with biological samples will be transferred to the data manager as an electronic file and merged with study data as appropriate.

Data from external providers (eg, central laboratory) will be validated as appropriate to ensure that it is consistent with the clinical data and included in the final database.

Clean file will be declared for the database once all data have been received, entered, validated and all queries resolved. The database will be locked after clean file has been declared. Treatment codes will not be broken until after clean file. Following database lock, all data will be extracted as SAS (Statistical Analysis Software) data sets for the statistical analysis to be performed by AstraZeneca.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate. Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Complete remission rate at 18 months post-RAI treatment

Patients will be considered to be in complete remission if they are alive and all of the criteria in Section 6.4.1 are met at 18 months post-RAI treatment.

Complete remission rate at 18 months post-RAI treatment is defined as the proportion of patients who have achieved complete remission at this time point. The complete remission rate will be calculated using all randomized patients as the denominator.

11.1.2 Clinical remission rate at 18 months post-RAI treatment

Patients will be considered to be in clinical remission if they are alive and all of the criteria in Section 6.4.6 are met at 18 months post-RAI treatment.

Clinical remission rate at 18 months post-RAI treatment is defined as the proportion of patients who have achieved clinical remission at this time point. The clinical remission rate will be calculated using all randomized patients as the denominator.

11.1.3 Thyroid cancer recurrence

The occurrence and date of any thyroid cancer recurrence will be recorded for patients who have previously entered either complete or clinical remission (at any point during the study or follow up periods). The rate of thyroid cancer recurrence will be calculated using only patients who have achieved remission as the denominator.

11.1.4 Survival status

The survival status and survival assessment date of all patients will be recorded. Survival time will be calculated as the time from the date of randomisation to the date of death. Patients who have not died at the time of the final study follow up will be censored at the last date the patient was known to be alive.

11.1.5 Further therapy

The dates and type of any further therapy for thyroid cancer will be recorded during the study and follow up periods.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Adverse events

Adverse events will be listed for each patient and summarised by treatment received according to the System Organ Class (SOC) and preferred term assigned to the event using the MedDRA. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs Version 4. The CTC Grade will be assigned by the Investigator.

AE summaries will include all of the following:

- Any AEs occurring after commencement of study treatment and within 30 days of the last dose of study medication
- AEs related to RAI or the combination of RAI and study treatment occurring between 30 days after the last dose of study medication and the final study visit at 3 years following the initial RAI dose
- All SAEs occurring after commencement of study treatment until the final study visit at 3 years following the initial RAI dose

AEs occurring before commencement of study treatment will not be included in AE summaries but will be included and identified in the patient listings.

11.2.2 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2.3 Vital signs, laboratory data, ECGs, ECHO/MUGA, physical examination and ophthalmologic examination

For change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF (Fredericia) will be calculated programmatically by AstraZeneca using the reported ECG values (RR and QT).

QTcF = QT / RR^ (1/3) where RR is in seconds

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality. For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded

The denominator in vital signs data should include only those patients with recorded data.

11.3 Calculation or derivation of PK variables

The final PK analyses will be the responsibility of Clinical Pharmacology and Pharmacometrics, AstraZeneca.

Using appropriate PK software the available PK data will be used to derive PK parameters such as, but not restricted to, C_{max}, AUC for Selumetinib, N-desmethyl selumetinib and any other metabolites determined.

The selumetinib, N-desmethyl selumetinib and metabolite concentration-time profiles, along with the derived PK variables, will be listed for each patient per dose and dosing day and summarised appropriately, as described in the SAP.

Population PK models may be used to derive the PK parameters and will aim to characterise variability in the population by investigating the influence of covariates such as weight, age, sex, and/or concomitant medications. In addition, if the data are suitable, potential relationships between plasma selumetinib and N-desmethyl selumetinib concentrations will be investigated using a graphical approach and/or appropriate PK/PD modelling techniques. A detailed PK analysis plan will be produced prior to any such investigations and will be reported separately.

11.4 Calculation or derivation of pharmacogenetic variables

Genetic data (except *BRAF* and *NRAS* data) will be reported separately to the CSR for this study.

11.5 Calculation or derivation of biomarker variables

11.5.1 Analysis of *NRAS* and *BRAF*

Tumour samples will be collected as outlined in the study plan and assessed for *BRAF* and *NRAS* biomarkers to identify patients for this primary patient population.

11.5.2 Further biomarker research analysis

Methods of analysis for all other biomarker research may include investigation of genetic variability, gene expression profiling, protein expression profiling.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Intention to treat (ITT) analysis set

The ITT analysis set will include all randomised patients. The ITT analysis set will be used for all efficacy analyses and treatment groups will be compared on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment will be included in the ITT analysis set.

12.1.2 *BRAF/NRAS* mutation positive analysis set

For the analysis of the *BRAF* and *NRAS* mutation positive population (primary objective), only those patients from the ITT population with genetic samples that are positive for *BRAF* or *NRAS* will be included.

12.1.3 Treatment-compliant (TC) analysis set

The treatment-compliant analysis set will be a subset of the ITT population containing patients that adhered to the minimum study treatment requirements specified in Section 3.1.1, i.e. patients who take study treatment twice daily for a **minimum** of 7 consecutive days prior to RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. Patients must also have had their RAI dose.

The TC analysis set will be used as a sensitivity analysis for the primary endpoint.

12.1.4 Safety analysis set

The safety analysis set will consist of all patients who received at least one dose of randomised treatment and for whom post dose data are available. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment combination received, ie, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

12.1.5 PK analysis set

PK data will be analysed according to treatment received. This population will comprise all patients who receive study treatment as per protocol and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the AstraZeneca Study Team Physician, Pharmacokineticist and Statistician prior to any analyses being performed.

12.2 Methods of statistical analyses

A comprehensive SAP will be prepared prior to start of recruitment (first subject in).

Since there are two correlated primary comparisons of interest (selumetinib vs. placebo in the overall population and selumetinib vs. placebo in the mutation-positive population), the Dunnett and Tamhane step-up procedure will be used to control the type I error rate (Dunnett and Tamhane 1992, Fernandes & Stone 2011). This procedure is an adaptation of the Hochberg approach, which accounts for the correlation between the primary endpoint comparisons. The correlation between the primary endpoint comparisons will be calculated as √w, where w is the proportion of the overall population who are in the mutation positive sub-group. The associated significance level for declaring statistical significance in the mutation positive sub-group adjusting for this correlation to maintain an overall 5% type I error rate whilst assigning 4% to the overall population will then be derived. For example, assuming that 55% of the overall population are in the mutation-positive sub-group, the correlation is 0.74. Using Dunnett and Tamhane step-up procedure, significance would therefore be declared if both the overall and mutation positive populations are significant at the 5% two-sided level, or if either the overall population is significant at the 4% level or the mutation-positive population is significant at the 1.625% level.

12.2.1 Complete remission rate at 18 months post-RAI treatment

The endpoint of complete remission rate will be compared between selumetinib in combination with RAI, and placebo in combination with RAI in the overall population using a logistic regression model with covariates histology status (papillary, follicular, poorly differentiated), mutation status (*BRAF/NRAS* positive, *BRAF/NRAS* negative) and age, provided there are enough data points for a meaningful analysis.

The primary endpoint of complete remission rate will be compared between selumetinib in combination with RAI vs. placebo in combination with RAI in the mutation positive population using a logistic regression model with covariates histology status (papillary, follicular, poorly differentiated) and age, provided there are enough data points for a meaningful analysis.

For each covariate, if the status is missing or unknown, patients will be assigned to the status that the majority of patients are known to have, e.g. if 55% of patients with known mutation status are BRAF/NRAS positive and 45% are BRAF/NRAS negative, a patient with missing mutation status will be assigned BRAF/NRAS positive. If a value for the continuous covariate age is missing, the mean will be imputed.

The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood confidence interval and 2-sided p-value. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above. The complete remission rate will be estimated for each treatment arm.

Sensitivity analyses

The primary endpoint analysis will be repeated using the treatment-compliant population.

A sensitivity analysis will be performed in which patients that were identified as being in complete remission outside of the specified time windows will be included in the logistic regression analysis and classed as being in complete remission to ensure there is no evaluation time bias between arms.

Elevated TSH can be caused by poor compliance and can mean a patient is less likely to achieve remission. A sensitivity analysis will be performed in which patients with high TSH are excluded from the logistic regression. A high TSH is defined as a value >10 mIU/L recorded at any point by standardised central laboratory analysis.

The extent to which the treatment effect is consistent across the subgroups histology status, mutation status, gender, race and age will be assessed for the overall primary population and across the subgroups histology status, gender, race and age for the mutation positive primary population. The presence of a quantitative interaction will be assessed by means of an overall global interaction test. This will be performed by comparing the fit (likelihood ratio test) of a model including all covariate-by-randomised treatment interaction terms, treatment and covariate terms with a model that excludes the interaction terms. If the global interaction test is found to be statistically significant at the 10% significance level, an attempt to determine the cause and type of interaction will be made. Stepwise backward selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

For quantitative interactions identified, the presence of any qualitative interactions will be assessed using the approach of Gail and Simon (Gail & Simon 1985). For categorical covariates the test statistics, based on the appropriate degrees-of-freedom, can be taken directly from the paper. For the continuous covariate, the approach will be adapted as follows:

Identify the cut-point ($-\beta_1/\beta_3$) of the covariate where the odds ratio for the treatment effect is 1, where β_1 is the treatment parameter estimate and β_3 is the treatment-by-covariate parameter estimate. Re-analyse the data separately for the values of the covariate above and below the cut-point and use the separate chi-square values in the Simon and Gail test.

Subgroup data (histology status, mutation status, gender, race and age) will be summarised by a forest plot where the odds ratio is plotted on the log scale. For this, age will be categorised as ≤45 or >45 years. The treatment effect and confidence intervals for each level of the subgroup will be obtained from a single model that contains a treatment, factor and treatment-by-factor interaction term.

12.2.2 Clinical remission rate at 18 months post-RAI treatment

The secondary endpoint of clinical remission rate will be analysed (for both study populations) as described in Section 12.2.1.

12.2.3 Thyroid cancer recurrence

Very few thyroid cancer recurrences are expected on this study, therefore no formal analysis of thyroid cancer recurrence data will be performed; data will be listed and summarised.

12.2.4 Survival status

Very few deaths are expected on this study therefore no formal analysis of survival data will be performed; data will be listed and summarised. Kaplan-Meier plots of survival may produced if appropriate.

12.2.5 Further therapy

No formal analysis of further therapy data will be performed; data will be listed and summarised. Kaplan-Meier plots of time to further therapy may produced if appropriate.

12.2.6 Safety data analysis

Safety data will not be formally analysed. All patients who commenced study treatment will be included in the assessment of safety and will be summarised by treatment received.

12.2.7 PK data analysis

The selumetinib, N-desmethyl selumetinib and metabolite concentration-time profiles, along with the derived PK variables, will be listed for each patient per dose and dosing day and summarised appropriately.

12.2.8 Genetics

Any genetic data analysis (other than *BRAF* and *NRAS*) will be reported outside the CSR for this study.

12.2.9 Biomarker data

BRAF and *NRAS* mutation assessment of tumour biopsy will be used to identify patients for this primary patient population.

The results of any other exploratory biomarker investigations will be reported outside of the CSR.

12.2.10 Interim analyses

There are no interim analyses planned for this study.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The two primary objectives of the study are to compare the efficacy of selumetinib with RAI versus placebo with RAI, by assessment of the complete remission rate at 18 months post-RAI treatment in the overall study population, and in a sub-group of patients whose tumours have *BRAF* and *NRAS* mutations. Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumentinib-containing arms, respectively, a total of 228 patients, randomised in a 2:1 ratio (152 and 76 patients in the selumentinib and placebo-containing arms, respectively) provides 80% power to show statistical significance, based on a two-sided 4% significance level. Assuming that the prevalence of the mutation-positive sub-group described is 55%, and the true complete remission rates in the mutation-positive sub-group are 30% and 62% for the placebo and selumentinib-containing arms, respectively, the expected numbers of 84 mutation-positive patients in the selumentinib arm and 42 mutation-positive patients in the placebo arm at the time of the analysis, provides 80% power to show statistical significance, based on a two-sided 1% significance level.

12.4 Data monitoring committee

Due to the short treatment duration in this study there will not be a data monitoring committee for this study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.5.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Physician. If the Study Delivery Team physician is not available, contact the Study Delivery Team Leader.

Name	Role in the study	Address & telephone number
Dr Jeffrey Skolnik	AstraZeneca Physician responsible for the protocol at central R&D site	1800 Concord Pike PO Box 15437 Wilmington DE 19850-5437 USA +1 302 885 7686 (desk) +1 302 897 8379 (cell) Fax +1 302 886 2622 Jeffrey.Skolnik@astrazeneca.com
Dr Marta Bucko-Justyna	AstraZeneca Study Delivery Team Leader responsible for the protocol at central R&D site	AstraZeneca R&D | Poland Clinical Operational Hub Postepu 18, Warsaw 02-676, Poland +48 22 541 55 96 (desk) +48 600 429 094 (cell) Fax: +48 22 541 55 10 Marta.Bucko-Justyna@astrazeneca.com
24-hour emergency cover at central R&D site.	24-hour emergency cover at central R&D site.	Alderley Park Macclesfield, Cheshire, SK10 4TG UK Contact AZ UK Lt Switchboard Tel: + 44 1625 582828

13.2 Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.5.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.5.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

The outcomes of any conception occurring from the date of the first dose, until 30 days after last dose, must be followed up and documented in the "Pregnancy Outcome Report" form.

Male patients must refrain from fathering a child for 12 weeks following the last dose of study treatment, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated. Restrictions from

fathering children should also take into account local recommendations following therapy with RAI.

Pregnancy of the patients' partner is not considered to be an AE. However, the outcome of all pregnancies (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

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Clinical Study Protocol Appendix A	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	24th January 2013
Protocol Dated	24th January 2013

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative	PPD	PPD

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

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AstraZeneca Research and Development site representative	PPD	PPD

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative	PPD	PPD

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Signature: PPD PPD

AstraZeneca

Clinical Study Protocol Appendix B	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	24th January 2013

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	24th January 2013

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample

containment standards are encouraged wherever possible when road or rail transport is used.

Clinical Study Protocol Appendix D	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	24th January 2013

Appendix D

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. ACTIONS REQUIRED IN CASES OF AST OR ALT ≥ 3X ULN OR TBL ≥ 2X ULN

The Investigator is responsible for, without delay, determining whether the subject meets potential Hy's law (PHL) criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN **or** TBL ≥ 2x ULN, please follow the instructions below.

- Review each laboratory report and if a subject has an increase in AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit:
  - Notify the AstraZeneca representative
  - Promptly enter the laboratory date into the laboratory CRF.

1.2 Determination and Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the subject **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP

- Inform the AZ representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

1.2.2 Potential Hy's Law Criteria met

If the subject **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- Notify the AZ representative who will then inform the central ST

The Study Physician (SP) contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data.

The Investigator:

- Follows the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigates the etiology of the event and perform diagnostic investigations as discussed with the SP
- Completes the Liver CRF Modules.
- If at any time (in consultation with the SP) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

1.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

For the purpose of this process a Hy's Law case is defined as:

Any subject with an increase in both Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum Alkaline Phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug

If there **is** an agreed alternative explanation for the AST or ALT **and TBL** elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** other explanation that would explain the AST or ALT and TBL elevations:

- Report an SAE (report term Hy's Law') according to AZ standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

– As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

2. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm

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Clinical Study Protocol Appendix E

Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	24th January 2013

Appendix E
Cockcroft-Gault Formula

COCKCROFT-GAULT FORMULA

The Cockcroft-Gault formula has been provided for reference, as the protocol allows for the serum creatinine clearance to be calculated using the Cockcroft-Gault formula (see Section 4.1, Inclusion criteria):

For serum creatinine values in µmol /L:

Estimated creatinine clearance rate (eCCr) (for men) = [(140 – age) x weight (kg) x 1.23] / creatinine (µmol/L)

eCCr (for women) = [(140 – age) x weight (kg) x 1.04] / creatinine (µmol/L)

For serum creatinine values in mg/dL:

eCCr (for men) = [140 – age] x weight (kg) / [72 x creatinine (mg/dL)]

eCCr (for women) = 0.85 x ([140 – age] x weight (kg) / [72 x creatinine (mg/dL)])

Reference: Cockcroft D, Gault MD. Nephron 16: 31-41, 1976.

Clinical Study Protocol Appendix F	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	24th January 2013

Appendix F
Low Iodine Diet

LOW IODINE DIET

Published data and opinion regarding the necessity for a low iodine diet prior to RAI therapy or a diagnostic whole body scan is variable. For the purpose of this study a low iodine diet will be mandated in order to standardise patient care and study data as best as possible. Compliance to a low iodine diet will not be recorded or assessed, and all randomised patients will receive RAI treatment as planned.

A low iodine diet is necessary at two occasions in the study:

Prior to RAI adjuvant treatment

All patients must be willing to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI therapy.

Prior to the primary endpoint Stage 2 assessments

All patients must be willing to adhere to a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose used prior to the primary endpoint WBS assessment (^{131}I nuclear medicine scan), until the diagnostic WBS assessment is completed. This is only relevant for patients who progress to Stage 2 primary endpoint assessments (refer to Section 6.4.2 of the main protocol).

What is Iodine?

Iodine is a mineral. It plays an important role in several processes that take place in the body. One is the production of a hormone called thyroxine, which occurs in the thyroid gland.

Where is Iodine Found?

The amount of iodine found in food varies. Much of the iodine we get comes from iodized salt and breads. Adults need 150 micrograms of iodine a day. This appendix describes an example of a low iodine diet typically used in this treatment setting. This is a diet with less than 50 micrograms of iodine per day. A local low iodine diet may be used instead, as long as it is equivalent to this appendix.

Why is a Low Iodine Diet Necessary?

The iodine in your diet can block the uptake of radioactive iodine by the thyroid gland.

What Should You Avoid?

Read all food labels to check for iodine content. Do NOT eat or use:

- Iodized salt.
- Sea salt in any form.
- Onion salt.

- Celery salt.
- Garlic salt.
- Seasoned salt.
- Kelp (seaweed).
- Any food that has:
  - **Iodates**
  - **Iodides**
  - **Algin**
  - **Alginates**
  - **Carrageen**
  - **Agar**
- Commercial breads and bakery products, because they often contain iodate.
- Milk (except for 1 ounce a day), egg yolks, and seafood.
- Vitamins and food supplements if they have iodine. If you have any doubt, do not take them.
- Food, pills, or capsules with food dyes or that are orange, red, or brown in color. Examples include red or pink cereals or candies/sweets.
- Antiseptics, such as tincture of iodine (Betadine®) applied on a cut.
- Cough medicines (especially those with red coloring).
- Supplements such as:
  - **Ensure®**
  - **Boost®**
  - **Commercial shakes**
  - **Nutrament®**.

- Restaurant and processed foods, because they are often high in iodine content.
- Soy products such as edamame, tofu, soy burgers etc.
- All canned foods, because the lining of the can contains iodine.

Do not stop taking any of your medicines unless your doctor tells you.

Ask your doctor about drinking alcohol during a low iodine diet.

This low iodine diet does not meet the suggested daily allowance for all nutrients. You will be on it for a short time only.

Drink Plenty of Fluids

Note: Unless your doctor tells you differently, you must drink at least 8 to 10, 8-ounce cups of fluid a day. This includes the drinks in the diet guidelines and as much water as you want.

LOW IODINE DIET GUIDELINES

Breads and Cereals **Total number of servings per day:** 6-8 (1 serving equals 1 slice of bread or 1/2 cup of cooked pasta)	
Include	**Avoid**
Plain cooked barley, oats, millet, buckwheat, bulgur wheat, quinoa; unsalted unprocessed preservative-free boxed cereals such as puffed rice and shredded wheat; rice, plain macaroni, spaghetti, noodles; unsalted grits, cream of rice or cream of wheat hot cereals; unsalted rice cakes, unsalted plain crackers, English muffins, plain unsalted popcorn, homemade breads prepared without commercial dough.	All commercial breads and rolls, processed boxed cereals, salted crackers, potato chips/crisps, pretzels, bagels, Melba toast, egg noodles, packaged rice and pasta mixes.

Meat and Meat Substitutes **Total number of servings per day:** Two–three (1 serving equals 3 ounces of meat, fish, poultry, or 2 Tablespoons of unsalted peanut or almond butter)	
Include	**Avoid**
Fresh beef, veal, pork, lamb, chicken and turkey; unsalted peanut or almond butter; freshwater fish such as carp, riverbass, lake trout, and river perch; fresh egg white.	Egg yolks and whole eggs, foods made with eggs; all fast foods; all canned fish such as salmon and tuna; seafood, shellfish (clams, crabs, oysters, lobsters), or any food made with fish stock; all processed meats; liver and all organ meats; all canned, dried, salted, or cured meats such as bacon, sausage, ham, frankfurters, chipped beef, luncheon meats (salami, bologna, pastrami); spicy meats such as chili, beef jerky, liverwurst; all canned or processed poultry such as turkey or chicken roll; tofu and soy products, such as soy burgers (e.g., Boca); salted peanut butter.

Milk and Milk Products **Total number of servings per day:** Zero	
Include None allowed Exception: Only 1 ounce of milk a day in your coffee or tea.	**Avoid** All milk (except for one ounce daily) and milk products such as condensed or evaporated milk, cheese, yogurt, puddings, ice cream, custard; any cream such as heavy/double or light/single cream, whipped cream, sour cream; any foods made with cream or milk or cheese such as soup, pizza, macaroni and cheese.

Fruits **Total number of servings per day:** Five (1 serving equals 1 small piece of fruit or 3/4 cup of juice)	
Include All fresh fruit, exception: limit bananas to 1 serving per day; fresh apple sauce; all natural frozen fruits; fresh fruit juices (including bottles or cartons of fruit juice without artificial coloring or preservatives); white grape juice.	**Avoid** Cranberries, all dried fruits, all canned fruits and canned fruit juices; jarred applesauce; cranberry and grape juice, canned or bottled cherries; rhubarb.

Vegetables **Total number of servings per day:** Four (1 serving equals 1/2 cup of cooked or 1 cup raw vegetable)	
Include All fresh vegetables except spinach, fresh potatoes without skin, all plain frozen vegetables without added salt, fresh or dried lentils and peas.	**Avoid** All canned vegetables and all canned vegetable juices, fresh or dried beans such as red kidney beans, lima beans, navy beans, pinto beans; canned legumes (such as beans, peas, and lentils); canned soups; sauerkraut, celery; commercially prepared potatoes (e.g., instant mashed potatoes); frozen vegetables with added salt; spinach.

Fat **Total number of servings per day:** Suggest four to six servings a day (1 serving equals 1 teaspoon of butter or oil)	
Include Unsalted margarine or sweet butter **(not more than 1 teaspoon of each per day),** oils, vegetable shortening, plain oil and white vinegar dressing.	**Avoid** Salted nuts and seeds, mayonnaise, commercial salad dressings and salad cream, and lard.

Beverages **Total number of servings per day:** No restrictions One serving equals 12 ounces of a carbonated beverage or 1 cup (8 ounces) of any of the other beverages listed	
Include	**Avoid**
Water; bottled carbonated beverages without added coloring (such as Sprite®, 7Up®, sodium-free seltzer); brewed coffee, tea steeped from tea leaves; white tea bags; fresh lemonade or fresh orangeade.	Mineral water containing sodium; all bottled, canned, or powdered: iced tea, lemonade, instant coffee, instant tea, instant iced-tea, fruit punch, and other powdered or commercial drinks, such as Hi-C® and Kool-Aid®; tea steeped from tea bags; soy milk and rice milk (which contain sea salt); ginger ale, Coke®, Pepsi® or any other carbonated beverages with added coloring.

Desserts and sweets **Total number of servings per day:** Two (See below for serving equivalents)	
Include	**Avoid**
Each of the following equals 1 serving: • 1 cup Knox® or equivalent clear gelatin • 2 tablespoons (T) sugar • 2T honey • 2T maple syrup • 2 regular size marshmallows • 1/2 cup natural sorbets with no coloring or added salt	All bakery products such as pies, cakes, pastries, danishes, muffins, doughnuts and cookies; sweet crackers/biscuits; Jell-O® (or equivalent jelly), colored gelatins; chocolate and chocolate desserts; candy.

Miscellaneous **Total number of servings per day:** Unlimited	
Include	**Avoid**
Pepper, spices such as cinnamon; herbs such as oregano; white vinegar, and non-iodized salt (contains trace amounts of iodine, use sparingly).	All salted foods such as salted nuts, Chinese food, soy sauce, catsup, Worcestershire sauce, chili sauce, all commercial sauces, tomato sauce, all gravies, olives, pickles, relish, bouillon cubes, soup bases, iodized salt, sea salt, onion salt, garlic salt, celery salt, seasoned salt, kelp (seaweed); molasses; any food containing food coloring, iodates, iodides, iodate dough conditioners or stabilizers, algin, alginate, carrageens, agar, or nori (seaweed); all sushi; red wine vinegar, balsamic vinegar (with caramel coloring); all additives, preservatives, or artificial colorings.

EXAMPLE MENU FOR A LOW IODINE DIET

BREAKFAST

1 Fruit	½ cup orange juice
3 Breads	½ cup oatmeal (no milk) 1-2 plain unsalted cracker/crispbreads
1 Meat	1 egg white omelet
Misc.	2 teaspoons sugar
1 Beverage	1 cup brewed coffee

MID MORNING SNACK

1 Bread	2 rice cakes
1 Fat	1 teaspoon unsalted butter
1 Beverage	1 cup water

LUNCH

1 Meat	3 oz fresh turkey breast
2 Fats	2 tsp oil
2 Breads	2 slices homemade white bread
1 Vegetable	1 cup Romaine lettuce
1 Beverage	1 cup fresh lemonade

MID AFTERNOON SNACK

1 Fruit	1 fresh apple
1 Meat	2 tablespoons unsalted peanut butter

DINNER

1 Meat	3 oz roast beef
2 Breads	1 baked potato (no skin)
2 Vegetables	1 cup fresh broccoli
2 Fats	2 tsp oil (used in cooking)
1 Fruit	1 orange
1 Beverage	1 cup white tea

BEDTIME SNACK

1 Fruit	1 small pear
1 Beverage	1 cup tea made from fresh tea leaves

Clinical Study Protocol Appendix G	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	24th January 2013

Appendix G
Guidance for Management of Adverse Events in Studies of Selumetinib

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LIST OF FIGURES

1. GUIDANCE FOR THE MANAGEMENT OF PATIENTS WITH RASH

Recommendations to start on day 1 of treatment with selumetinib‡ and for the duration of treatment

- Use skin moisturiser (thick, alcohol-free) at bedtime
- Avoid excessive exposure to sunlight
- Use sunglasses/sunscreen (PABA-free, SPF ≥15; UVA and UVB protection) as needed
- Use of topical retinoids or benzoyl peroxide is not recommended

CTC Grade 1 rashes

Mild or moderate strength topical steroid

and/or topical antibiotic

CTC Grade 2 rashes

Moderate strength topical steroid

and oral antibiotic

CTC grade ≥3 rashes
CTC grade 2 rashes considered by the patient to be intolerable

Moderate strength topical steroid

and oral antibiotic
(consider broad spectrum/Gram negative cover if infection suspected)

Consider referral to a dermatologist: manage rash per recommendation

Interrupt selumetinib‡ until rash improves to grade 2 or less

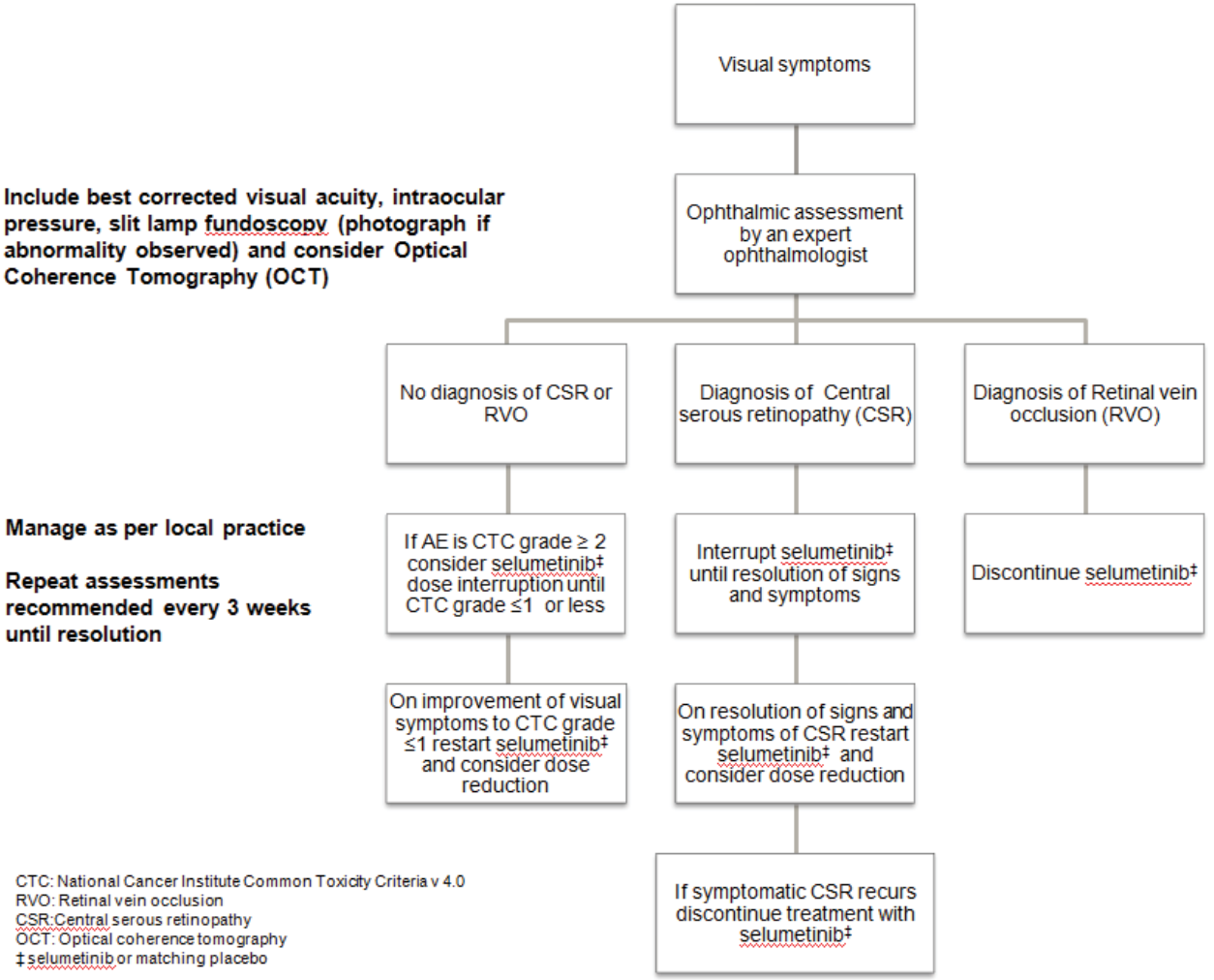
Selumetinib‡ may be restarted at original dose or reduced at the discretion of the investigator

‡ selumetinib or matching placebo
Version: Final 2.0 28Sep2012

Table 1 Example topical steroids and antibiotics (use according to local guidelines)

Topical steroids moderate strength	Triamcinolone acetonide 0.025% Fluticasone proprionate 0.05% Desonide 0.05% Aclometasone 0.05%
Topical antibiotics	Clindamycin 1 - 2% Metronidazole 1% Erythromycin 1% - 2% Silver sulphadiazine 1%
Oral antibiotics	Doxycycline 100 mg bd Minocycline 100 mg bd Oxytetracycline 500 mg bd

2. GUIDANCE FOR MANAGEMENT OF PATIENTS WITH VISUAL SYMPTOMS



3. RECOMMENDATIONS FOR DIARRHOEA MANAGEMENT

Diarrhoea may occur during treatment with selumetinib (AZD6244) and action should be taken as soon as symptoms develop. The recommendations for diarrhoea management are based on guidelines from the American Society of Clinical Oncology (J Clin Oncol 2004; 22:2918-26). These guidelines recommend that treatment-induced diarrhoea should be carefully monitored and treated aggressively to ensure that severe complications are avoided and that treatment is not delayed.

- Patients should be made aware that they may experience diarrhoea and be encouraged to record the number of stools and report possible associated symptoms
- Patients should be given loperamide (in accordance with local regulation and local practice) to take home with them and be advised to start immediately after the first episode of unformed stool.
- Patients should be given dietary advice in case of diarrhoea (eg. BRAT [bananas, rice, apple sauce, toast, plain pasta] diet; readily digestible food; avoidance of lactose-containing products, fried, fatty or spicy food) and increase fluid intake (8 to 10 glasses of clear fluids daily, including water and fluids containing salt and sugar, such as sports drinks and clear broth).
- Patients should seek advice early, from their physician or study nurse, if:

  (a) Persistent Grade 1 or 2 diarrhoea (refer to Section 3.2), or

  (b) Grade 3 or 4 diarrhoea, or

  (c) Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension.

Table 2 CTCAE (version 4) grading for diarrhoea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 1	Increase in number of stools per day (<4)	Mild increase in loose watery colostomy output compared with pre-treatment
Grade 2	Increase in number of stools per day (4-6) or nocturnal episodes	Moderate increase in loose watery colostomy output compared with pre-treatment, not interfering with normal activity
Grade 3	Increase of more than 7 stools per day or incontinence or needing support for dehydration.	Severe increase in loose watery colostomy output compared with pre-treatment and interfering with normal activity

Table 2 CTCAE (version 4) grading for diarrhoea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 4	Life-threatening consequences (eg, hemodynamic collapse)	

3.1 Initial management of uncomplicated Grade 1 or 2 diarrhoea

- Patients should immediately start loperamide after the first episode of diarrhoea (4 mg initially) and continue loperamide (2 mg every 4 hours or after each unformed stool) until they have been free from diarrhoea for at least 12 hrs
- If after 12 hours of loperamide treatment the diarrhoea is not improving or resolved, the patient should be instructed to contact the centre and to increase to high dose loperamide (2 mg every 2 hours, or 4 mg every 4 hours at night) and continue to take loperamide until they have been free from diarrhoea for at least 12 hrs. Additional treatment may be considered according to local practice.

3.2 Management of persistent (>24h) Grade 1 or 2 diarrhoea despite loperamide at high dose

The patient should be seen by the physician or study nurse for full evaluation and the following should be considered:

- Rehydration and electrolytes replacement as appropriate
- Infectious causes and aetiologies such as Clostridium difficile or viral gastroenteritis;
- Antibiotics if appropriate (for example an oral fluroquinolone for 7 days) particularly if the patient is neutropenic ($<1 \times 10^9$/L) or has a fever;
- Discontinuation of loperamide and start of octreotide (Sandostatin);

It may also be appropriate to consider:

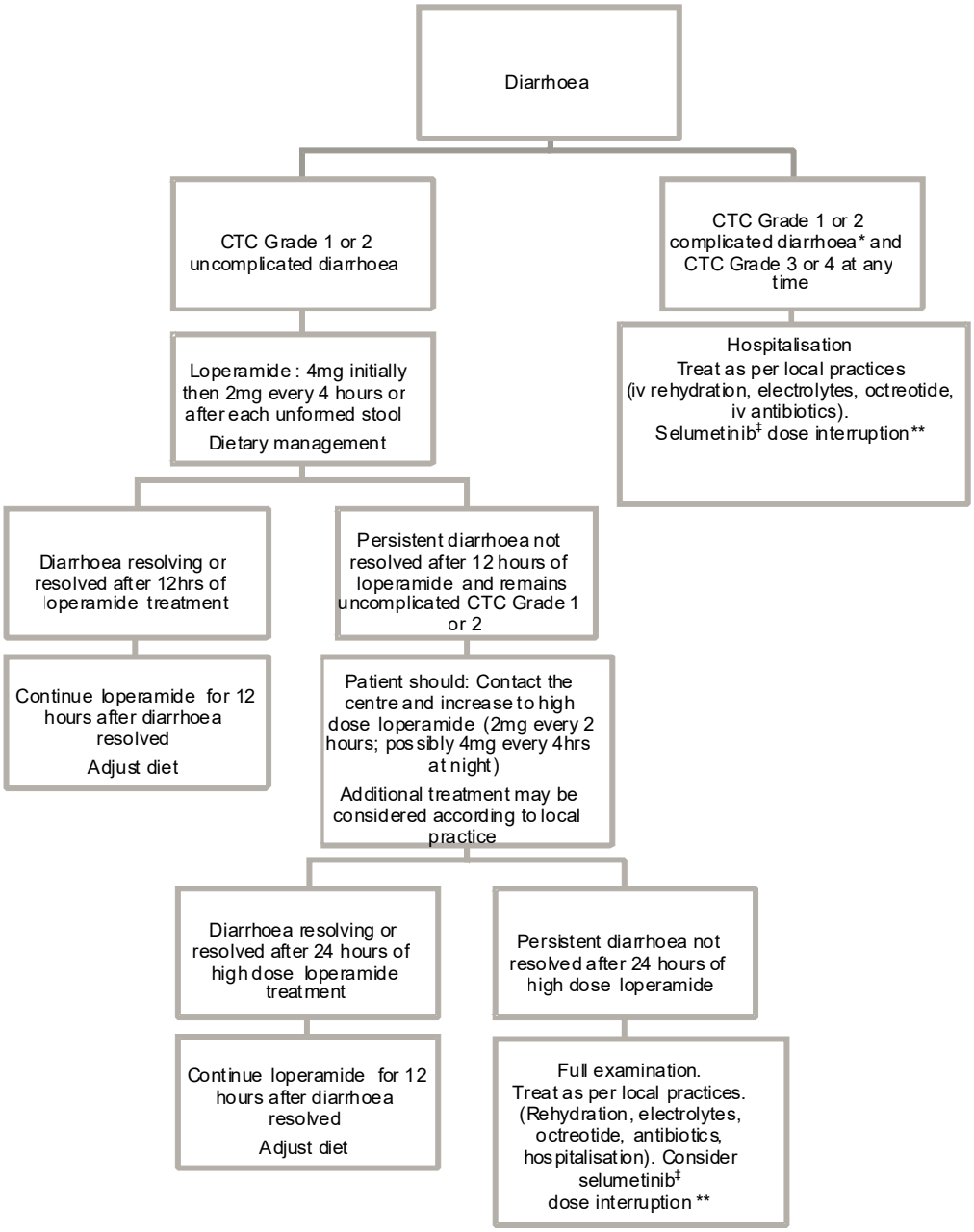
- Addition of other second-line anti-diarrhoeal agents according to local practice
- Selumetinib (or matching placebo) interruption until resolution of the diarrhoea
- Hospitalisation

3.3 Management of any grade uncontrolled or complicated diarrhoea, or Grade 3-4 diarrhoea

- Hospitalisation and full evaluation,

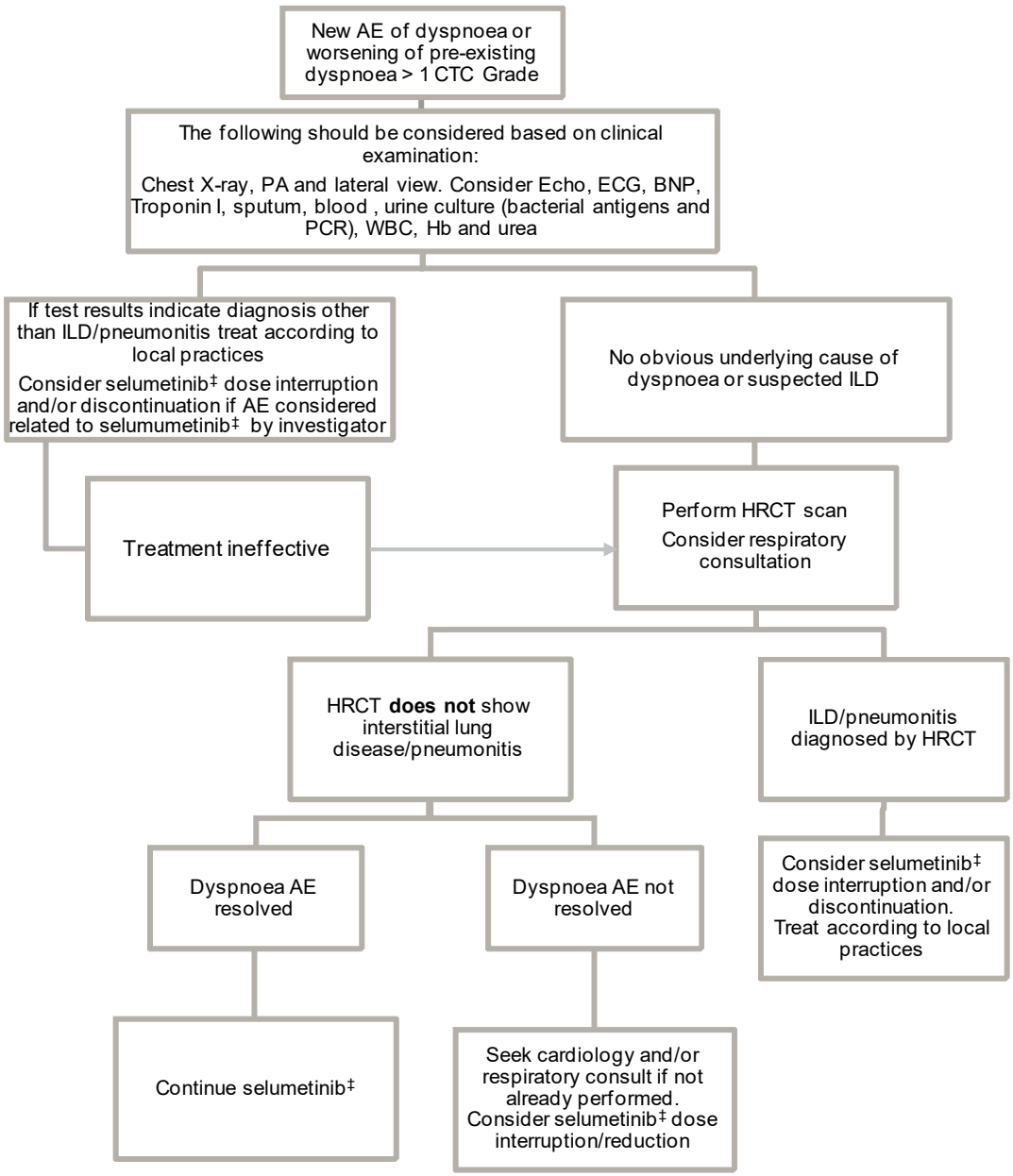
- Intravenous fluids, electrolytes and antibiotics if needed (eg. fluroquinolone)
- Interrupt selumetinib (or matching placebo) until diarrhoea and associated symptoms resolve
- Start octreotide (Sandostatin).
- In studies involving combination of selumetinib (or matching placebo) with other anti-cancer treatment, interruption or delay of the combination agent may be considered according to manufacturer's guidance or local practice.

Figure 1 Guidance for the management of patients with diarrhoea



*Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension
****Consider interruption or delay of combination anticancer agent if applicable**
‡ selumetinib or matching placebo
Document version: Final 2.0 28Sept2012

4. RECOMMENDATIONS FOR INVESTIGATIONS OF PATIENTS WITH A NEW OR WORSENING DYSPNOEA



BNP: Brain Natriuretic Peptide
CTC: National Cancer Institute common toxicology criteria
Echo: Echocardiography
Hb: Haemoglobin
HRCT: High resolution computerised tomography
‡ selumetinib or matching placebo

ILD: Interstitial Lung Disease
PA: posteroanterior
PCR: Polymerase chain reaction
WBC: White blood cells
Document Version: Final 2.0 28 Sept 2012

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Date	3 April 2013
Protocol Dated	24 January 2013

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

This protocol amendment affects all the centres participating in this study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

Study Plan Table 3

Previous text:

Table 3 Study Plan (Note, only rows with changes are shown)

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to Table 4	± 2 months	± 1 month	
Physical examination	X		X				X						6.5.6
Plasma/serum sample for exploratory analysis[b]		X											6.10.2
Optional genetic consent & sample (whole blood)		X											6.9
Vital signs (including height at screening), weight	X	X					X						6.5.8
Clinical chemistry	X		X				X						6.5.5
Haematology	X		X				X			X		X	6.5.5
ECG[e]	X	X		X			X						6.5.7.2
ECHO/MUGA[f]	X												6.5.7.1
Ophthalmologic examination[f]	X												6.5.9.2

Table 3 Study Plan (Note, only rows with changes are shown)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to Table 4	± 2 months	± 1 month	
PK blood samples[h]		X		X									6.7
Thyrogen injection				Xx2						Xx2[a]			5.5.4.1
Tumour biopsy on progression (optional)	Optional sample on disease progression (for example, if the patient is re-treated for persistent or recurrent thyroid cancer, or has further surgery).												6.10.3

[b] Provision of these samples is mandatory in this study.
[f] These assessments must be performed during the screening period, and then only on symptomatology according to the relevant protocol section.

Revised text:

Table 3 Study Plan (Note, only rows with changes are shown)

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to Table 4	± 2 months	± 1 month	
Physical examination	X		X	**X (Day 29 or 30)**			X						6.5.6
Plasma/serum sample for exploratory analysis[b]		X **(pre-dose)**											6.10.2
Optional genetic consent & sample (whole blood)		**X (pre-dose)**											6.9
Vital signs (including height at screening), weight	X	X **(pre-dose)**	**X**	**X (Day 29 or 30)**			X						6.5.8
Clinical chemistry	X	**X (pre-dose)**	X	**X (Day 29 or 30)**			X						6.5.5
Haematology	X	**X (pre-dose)**	X	**X (Day 29 or 30)**			X			X		X	6.5.5
ECG[e]	X	X		X[e] **(Day 29 or 30)**			X						6.5.7.2

Table 3 Study Plan (Note, only rows with changes are shown)

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to Table 4	± 2 months	± 1 month	
ECHO/MUGA[f]	X						**X**						6.5.7.1
Ophthalmologic examination[f]	X						**X**						6.5.9.2
PK blood samples[h]		X		X[h] **(Day 29 or 30)**									6.7
Thyrogen injection				Xx2 **(Day 29 and 30)**						Xx2[a]			5.5.4.1
Tumour biopsy on progression (optional)	Optional sample on disease progression (for example, if the patient is re-treated for persistent or recurrent thyroid cancer, or has further surgery). **Note that both a plasma and serum sample for exploratory analysis should also be taken on disease progression.**												6.10.3 **6.10.2**

[b] Provision of these samples is mandatory in this study. **Samples should also be obtained on progression (refer to Section 6.10.2).**
[f] These assessments must also be performed on symptomatology according to the relevant protocol section.

Reason for Amendment:

FDA strongly recommends adding additional safety assessments to the protocol:

- Clinical chemistry and haematology assessments on Day 30
- A focused physical examination on Day 30
- Collection of vital signs (except height) on Day 14, and 30
- An ophthalmologic examination (including slit lamp examination) and echocardiogram or MUGA scan at the Week 10 visit to allow a comparison with baseline in all patients.

AstraZeneca added further clarification:

- Day 1 samples should be taken pre-dose as indicated.
- Clinical chemistry and haematology added on Day 1.
- Clarification of sample requirements for Day 29 and/or 30.
- Clarification of requirements for progression plasma/serum sample for exploratory biomarkers.

Section of protocol affected:

Table 9 Volume of blood to be drawn from each patient

Previous text:

Table 1 Volume of blood to be drawn from each patient

Assessment		Maximum sample volume [a] (mL)	Typical number of samples (over 18+ months)	Total volume (mL)
Safety	Clinical chemistry (local analysis)	5	3	15
	Haematology (local analysis)	3	5	15
Efficacy	Tg, TSH, TgAb (central analysis)	10	4	40
PK		2	8	16
Genetics at randomisation (optional)		10	1	10
Exploratory biomarkers at randomisation, serum		10	1	10
Exploratory biomarkers at randomisation, plasma		10	1	10
Exploratory biomarkers on progression, serum		10	1	10
Exploratory biomarkers on progression, plasma		10	1	10
Total				136

Revised text:

Table 2 Volume of blood to be drawn from each patient

Assessment		Maximum sample volume [a] (mL)	Typical number of samples (over 18+ months)	Total volume (mL)
Safety	Clinical chemistry (local analysis)	5	**5**	**25**
	Haematology (local analysis)	3	**7**	**21**
Efficacy	Tg, TSH, TgAb (central analysis)	10	4	40
PK		2	8	16
Genetics at randomisation (optional)		10	1	10
Exploratory biomarkers at randomisation, serum		10	1	10
Exploratory biomarkers at randomisation, plasma		10	1	10
Exploratory biomarkers on progression, serum		10	1	10
Exploratory biomarkers on progression, plasma		10	1	10
Total				**152**

Reason for Amendment:

Additional clinical chemistry and haematology assessments at FDA request.

Section of protocol affected:

Table 4: Study Plan for the 18 month Primary Endpoint Assessments

Previous text:

Clinical chemistry/haematology (required for Stage 1)

Revised text:

Haematology (required for Stage 1)

Reason for Amendment:

Clarification by AstraZeneca to make consistent with Table 3. Only haematology is required at Visit 10 (18 months post-RAI dose).

Section of protocol affected:

Inclusion criteria 13

Previous text:

Male patients with sexual partners who are pregnant or who could become pregnant (ie, women of child-bearing potential) must agree to use acceptable methods of contraception for 12 weeks after completing study therapy, or longer if required for standard RAI administration restrictions and in accordance with local labels, to avoid pregnancy and/or potential adverse effects.

Revised text:

Male patients with sexual partners who are pregnant or who could become pregnant (ie, women of child-bearing potential) must agree to use acceptable methods of contraception **until** 12 weeks after completing study therapy, or longer if required for standard RAI administration restrictions and in accordance with local labels, to avoid pregnancy and/or potential adverse effects.

Reason for Amendment:

Clarification to the inclusion criterion 13 by AstraZeneca.

Section of protocol affected:

Exclusion criteria 2

Previous text:

Diagnosis of anaplastic thyroid cancer, medullary thyroid cancer, or Hürthle cell carcinoma (refer to inclusion criterion 3 for further details on Hürthle cell eligibility).

Revised text:

Diagnosis of anaplastic thyroid cancer, medullary thyroid cancer, or Hürthle cell carcinoma (refer to inclusion criterion **4** for further details on Hürthle cell eligibility).

Reason for Amendment:

Correction to the cross reference by AstraZeneca (administrative change).

Section of protocol affected:

6.4.3 Blood sample assessments for efficacy

Previous text:

Investigators may also perform local biochemical analysis for these parameters as per standard site practice if desired, however this data will not be used for study-related decision making. If local analysis is performed, the data may be collected by eCRF for the clinical study database, and Investigators must ensure that the maximum permissible blood volumes for individual patients at their institutions are not exceeded.

Revised text:

Investigators may also perform local biochemical analysis for these parameters as per standard site practice if desired, however this data will not be used for study-related decision making. If local analysis is performed, Investigators must ensure that the maximum permissible blood volumes for individual patients at their institutions are not exceeded.

Reason for Amendment:

Clarification to data collection plans by AstraZeneca.

Section of protocol affected:

6.4.4.2 Whole body diagnostic ^{131}I nuclear medicine scan (WBS)

Previous text:

WBS definition of structural DTC

Any patient with increased ^{131}I uptake considered not to be anatomically normal (where normal includes uptake in the salivary glands, stomach, gastrointestinal, urinary tract and bladder), that is biologically consistent with DTC will be classified as not in complete remission for the primary endpoint of this study (due to having RAI-avid structural DTC).

For the thyroid bed, < 0.1% uptake on the region-of-interest method drawn over the thyroid bed will be considered normal/negative (no disease). If uptake in the thyroid bed is ≥ 0.1% then these patients will be deemed not to be in remission due to the presence of RAI-avid disease.

Note that if an abnormality identified by US in stage 1, is subsequently shown to be RAI avid/positive on WBS in stage 2, the WBS data takes precedent over a negative biopsy/FNA from the same area.

The WBS evaluation will be made by blinded, independent central review.

Revised text:

WBS definition of structural DTC

The WBS evaluation will be made by blinded, independent central review.

If the central review determines no visible ^{131}I uptake then the WBS for that patient will be considered normal/negative (no disease). Areas considered to be anatomically normal (for example uptake in the salivary glands, stomach, gastrointestinal, urinary tract and bladder) will not be considered disease.

If the central review determines there is a low level of visible uptake in the thyroid bed:

- **Uptake must be < 0.1% to be considered normal/negative (no disease).**
- **If uptake in the thyroid bed region is ≥ 0.1%, the patient will be deemed not to be in remission due to the presence of iodine-avid DTC.**

The % uptake in the thyroid bed (using the region-of-interest method drawn over the thyroid bed) will be measured and calculated by the local Investigator site and entered into the eCRF, to be made available to the central reviewer.

If an abnormality identified by US is subsequently shown to be RAI avid on WBS, the WBS data takes precedent over a negative biopsy/FNA.

Reason for Amendment:

Clarification to the WBS central review process by AstraZeneca.

Section of protocol affected:

6.4.4.3 Neck MRI and 6.4.4.4 Chest CT

Previous text:

Post-operative (screening)

This baseline assessment is performed to determine study eligibility according to criterion 6 in Section 4.1). The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Revised text:

This baseline assessment is performed to determine study eligibility according to Section 4.1. The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Reason for Amendment:

Correction of cross-reference by AstraZeneca (administrative change).

Section of protocol affected:

6.5.3 Recording of adverse events

Previous text:

N/A

Revised text:

All adverse events will be graded according to NCI CTCAE Version 4.

Reason for Amendment:

Clarification at FDA request.

Section of protocol affected:

6.5.3 Adverse event variables

Previous text:

Variables

The following variables will be collected for each AE (note, only criteria with changes are shown):

- Maximum CTCAE grade
- AE caused patient's withdrawal from study (yes or no)

Revised text:

The following variables will be collected for each AE (note, only criteria with changes are shown):

- CTCAE grade information
- AE caused patient's withdrawal from study **treatment**

Reason for Amendment:

Clarification to data collection by AstraZeneca (CTCAE grade changes will be collected in the eCRF).

Section of protocol affected:

6.5.5 Laboratory safety Assessment

Previous text:

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (Table 3).

Revised text:

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (Table 3). **For samples taken after Day 1 during the study treatment period, the sample may be taken any time of day (ie, it does not matter whether it is pre-dose or post-dose). Day 1 samples should be taken pre-dose.**

Reason for Amendment:

Clarification of sampling times by AstraZeneca.

Section of protocol affected:

6.5.7.1 ECHO or MUGA and 6.5.9.2 Ophthalmologic examination

Previous text:

These assessments will be conducted at screening.

Revised text:

These assessments will be conducted at **the timepoints indicated in the Study Plan (Table 3).**

Reason for Amendment:

To ensure consistency with addition of Week 10 assessments at FDA request.

Section of protocol affected:

6.10.1 *BRAF* and *NRAS* patient population

Previous text:

Archival tumour sample from every patient will be analysed for *BRAF* and *NRAS* mutational status centrally using standardised methodology. Full analytical methodology details will be provided in the CSR.

The genetic analysis of archival tumour samples to identify the *BRAF* and *NRAS* patient population will be performed retrospectively in the study (after randomisation but prior to the primary endpoint data analysis).

Revised text:

Archival tumour sample from every patient will be analysed for *BRAF* and *NRAS* mutational status centrally using standardised methodology. Full analytical methodology details will be provided in the CSR.

The genetic analysis of archival tumour samples to identify the *BRAF* and *NRAS* patient population will be performed retrospectively in the study (after randomisation but prior to the primary endpoint data analysis).

***BRAF/NRAS* positive = mutations in *BRAF/NRAS* have been detected**

***BRAF/NRAS* negative = no mutation in *BRAF/NRAS* has been detected**

***BRAF/NRAS* unknown = mutation status in *BRAF/NRAS* cannot be confirmed**

Reason for Amendment:

Clarification of *BRAF/NRAS* mutation status definitions by AstraZeneca

Section of protocol affected:

6.10.1.1 Archival tumour sample

Previous text:

- 20 pre-cut sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides, including one stained with haematoxylin and eosin. Each section is to be 5 μm thick.

Revised text:

- 20 pre-cut sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 μm thick.

Reason for Amendment:

Haematoxylin and eosin stained sections will be prepared by the AstraZeneca appointed central laboratory in order to ensure sample processing consistency for all samples received as part of the study.

Persons who initiated the Amendment:

AstraZeneca at FDA request.

Clinical Study Protocol Amendment No 1
Appendix A

Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	3 April 2013
Protocol Dated	24 January 2013

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

PPD

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative	PPD	PPD

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSPhave been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

Signature: PPD PPD

Clinical Study Protocol Amendment	
Amendment Number	2
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Date	15 July 2013
Protocol Dated	24 January 2013

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyrod Cancer

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

This protocol amendment affects all the centres participating in this study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

Protocol Synopsis and section 2. Study Objectives

Previous text:

2.1 Primary objectives

- To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months

post RAI treatment in the overall study population. Complete remission is defined in Section 6.4.1.

- To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

2.2 Secondary objectives

1. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the overall study population. Clinical remission is defined in Section 6.4.6.

2. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

3. To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

4. To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

Revised text:

2.1 Primary objective

To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment **in the intention to treat (ITT) study population**. Complete remission is defined in Section 6.4.1.

2.2 Secondary objectives

1. To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

2. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment **in the ITT study population**. Clinical remission is defined in Section 6.4.6.

3. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-

group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

4. To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

5. To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

Reason for Amendment:

FDA comments. Efficacy in the genetic sub-group population of *BRAF* or *NRAS* mutation positive patients will be considered a secondary objective (rather than co-primary).

Terminology clarification for the overall study population; now defined as the intention to treat (ITT) population.

Section of protocol affected:

Protocol Synopsis, Statistical methods

Previous text:

Approximately 228 patients will be randomised in a 2:1 ratio in this study. The primary analysis will be performed when patients have been followed for 18 months following their RAI treatment. There will be two primary analysis populations: the first will comprise all randomised patients (overall population); the second will comprise the sub-group of randomised patients with tumours known to be mutation positive for *BRAF* or *NRAS*. The primary endpoint of complete remission rate will be analyzed using a logistic regression model with covariates histology status (papillary, follicular, poorly differentiated), mutation status (overall population only, *BRAF/NRAS* positive, *BRAF/NRAS* negative) and age, provided there are enough data points for a meaningful analysis. There will be two primary analysis populations: the first will comprise all randomised patients; the second will comprise the sub-group of randomised patients with tumours known to be mutation positive for *BRAF* or *NRAS.* To control the type I error rate for the study and account for the correlation between the two primary endpoints, the Dunnett and Tamhane step-up procedure will be used. The correlation between the primary endpoint comparisons will be calculated as $\sqrt{w}$, where w is the proportion of the overall population who are in the mutation positive sub-group. The associated significance level for declaring statistical significance in the mutation positive sub-group adjusting for this correlation to maintain an overall 5% type I error rate whilst assigning 4% to the overall population will then be derived.

Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumetinib-containing arms, respectively, the study will have 80% power to demonstrate a statistically significant difference at the 4% (2-sided) significance level.

Assuming the true complete remission rates in the mutation-positive sub-group are 30% and 62% for the placebo and selumetinib-containing arms, respectively, the study will have 80% power to demonstrate a statistically significant difference at the 1% (2-sided) significance level.

All secondary endpoints will be analysed at the time of the primary analysis. Exploratory biomarker analysis may be analysed after the time of the primary analysis and reported separately to the CSR (apart from the somatic genetic data required for analysis of the second primary endpoint).

All randomised patients will continue to be followed until the final study visit (3 years after their RAI treatment). At this time, data on clinical status, incidence of re-treatment and long-term safety will be summarised.

Revised text:

Approximately 228 patients will be randomised in a 2:1 ratio in this study. The primary analysis will be performed when patients have been followed for 18 months following their RAI treatment. **The primary analysis population will comprise all randomised patients (ITT population) and the primary endpoint of complete remission rate at 18 months will be analyzed using a logistic regression model including treatment as the only covariate. Results will be presented in terms of the odds ratio, 95% confidence interval and associated p-value. Logistic regression modelling including treatment and covariates histology status, mutation status and age, will be performed as sensitivity analyses provided there are enough data points for a meaningful analysis**.

Assuming the true complete remission rates in the ITT study population are 30% and 50% for the placebo and selumetinib-containing arms, respectively, the study will have **at least** 80% power to demonstrate a statistically significant difference at the 5% (2-sided) significance level.

All secondary endpoints will be analysed at the time of the primary analysis. Exploratory biomarker analysis may be analysed after the time of the primary analysis and reported separately to the CSR (apart from the somatic genetic data required for analysis of the second primary endpoint).

All randomised patients will continue to be followed until the final study visit (3 years after their RAI treatment). At this time, data on clinical status, incidence of re-treatment and long-term safety will be summarised.

Reason for Amendment:

AstraZeneca amended this section of the protocol to accommodate changes made to the section 12 as a result of moving the co-primary objective to secondary.

Section of protocol affected:

3.2 Rationale for study design, doses and control group

Previous text:

The primary efficacy endpoint will be assessed in patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that these patients are not likely to be the only population to benefit. Incorporation of a genetically predefined study population enables this hypothesis to be examined (mutation analysis of samples to identify the genetically predefined study population will be performed post-randomisation, and prior to data base lock for the primary endpoint data analysis).

Revised text:

A secondary efficacy endpoint will be assessed in patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that these patients are not likely to be the only population to benefit. Incorporation of a genetically predefined study population enables this hypothesis to be examined (mutation analysis of samples to identify the genetically predefined study population will be performed post-randomisation, and prior to data base lock for the primary endpoint data analysis).

Reason for Amendment:

AstraZeneca amended this section due to changes in the study primary and secondary objectives.

Section of protocol affected:

4.1 Inclusion criteria

Previous text:

14. Adequate organ function as defined by:

(a) ANC ≥ 1.5x109/L (1500 per mm3)

(b) Platelets ≥ 100 x 109/L (100,000 per mm3)

Revised text:

14. Adequate organ function as defined by:

(a) ANC $\geq$ 1.5 x 10^9/L (1500 per mm^3)

(b) Platelets $\geq$ 100 x 10^9/L (100,000 per mm^3)

Reason for Amendment:

AstraZeneca corrected text formatting errors.

Section of protocol affected:

4.2 Exclusion criteria

Additional text:

7. **Receiving herbal supplements or medications known to be strong inhibitors or inducers of the CYP1A2, CYP2C19 and CYP3A4 enzymes unless such products can be safely discontinued at least 14 days before the first dose of study medication.**

Reason for Amendment:

Exclusion criterion added at FDA request.

Section of protocol affected:

6.2 Data collection at enrolment

Additional text:

13. Local derived *BRAF* and/or *NRAS* mutation status (where available)

Reason for Amendment:

Clarification to data collection plans by AstraZeneca.

Section of protocol affected:

6.5.7.2 Resting 12-lead ECG

Previous text:

During the treatment phase of the study, patients will have single 12-lead ECGs assessments at the following timepoints:

- 1-2 hours after the first dose of study treatment on Day 1

- 1-2 hours after the first dose of study treatment on Day 29 or 30
- At the 30-day follow up visit following completion of study treatment
- Single ECGs must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event
- A single 12-lead ECG is also required at premature discontinuation of treatment

Revised text:

During the treatment phase of the study, patients will have single 12-lead ECGs assessments at the following timepoints:

- 1-2 hours after the first dose of study treatment on Day 1
- 1-2 hours after the morning dose of study treatment on Day 29 or 30
- At the 30-day follow up visit following completion of study treatment
- Single ECGs must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event
- A single 12-lead ECG is also required at premature discontinuation of treatment

Reason for Amendment:

Clarification by AstraZeneca.

Section of protocol affected:

6.10.1 *BRAF* and *NRAS* patient population

Previous text:

Archival tumour sample from every patient will be analysed for *BRAF* and *NRAS* mutational status centrally using standardised methodology. Full analytical methodology details will be provided in the CSR.

The genetic analysis of archival tumour samples to identify the *BRAF* and *NRAS* patient population will be performed retrospectively in the study (after randomisation but prior to the primary endpoint data analysis).

BRAF/NRAS positive = mutations in *BRAF/NRAS* have been detected

BRAF/NRAS negative = no mutation in *BRAF/NRAS* has been detected

BRAF/NRAS unknown = mutation status in *BRAF/NRAS* cannot be confirmed

Revised text:

Archival tumour sample from each patient will be analysed for *BRAF* and *NRAS* mutational status centrally using standardised methodology. **Analysis may include, but is not limited to, *BRAF* V600E and *NRAS* Q61R, Q61K, Q61L.** Full analytical methodology details will be provided in the CSR.

The genetic analysis of archival tumour samples to identify the *BRAF* and *NRAS* patient population will be performed retrospectively in the study (after randomisation but prior to the primary endpoint data analysis).

BRAF/NRAS positive = mutations in *BRAF/NRAS* have been detected

BRAF/NRAS **not detected** = no mutation in *BRAF/NRAS* has been detected

BRAF/NRAS unknown = mutation status in *BRAF/NRAS* cannot be confirmed

Reason for Amendment:

FDA comments.

Clarification of terminology by AstraZeneca.

Section of protocol affected:

7.1 Volume of blood

Table 9 Volume of blood to be drawn from each patient

Previous text:

Table 9 Volume of blood to be drawn from each patient

Assessment		**Maximum sample volume [a] (mL)**	**Typical number of samples (over 18+ months)**	**Total volume (mL)**
Safety	Clinical chemistry (local analysis)	5	5	25
	Haematology (local analysis)	3	7	21
Efficacy	Tg, TSH, TgAb (central analysis)	10	4	40
PK		2	8	16
Genetics at randomisation (optional)		10	1	10

Table 9 Volume of blood to be drawn from each patient

Assessment		Maximum sample volume [a] (mL)	Typical number of samples (over 18+ months)	Total volume (mL)
Safety	Clinical chemistry (local analysis)	5	5	25
	Haematology (local analysis)	3	7	21
Efficacy	Tg, TSH, TgAb (central analysis)	10	4	40
PK		2	8	16
Exploratory biomarkers at randomisation, serum		10	1	10
Exploratory biomarkers at randomisation, plasma		10	1	10
Exploratory biomarkers on progression, serum		10	1	10
Exploratory biomarkers on progression, plasma		10	1	10
	Total			152

[a] All volumes presented are maximums. The actual volume requirements will be detailed in the Laboratory Manual.

Revised text:

Table 9 Volume of blood to be drawn from each patient

Assessment		Maximum sample volume [a] (mL)	Typical number of samples (over 18+ months)	Total volume (mL)
Safety	Clinical chemistry (local analysis)	5	5	25
	Haematology (local analysis)	3	7	21
Efficacy	Tg, TSH, TgAb (central analysis)	10	4[b]	40
PK		2	8	16
Genetics at randomisation (optional)		10	1	10
Exploratory biomarkers at randomisation, serum		10	1	10
Exploratory biomarkers at randomisation, plasma		10	1	10
Exploratory biomarkers on progression, serum		10	1	10
Exploratory biomarkers on progression, plasma		10	1	10
	Total			152 [b]

[a] All volumes presented are maximums. The actual volume requirements will be detailed in the Laboratory Manual.

[b] **For efficacy samples up to 2 repeat samples may be required, this would result in 10-20 mL additional blood and bring the maximum total to 172 mL.**

Reason for Amendment:

Clarification to blood sampling plan and total blood volumes by AstraZeneca.

Section of protocol affected:

11.5.1 Analysis of *NRAS* and *BRAF*

Previous text:

Tumour samples will be collected as outlined in the study plan and assessed for *BRAF* and *NRAS* biomarkers to identify patients for this primary patient population.

Revised text:

Tumour samples will be collected as outlined in the study plan and assessed for *BRAF* and *NRAS* **mutational status (as detailed in section 6.10.1)** to identify patients for **this patient population.**

Reason for Amendment:

Clarifications by AstraZeneca.

Section of protocol affected:

12.1.2 *BRAF/NRAS* mutation positive analysis set

Previous text:

For the analysis of the *BRAF* and *NRAS* mutation positive population (primary objective), only those patients from the ITT population with genetic samples that are positive for *BRAF* or *NRAS* will be included.

Revised text:

For the analysis of the *BRAF* and *NRAS* mutation positive population **(secondary objective)**, only those patients from the ITT population with genetic samples that are positive for *BRAF* or *NRAS* will be included.

Reason for Amendment:

AstraZeneca amended this section due to changes in the study primary and secondary objectives.

Section of protocol affected:

12.1.4 Safety analysis set

Previous text:

The safety analysis set will consist of all patients who received at least one dose of randomised treatment and for whom post dose data are available. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment combination received, ie, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

Revised text:

The safety analysis set will consist of all patients who received at least one dose of randomised treatment. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment combination received, ie, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

Reason for Amendment:

Clarification by AstraZeneca.

Section of protocol affected:

12.2 Methods of statistical analyses

Previous text:

A comprehensive SAP will be prepared prior to start of recruitment (first subject in).

Since there are two correlated primary comparisons of interest (selumetinib vs. placebo in the overall population and selumetinib vs. placebo in the mutation-positive population), the Dunnett and Tamhane step-up procedure will be used to control the type I error rate (Dunnett and Tamhane 1992, Fernandes & Stone 2011). This procedure is an adaptation of the Hochberg approach, which accounts for the correlation between the primary endpoint comparisons. The correlation between the primary endpoint comparisons will be calculated as $\sqrt{w}$, where w is the proportion of the overall population who are in the mutation positive sub-group. The associated significance level for declaring statistical significance in the mutation

positive sub-group adjusting for this correlation to maintain an overall 5% type I error rate whilst assigning 4% to the overall population will then be derived. For example, assuming that 55% of the overall population are in the mutation-positive sub-group, the correlation is 0.74. Using Dunnett and Tamhane step-up procedure, significance would therefore be declared if both the overall and mutation positive populations are significant at the 5% two-sided level, or if either the overall population is significant at the 4% level or the mutation-positive population is significant at the 1.625% level.

12.2.1 Complete remission rate at 18 months post-RAI treatment

The endpoint of complete remission rate will be compared between selumetinib in combination with RAI, and placebo in combination with RAI in the overall population using a logistic regression model with covariates histology status (papillary, follicular, poorly differentiated), mutation status (*BRAF/NRAS* positive, *BRAF/NRAS* negative) and age, provided there are enough data points for a meaningful analysis.

The primary endpoint of complete remission rate will be compared between selumetinib in combination with RAI vs. placebo in combination with RAI in the mutation positive population using a logistic regression model with covariates histology status (papillary, follicular, poorly differentiated) and age, provided there are enough data points for a meaningful analysis.

For each covariate, if the status is missing or unknown, patients will be assigned to the status that the majority of patients are known to have, e.g. if 55% of patients with known mutation status are *BRAF/NRAS* positive and 45% are *BRAF/NRAS* negative, a patient with missing mutation status will be assigned *BRAF/NRAS* positive. If a value for the continuous covariate age is missing, the mean will be imputed.

The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood confidence interval and 2-sided p-value. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above. The complete remission rate will be estimated for each treatment arm.

Sensitivity analyses

The primary endpoint analysis will be repeated using the treatment-compliant population.

A sensitivity analysis will be performed in which patients that were identified as being in complete remission outside of the specified time windows will be included in the logistic regression analysis and classed as being in complete remission to ensure there is no evaluation time bias between arms.

Elevated TSH can be caused by poor compliance and can mean a patient is less likely to achieve remission. A sensitivity analysis will be performed in which patients with high TSH

are excluded from the logistic regression. A high TSH is defined as a value >10 mIU/L recorded at any point by standardised central laboratory analysis.

The extent to which the treatment effect is consistent across the subgroups histology status, mutation status, gender, race and age will be assessed for the overall primary population and across the subgroups histology status, gender, race and age for the mutation positive primary population. The presence of a quantitative interaction will be assessed by means of an overall global interaction test. This will be performed by comparing the fit (likelihood ratio test) of a model including all covariate-by-randomised treatment interaction terms, treatment and covariate terms with a model that excludes the interaction terms. If the global interaction test is found to be statistically significant at the 10% significance level, an attempt to determine the cause and type of interaction will be made. Stepwise backward selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

For quantitative interactions identified, the presence of any qualitative interactions will be assessed using the approach of Gail and Simon (Gail & Simon 1985). For categorical covariates the test statistics, based on the appropriate degrees-of-freedom, can be taken directly from the paper. For the continuous covariate, the approach will be adapted as follows:

Identify the cut-point ($-\beta_1/\beta_3$) of the covariate where the odds ratio for the treatment effect is 1, where β_1 is the treatment parameter estimate and β_3 is the treatment-by-covariate parameter estimate. Re-analyse the data separately for the values of the covariate above and below the cut-point and use the separate chi-square values in the Simon and Gail test.

Subgroup data (histology status, mutation status, gender, race and age) will be summarised by a forest plot where the odds ratio is plotted on the log scale. For this, age will be categorised as ≤45 or >45 years. The treatment effect and confidence intervals for each level of the subgroup will be obtained from a single model that contains a treatment, factor and treatment-by-factor interaction term.

12.2.2 Clinical remission rate at 18 months post-RAI treatment

The secondary endpoint of clinical remission rate will be analysed (for both study populations) as described in Section 12.2.1.

Revised text:

A comprehensive SAP will be prepared prior to start of recruitment (first subject in).

Since there is only one primary endpoint/comparison of interest (complete remission rate at 18 months for selumetinib vs. placebo in the ITT population) the primary endpoint will be considered statistically significant if the two-sided p-value is less than 0.05.

12.2.1 Complete remission rate at 18 months post-RAI treatment

The **primary** endpoint of complete remission rate **at 18 months** will be compared between selumetinib in combination with RAI, and placebo in combination with RAI in the ITT population using **a logistic regression model including treatment as the only covariate. Results will be presented in terms of the odds ratio, 95% confidence interval and associated p-value. A sensitivity analysis will be performed using a** logistic regression model **including treatment and adjusted for the** covariates histology status (papillary, follicular, poorly differentiated), mutation status (*BRAF/NRAS* positive, *BRAF/NRAS* **not detected**) and age, provided there are enough data points for a meaningful analysis.

A secondary analysis of complete remission rate will be **performed to** compare selumetinib in combination with RAI vs. placebo in combination with RAI in the ***BRAF/NRAS*** mutation positive population using **a logistic regression model including treatment as the only covariate. A sensitivity analysis will be performed using** a logistic regression model **adjusted for the** covariates histology status (papillary, follicular, poorly differentiated) and age, provided there are enough data points for a meaningful analysis.

For the sensitivity analyses using each covariate adjusted logistic regression models, the following missing data approach for each covariate will be adopted:

- **Missing age; impute the mean of observed ages**
- **Missing histology status; add an additional 'unknown' category to make 4 categories (papillary, follicular, poorly differentiated, and unknown)**
- **Missing mutation status; add an additional 'unknown' category to make 3 categories (*BRAF/NRAS* positive, *BRAF/NRAS* not detected and unknown)**

The results of the **analyses, in terms of treatment effects**, will be presented as odds ratios together with their associated 95% profile likelihood confidence intervals and 2-sided p-values. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above. The complete remission rate **and 95% confidence interval** will be estimated for each treatment arm.

Sensitivity analyses for **the primary endpoint**

The primary endpoint analysis, **a logistic regression model including treatment as the only covariate for complete remission rate at 18 months**, will be repeated:

- using the treatment-compliant population.

- **to allow** patients that were identified as being in complete remission outside of the specified time windows to be classed as being in complete remission, in order to investigate time bias between arms.

- **excluding patients with high TSH**. Elevated TSH can be caused by poor compliance and can mean a patient is less likely to achieve remission, therefore this sensitivity analysis excludes patients with high TSH, which is defined as a value >10 mIU/L recorded at any point by standardised central laboratory analysis.

Treatment by covariate interactions

The extent to which the treatment effect is consistent across the subgroups histology status, mutation status **(ITT population only)**, gender, race and age will be assessed **in the ITT** population and **in the *BRAF/NRAS*** mutation positive population. The presence of a quantitative interaction will be assessed by means of an overall global interaction test. This will be performed by comparing the fit (likelihood ratio test) of a model including all covariate-by-randomised treatment interaction terms, treatment and covariate terms with a model that excludes the interaction terms. If the global interaction test is found to be statistically significant at the 10% significance level, an attempt to determine the cause and type of interaction will be made. Stepwise backward selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

For quantitative interactions identified, the presence of any qualitative interactions will be assessed using the approach of Gail and Simon (Gail & Simon 1985). For categorical covariates the test statistics, based on the appropriate degrees-of-freedom, can be taken directly from the paper. For the continuous covariate, the approach will be adapted as follows:

Identify the cut-point ($-\beta_1/\beta_3$) of the covariate where the odds ratio for the treatment effect is 1, where β_1 is the treatment parameter estimate and β_3 is the treatment-by-covariate parameter estimate. Re-analyse the data separately for the values of the covariate above and below the cut-point and use the separate chi-square values in the Simon and Gail test.

Subgroup data

Subgroup data (histology status, ***BRAF* or *NRAS* mutation status,** gender, race and age) will be summarised by a forest plot where the odds ratio is plotted on the log scale. For this, age will be categorised as ≤45 or >45 years. The treatment effect and **95%** confidence intervals for each level of the subgroup will be obtained from a single **logistic regression** model that contains a treatment, factor and treatment-by-factor interaction term.

12.2.2 Clinical remission rate at 18 months post-RAI treatment

The secondary endpoint of clinical remission rate will be analysed as described in Section 12.2.1, **except for primary endpoint specific sensitivity analyses and treatment by covariate interaction testing.**

Reason for Amendment:

FDA comments. Clarification of terminology from the FDA response document submitted by AstraZeneca on 27th June 2013.

Section of protocol affected:

12.3 Determination of sample size

Previous text:

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The two primary objectives of the study are to compare the efficacy of selumetinib with RAI versus placebo with RAI, by assessment of the complete remission rate at 18 months post-RAI treatment in the overall study population, and in a sub-group of patients whose tumours have BRAF and NRAS mutations. Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumentinib-containing arms, respectively, a total of 228 patients, randomised in a 2:1 ratio (152 and 76 patients in the selumentinib and placebo-containing arms, respectively) provides 80% power to show statistical significance, based on a two-sided 4% significance level. Assuming that the prevalence of the mutation-positive sub-group described is 55%, and the true complete remission rates in the mutation-positive sub-group are 30% and 62% for the placebo and selumentinib-containing arms, respectively, the expected numbers of 84 mutation-positive patients in the selumentinib arm and 42 mutation-positive patients in the placebo arm at the time of the analysis, provides 80% power to show statistical significance, based on a two-sided 1% significance level.

Revised text:

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The primary objective of the study is to compare the efficacy of selumetinib with RAI versus placebo with RAI, by assessment of the complete remission rate at 18 months post-RAI treatment in the ITT study population. Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumentinib-containing arms, respectively, a total of 228 patients, randomised in a 2:1 ratio (152 and 76 patients in the selumentinib and placebo-containing arms, respectively) provides **at least** 80% power to show statistical significance, based on a two-sided 5% significance level.

Reason for Amendment:

FDA comments.

Section of protocol affected:

14. List of references

Removed text:

Dunnett and Tamhane 1992
Dunnett CW, Tamhane AC. A Step-Up Multiple Test Procedure. J Am Stat Assoc 1992; 87(417):162-170.

Fernandes & Stone 2011
Fernandes N & Stone A. Multiplicity adjustments in trials with two correlated comparisons of interest. Stat Methods Med Res. 2011;20(6):579-594.

Reason for Amendment:

AstraZeneca removed two publications related to statistics (Dunnett and Tamhane 1992, Fernandes & Stone 2011) due to changes in statistical methods (the Dunnett and Tamhane step-up procedure).

Persons who initiated the Amendment:

AstraZeneca at FDA request.

AstraZeneca

Clinical Study Protocol Amendment No 2 Appendix A	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	15 July 2013
Protocol Dated	24 January 2013

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

PPD

PPD

Signing on behalf of:

PPD

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative	PPD	PPD

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

Signature:

Clinical Study Protocol Amendment	
Amendment Number	3
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Date	01 July 2014
Protocol Dated	24 January 2013

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

This protocol amendment affects all the centres participating in this study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

1.1.5.4 The pharmacokinetics of Selumetinib in subjects of Asian ethnicity

Previous text:

Blank

Revised text:

Plasma exposure of Selumetinib (Cmax and AUC) is higher, at a population level, in subjects of Asian ethnicity by approximately 1.5- to 2-fold in non-Japanese Asians and Japanese subjects, compared with Western subjects. However, the pharmacokinetics of Selumetinib

show considerable variation and there is overlap in the range of exposure experienced by Asian and Western subjects (some individual Asian subjects have similar plasma levels to those in Western subjects). The higher average plasma exposure was not associated with a change in the tolerability profile of single dose Selumetinib.

The pharmacokinetics of Selumetinib were investigated in study D1532C00086, conducted in the UK involving healthy volunteers of Asian ethnicity (defined as being born in an Asian country, and expatriate for not longer than 5 years, and with maternal and paternal grandparents of Asian ethnicity). The subjects who received Selumetinib in Study D1532C00086 were of the following ethnicities: Japanese, Chinese, Filipino, Malay, Malaysian, Maldivian, Singaporean, Thai, Indian and Vietnamese and it is not known in these groups whether Selumetinib exposure will be similar to Western subjects or to subjects of the specific Asian ethnicities included in Study D1532C00086.

The pharmacokinetic findings from study D1532C00086 do not support excluding subjects of Asian ethnicity from studies of Selumetinib. However, as it is possible that Asian subjects may experience higher Selumetinib plasma exposure (than would be expected in Western subjects receiving the same dose of Selumetinib), there could be a potential for a higher risk of adverse events.

The number of Asian patients with advanced cancer who have received treatment with Selumetinib is very low. Emerging information from ongoing study D1532C00067 of Japanese patients receiving selumetinib + docetaxel for second-line treatment of NSCLC suggests that febrile neutropenia may occur more commonly in Japanese patients (3 of 8 patients treated, although comparative data in Japanese patients receiving docetaxel monotherapy is not available) than might be predicted from studies conducted in Western subjects.

Patients of Asian ethnicity are not excluded from studies evaluating Selumetinib. However, when considering enrolling an individual of Asian ethnicity to a Selumetinib clinical study, investigators should make a clinical judgment as to whether the potential risk of experiencing higher Selumetinib plasma levels outweighs the potential benefit of treatment with Selumetinib. The Patient Information and Consent form for studies of Selumetinib includes information on the possibility of higher Selumetinib plasma levels and occurrence of adverse events in Asian subjects than in subjects who are not of Asian origin. Investigators should be aware of the potentially higher risk of adverse events when monitoring patients of Asian ethnicity receiving treatment in clinical studies of Selumetinib.

Reason for Amendment:

Availability of preliminary study D1532C00086 data suggesting that subjects of Asian descent may experience a higher exposure of Selumetinib than the majority of subjects of non Asian descent receiving an equivalent dose of Selumetinib.

Section of protocol affected:

3.1.1. Treatment Plan

Previous text:

2. It is essential that patients remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator until the patient has been on study treatment for a minimum of 7 consecutive days beforehand.

3. Study treatment with selumetinib or placebo will typically last for 36 days, but must be for no longer than 43 days (this allows the planned RAI to be postponed by up to 1 week if absolutely necessary).

7. Twice daily dosing of selumetinib/placebo will continue for 5 days following RAI therapy (Day 36 will typically be the last day of study treatment, but this can be extended to day 43 if necessary)

Revised text:

2. Patients should remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator to allow the patient to receive study treatment for a minimum of 7 consecutive days beforehand.

3. Study treatment with selumetinib or placebo will typically last for 36 days, but must be for no longer than 43 days. The planned RAI can be postponed by up to 1 week if absolutely necessary.

7. Twice daily dosing of selumetinib/placebo should continue for 5 days following RAI therapy

8. If a patient suspends study drug (selumetinib or placebo) treatment for more than 14 days they are no longer eligible to re-start the treatment but will be followed according to the study plan.

Reason for Amendment:

Amended to clarify visit window for RAI treatment dose administration and provide clear instruction on allowed IP interruption.

Section of protocol affected:

Table 3 Study Plan

Previous text

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Informed consent	X												
Physical examination	X		X	X (Day 29 or 30)			X						6.5.6
Additional screening procedures	X												6.2
Provision of archival tumour[b]		X											6.10.1.1
Plasma/serum sample for exploratory analysis[b]		X (pre-dose)											6.10.2
Pregnancy test	X				X					X[a]			6.5.9.1
Optional genetic consent & sample (whole blood)		X (pre-dose)											6.9
Adverse events[c]	X →	→	→	→	→	→	→	→	→	→	→	→	6.5.3
Concomitant medications	X →	→	→	→	→	→	→	→	→	→	→	→	5.6
Telephone follow up for safety[d]								X			X		6.5.3

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Vital signs (including height at screening), weight	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.8
Clinical chemistry	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.5
Haematology	X	X (pre-dose)	X	X (Day 29 or 30)			X			X		X	6.5.5
Urinalysis	X		X				X						6.5.5
ECG[e]	X	X		X[e] (Day 29 or 30)			X						6.5.7.2
ECHO/MUGA[f]	X						X						6.5.7.1
Ophthalmologic examination[f]	X						X						6.5.9.2
Selumetinib/placebo dosing[g] twice daily		→	→	→	→	→							5.5.2

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
PK blood samples[h]		X		X[h] (Day 29 or 30)									6.7
Low iodine diet[i]				X	X					X[a]			5.1.1
Thyrogen injection				Xx2 (Day 29 and 30)						Xx2[a]			5.5.4.1
^{131}I (RAI) treatment single 100 mCi dose					X								5.5.4.2
^{131}I 5 diagnostic dose for WBS single 5 mCi dose										X[a]			5.5.4.2
^{131}I nuclear medicine WBS scan						X[j]				X[a]			6.4.4.2
Re-treatment assessment[k]									X	X		X	5.9
Blood sample for TSH									X	X			6.4.3.3
Blood sample for suppressed Tg									X[n]	X			6.4.3.1

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Blood sample for TgAb	X								X	X			6.4.3.4
Blood sample for rhTSH-stimulated Tg										X[a]			6.4.3.2
Neck ultrasound	X[l]								X	X			6.4.4.1
Neck MRI	X[l]									X[a]			6.4.4.3
Chest CT without contrast	X[l]									X[a]			6.4.4.4
Final follow-up assessment of clinical status												X	6.4.8
Biopsy/FNA for disease confirmation									X[m]	X[m]			6.4.4.5
Tumour biopsy on progression (optional)	Optional sample on disease progression (for example, if the patient is re-treated for persistent or recurrent thyroid cancer, or has further surgery). Note that both a plasma and serum sample for exploratory analysis should also be taken on disease progression.												6.10.3 6.10.2

Revised Text:

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post RAI (visit 5)	9 months post RAI (visit 5)	18 months post RAI (visit 5)	27 months post RAI (visit 5)	3 years post RAI (visit 5)	
Visit Window	N/A	N/A	±1wk	+1wk	+1wk	+1wk	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Informed consent	X												
Physical examination	X		X	X (Day 29 or 30)			X						6.5.6
Additional screening procedures	X												6.2
Provision of archival tumour[b]		X											6.10.1.1
Plasma/serum sample for exploratory analysis[b]		X (pre-dose)											6.10.2
Pregnancy test	X				X					X[a]			6.5.9.1
Optional genetic consent & sample (whole blood)		X (pre-dose)											6.9
Adverse events[c]	X →	→	→	→	→	→	→	→	→	→	→	→	6.5.3
Concomitant medications	X →	→	→	→	→	→	→	→	→	→	→	→	5.6
Telephone follow up for safety[d]								X			X		6.5.3

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post RAI (visit 5)	9 months post RAI (visit 5)	18 months post RAI (visit 5)	27 months post RAI (visit 5)	3 years post RAI (visit 5)	
Visit Window	N/A	N/A	±1wk	+1wk	+1wk	+1wk	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Vital signs (including height at screening), weight	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.8
Clinical chemistry	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.5
Haematology	X	X (pre-dose)	X	X (Day 29 or 30)			X			X		X	6.5.5
Urinalysis	X		X				X						6.5.5
ECG[e]	X	X		X[e] (Day 29 or 30)			X						6.5.7.2
ECHO/MUGA[f]	X						X						6.5.7.1
Ophthalmologic examination[f]	X						X						6.5.9.2
Selumetinib/placebo dosing[g] twice daily		→	→	→	→	→							5.5.2

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post RAI (visit 5)	9 months post RAI (visit 5)	18 months post RAI (visit 5)	27 months post RAI (visit 5)	3 years post RAI (visit 5)	
Visit Window	N/A	N/A	±1wk	+1wk	+1wk	+1wk	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
PK blood samples[h]		X		X[h] (Day 29 or 30)									6.7
Low iodine diet[i]				X	X					X[a]			5.1.1
Thyrogen injection				Xx2 (Day 29 and 30)						Xx2[a]			5.5.4.1
^{131}I (RAI) treatment single 100 mCi dose					X								5.5.4.2
^{131}I 5 diagnostic dose for WBS single 5 mCi dose										X[a]			5.5.4.2
^{131}I nuclear medicine WBS scan						X[j]				X[a]			6.4.4.2
Re-treatment assessment[k]									X	X		X	5.9
Blood sample for TSH									X	X			6.4.3.3
Blood sample for suppressed Tg									X[n]	X			6.4.3.1
Blood sample for TgAb	X								X	X			6.4.3.4

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post RAI (visit 5)	9 months post RAI (visit 5)	18 months post RAI (visit 5)	27 months post RAI (visit 5)	3 years post RAI (visit 5)	
Visit Window	N/A	N/A	±1wk	+1wk	+1wk	+1wk	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Blood sample for rhTSH-stimulated Tg										X[a]			6.4.3.2
Neck ultrasound	X[l]								X	X			6.4.4.1
Neck MRI	X[l]									X[a]			6.4.4.3
Chest CT without contrast	X[l]									X[a]			6.4.4.4
Final follow-up assessment of clinical status												X	6.4.8
Biopsy/FNA for disease confirmation									X[m]	X[m]			6.4.4.5
Tumour biopsy on progression (optional)	Optional sample on disease progression (for example, if the patient is re-treated for persistent or recurrent thyroid cancer, or has further surgery). Note that both a plasma and serum sample for exploratory analysis should also be taken on disease progression.												6.10.3 6.10.2

Reason for Amendment:

Amended to clarify visit window for RAI treatment dose administration, visit 4 and visit 6.

Section of protocol affected:

4.1 Inclusion criteria:

Previous text:

14. Adequate organ function as defined by:

(a) ANC ≥ 1.5x109/L (1500 per mm3)

(b) Platelets ≥ 100 x 109/L (100,000 per mm3)

(c) Hemoglobin ≥ 9 g/dL

(d) ALT/SGOT and AST/SGPT < 2.5 X upper limit of normal (ULN).

(e) Bilirubin ≤ 1.5 X ULN (with the exception that patients with elevated unconjugated bilirubin due to a pre-existing diagnosis of Gilbert's syndrome are eligible for the study)

(f) Serum creatinine clearance > 50mL/min by either Cockcroft-Gault formula (see Appendix E) or 24hr urine collection analysis.

Revised text:

14. Adequate organ function as defined by following lab values before randomization:

(a) ANC ≥ 1.5x109/L (1500 per mm3)

(b) Platelets ≥ 100 x 109/L (100,000 per mm3)

(c) Hemoglobin ≥ 9 g/dL

(d) ALT/SGOT and AST/SGPT < 2.5 X upper limit of normal (ULN).

(e) Bilirubin ≤ 1.5 X ULN (with the exception that patients with elevated unconjugated bilirubin due to a pre-existing diagnosis of Gilbert's syndrome are eligible for the study)

(f) Serum creatinine clearance > 50mL/min by either Cockcroft-Gault formula (see Appendix E) or 24hr urine collection analysis.

Retest is allowed within screening period.

Reason for Amendment:

Amended to specify time frame for assessment of adequate organ function criterion.

Section of protocol affected:

4.2 Exclusion criteria:

Previous text:

4. Previous treatment with ^{131}I (RAI) or external beam radiation therapy (EBRT) at any time in the past.

10. Patients with clinically significant cardiovascular disease as defined by the following:

    (a) Uncontrolled hypertension (BP ≥150/95 despite optimal therapy)

22. Previous enrolment or treatment in the present study.

Revised text:

4. Previous treatment with ^{131}I (RAI) at any time in the past or external beam radiation therapy (EBRT) within 6 months before randomization.

10. Patients with clinically significant cardiovascular disease as defined by the following:

    (a) Uncontrolled hypertension (at randomization: BP ≥150/95 despite optimal therapy)

22. Previous treatment in the present study.

Reason for Amendment:

Amended to allow patient's rescreening, enrolment of patients without EBRT therapy in 6 months before randomization and specify time frame for assessment of blood pressure and adequate organ function criterion.

Section of protocol affected:

5.1.2 Other study restrictions

Previous text:

5. Selumetinib capsules contain D-α- Tocopheryl polyethylene glycol 1000 succinate (TPGS, a water-soluble form of vitamin E) as an excipient. Patients should not therefore take vitamin E supplements or multivitamin supplements which provide a total daily dose in excess of 100% of the recommended daily allowance for vitamin E. The maximum dose of vitamin E patients may receive from selumetinib is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided. High doses of vitamin E

have been reported to potentiate the anticoagulant activity of coumadins such as warfarin. Patients who are taking coumadin anticoagulants should increase the frequency of assessment of anticoagulation, such as INR measurements, upon initiation of dosing with study treatment.

Revised text:

5. Selumetinib/placebo capsules contain vitamin E in form of D-α-tocopheryl polyethlen glycol 1000 succinate (TPGS), a water-soluble form of vitamin E which acts as a formulation excipient. The maximum daily dose of vitamin E that a study subject may receive from selumetinib /placebo is approximately 261.6 mg/day. Therefore

    - Patients should not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interrupt blood coagulation processes.

    - Selumetininb/placebo should be administered with caution in patients who are also receiving concomitant coumarin anticoagulant medications, e.g. warfarin. These patients should have their INR monitored/anticoagulant assessments conducted more frequently and the dose of anticoagulant should be adjusted accordingly.

Reason for Amendment:

The new calculation considers that the selumetinib/placebo capsules contain vitamin E in the form of D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of vitamin E. Intake of selumetinib/placebo capsules may therefore lead to a higher release of the active vitamin E.

Section of protocol affected:

5.2 Patient enrolment, randomisation and initiation of investigational product

Previous text:

The Principal Investigator or delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 4.1 and 4.2

3. Call IVRS/IWRS to assign the eligible patient a unique enrolment number (beginning with ‘E#’), and randomisation code (subject number). Randomisation codes will start at 001 and go up.

Randomisation codes will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for randomisation.

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused.

If a patient withdraws from the study, after they have been enrolled or have received study treatment then they cannot re-enter the study.

Revised text:

The Principal Investigator or delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 4.1 and 4.2

3. Call IVRS/IWRS to assign the eligible patient a unique enrolment number (beginning with 'E#'), and randomisation code (subject number). Randomisation codes will start at 001 and go up.

Randomisation codes will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for randomisation.

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused.

If a patient withdraws from the study, after they have received study treatment then they cannot re-enter the study

If a patient is re-screened, a new E-code will always be assigned.

Reason for Amendment:

To allow patient's rescreening.

Section of protocol affected:

5.3 Procedures for handling patients incorrectly enrolled, randomised or initiated on investigational product

Previous text:

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are incorrectly enrolled but are not yet randomised or initiated on treatment should be withdrawn from the study.

Where patients that do not meet the inclusion and/or exclusion criteria, are enrolled in error, or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the AstraZeneca Physician immediately.

The AstraZeneca Physician must ensure all such contacts are appropriately documented.

Revised text:

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the study criteria are enrolled in error, incorrectly randomised, a discussion must occur between AstraZeneca Study Physician and the Investigator regarding the patient's safety and well-being and whether to continue or discontinue the patient from the study treatment. The AstraZeneca Study Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their therapy stopped, then followed up for the primary endpoint assessments and safety. Those patient randomised in error should remain in the study and be followed for the primary endpoint assessments and safety where possible.

Reason for Amendment

Amended to provide clear instruction on handling patients that are incorrectly enrolled, randomised or initiated on investigational product.

Section of protocol affected:

5.5.3.1 Selumetinib dose reduction or interruption

Previous text:

It is essential that patients remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator until the patient has been on study treatment for a minimum of 7 consecutive days (as long as the total duration of study treatment does not exceed 43 days, this allows the planned RAI to be postponed by up to 1 week if absolutely necessary).

For all adverse events reported in this study that are considered at least partly causal to administration of selumetinib, the following dose modification guidance should be applied.

Study treatment with selumetinib/placebo should be temporarily interrupted if one of the following AEs are observed (and considered causal to study treatment), **despite optimal supportive care** (ie, supportive treatment may be given prior to withholding study treatment):

- Any intolerable adverse event regardless of Grade

- Any adverse events ≥ CTCAE Grade 3

On improvement of the adverse event to Grade 1 (Grade 2 for rash) or baseline, study treatment may be restarted at the original dose or may be reduced at the discretion of the investigator. One dose reduction of study treatment to 50 mg twice daily is permitted before permanent discontinuation.

- If a further episode of the same AE subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the AE.
- If a different AE subsequently requires dose interruption, selumetinib may be restarted at the same dose or at the next dose level down on improvement of the AE.
- Selumetinib should not be re-escalated to an earlier dose level on improvement of an AE.
- The schedule of assessments described in Table 3 should continue relative to Day 1 in the event of selumetinib dose interruption or reduction.

Therefore, the dose reduction/adjustment algorithm in the study allows for 2 steps only:

75 mg twice daily (initial dose)

↓

50 mg twice daily

↓

permanent discontinuation

All dose delays, reductions and adjustments will be recorded in the appropriate electronic Case Report Form (eCRF).

The guidance above should also be followed for dose interruptions or reductions for adverse events of rashes or diarrhoea. Guidance for interruption or reduction of treatment with selumetinib may be considered for particular events, as indicated in the algorithms provided as a separate study aid in the "Guidance for Management of Specific Adverse Events in Studies of Selumetinib" (refer to Section 5.5.3.2).

Revised text:

Patients should remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be postponed up to 1 week at the discretion of the

Investigator to allow the patient receive study treatment for a minimum of 7 consecutive days (as long as the total duration of study treatment does not exceed 43 days)

For all adverse events reported in this study that are considered at least partly causal to administration of selumetinib, the following dose modification guidance should be applied.

Study treatment with selumetinib/placebo should be temporarily interrupted if one of the following AEs are observed (and considered causal to study treatment), **despite optimal** s**upportive care** (ie, supportive treatment may be given prior to withholding study treatment):

- Any intolerable adverse event regardless of Grade
- Any adverse events ≥ CTCAE Grade 3

On improvement of the adverse event to Grade 1 (Grade 2 for rash) or baseline, study treatment may be restarted at the original dose or may be reduced at the discretion of the investigator. One dose reduction of study treatment to 50 mg twice daily is permitted before permanent discontinuation.

- If a further episode of the same AE subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the AE.
- If a different AE subsequently requires dose interruption, selumetinib may be restarted at the same dose or at the next dose level down on improvement of the AE.
- Selumetinib should not be re-escalated to an earlier dose level on improvement of an AE.
- The schedule of assessments described in Table 3 should continue relative to Day 1 in the event of selumetinib dose interruption or reduction.

Therefore, the dose reduction/adjustment algorithm in the study allows for 2 steps only:

75 mg twice daily (initial dose)

↓

50 mg twice daily

↓

permanent discontinuation

If a patient suspends study treatment (selumetinib or placebo) for more than 14 days they are no longer eligible to re-start the study treatment.

All dose delays, reductions and adjustments will be recorded in the appropriate electronic Case Report Form (eCRF).

The guidance above should also be followed for dose interruptions or reductions for adverse events of rashes or diarrhoea. Guidance for interruption or reduction of treatment with selumetinib may be considered for particular events, as indicated in the algorithms provided as a separate study aid in the "Guidance for Management of Specific Adverse Events in Studies of Selumetinib" (refer to Section 5.5.3.2).

Reason for Amendment:

Amended to provide clear instruction on allowed IP interruption and treatment plan.

Section of protocol affected:

5.6 Concomitant medications

Previous text:

- The maximum dose of vitamin E patients may receive from selumetinib is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided in patients receiving the capsule formulation.

Revised text:

- The maximum dose of vitamin E patients may receive from selumetinib is approximately 261.6 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided in patients receiving the capsule formulation.

Reason for Amendment:

The new calculation considers that the selumetinib/placebo capsules contain vitamin E in the form of D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of vitamin E. Intake of selumetinib/placebo capsules may therefore lead to a higher release of the active vitamin E.

Section of protocol affected:

5.8.1 Procedures for premature discontinuation of a patient from investigational product

Previous text:

A patient that decides to prematurely discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.5.3 and 6.5.4), and all study drugs should be returned by the patient. In this situation, a treatment

discontinuation visit will be conducted as soon as possible after the patient received the last dose of study drug (selumetinb/placebo). A single 12-lead ECG is also required at premature discontinuation of treatment.

If a patient is withdrawn from the study (ie, withdraws consent for follow-up procedures), see Section 5.10.

Collection of all AEs/SAEs will continue until 30 days after the last dose of study drug (selumetinib/placebo) for prematurely withdrawn patients. As long as the patient does not withdraw consent, follow up in this study will continue as planned.

Any patient with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (±7days) after discontinuation.

Revised text:

A patient that decides to prematurely discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.5.3 and 6.5.4), and all study drugs should be returned by the patient. In this situation, a treatment discontinuation visit will be conducted as soon as possible after the patient received the last dose of study drug (selumetinb/placebo). A single 12-lead ECG, physical examination, vital signs measurement, clinical chemistry, haematology is also required at premature discontinuation of treatment. As long as the patient does not withdraw consent, study visits will be continued according to study plan. RAI treatment will be administered as soon as possible after last dose of investigational product and WBS will be performed 3-10 days following the RAI dose.

RAI treatment must be preceded by 0.9 mg intra-muscular injection of thyrogen administered 2 days immediately prior to RAI.

30 days post treatment visit will be conducted 30 days (+/- 2days) after last dose of investigational product or RAI (whatever latest). The schedule of follow – up assessments described in Table 3 should continue relative to RAI treatment in the event of selumetinib premature discontinuation.

A patient that decides to prematurely discontinue investigational product and has not received RAI treatment should continue study visits according to study plan. The schedule of follow – up assessments described in Table 3 should continue relative to planned date of RAI treatment.

If a patient is withdrawn from the study (ie, withdraws consent for follow-up procedures), see Section 5.10.

Any patient with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (±7days) after discontinuation.

Reason for Amendment:

To provide clear and detailed instruction on handling IP discontinued patients.

Section of protocol affected:

6.4.4.2 WBS definition of structural DTC

Previous text:

The WBS evaluation will be made by blinded, independent central review.

If the central review determines no visible 131I uptake then the WBS for that patient will be considered normal/negative (no disease). Areas considered to be anatomically normal (for example uptake in the salivary glands, stomach, gastrointestinal, urinary tract and bladder) will not be considered disease.

If the central review determines there is a low level of visible uptake in the thyroid bed:

- Uptake must be < 0.1% to be considered normal/negative (no disease).

- If uptake in the thyroid bed region is ≥ 0.1%, the patient will be deemed not to be in remission due to the presence of iodine-avid DTC.

The % uptake in the thyroid bed (using the region-of-interest method drawn over the thyroid bed) will be measured and calculated by the local Investigator site and entered into the eCRF, to be made available to the central reviewer.

If an abnormality identified by US is subsequently shown to be RAI avid on WBS, the WBS data takes precedent over a negative biopsy/FNA

Revised text:

The WBS evaluation will be made by blinded, independent central review.

If the central review determines no visible 131I uptake then the WBS for that patient will be considered normal/negative (no disease). Areas considered to be anatomically normal (for example uptake in the salivary glands, stomach, gastrointestinal, urinary tract and bladder) will not be considered disease.

If the central review determines there is a low level of visible uptake in the thyroid bed:

- Uptake must be < 0.1% to be considered normal/negative (no disease).

- If uptake in the thyroid bed region is ≥ 0.1%, the patient will be deemed not to be in remission due to the presence of iodine-avid DTC.

The % uptake in the thyroid bed will be assessed by the local Investigator site according to the local clinical practice and entered into the eCRF to be made available to the central reviewer.

If an abnormality identified by US is subsequently shown to be RAI avid on WBS, the WBS data takes precedent over a negative biopsy/FNA

Reason for Amendment:

This change has been made in order to reflect the current situation in the clinical practice and allows the study to be more breadth in terms of used existing clinical practice approaches.

Section of protocol affected:

6.5.5 Laboratory safety assessments

Previous text:

Table 7 Laboratory safety assessments

Clinical chemistry	Haematology	Urinalysis [a]
s-Albumin	Erythrocyte count	u-Albumin
s-ALT	Haemoglobin	u-Creatinine
s-AST	Platelet count	
s-ALP	Leucocyte cell count	
s-Total Calcium	Leucocyte differential count (absolute count):	
s-Creatinine	Neutrophils	
s-Gamma glutamyl transferase (γGT)	Eosinophils	
s-Glucose	Basophils	
s-Magnesium	Lymphocytes	
s-Phosphate	Monocytes	
s-Potassium		
s-Sodium		
s-Total protein		
s-Total bilirubin		
s-Urea nitrogen		
s-Creatine kinase		

[a] A single-spot urine specimen will be collected on the day of scheduled visit, at sites where the local laboratory is able to determine the concentration of urine albumin and urine creatinine from a single-spot urine specimen. Investigational sites unable to report these parameters will perform routine urinalysis according to the local standard of care.
s serum
u urine

Revised text:

Table 7 Laboratory safety assessments

Clinical chemistry	Haematology	Urinalysis [a]
s, p-Albumin	Erythrocyte count	u-Albumin
s, p-ALT	Haemoglobin	u-Creatinine
s, p-AST	Platelet count	
s, p-ALP	Leucocyte cell count	
s, p-Total Calcium	Leucocyte differential count (absolute count or percentage):	
s, p-Creatinine	Neutrophils	
s, p-Gamma glutamyl transferase (γGT)	Eosinophils	
s, p-Glucose	Basophils	
s, p-Magnesium	Lymphocytes	
s, p-Phosphate	Monocytes	
s, p-Potassium		
s, p-Sodium		
s, p-Total protein		
s, p-Total bilirubin		
s, p-Urea nitrogen		
s, p-Creatine kinase		

[a] A single-spot urine specimen will be collected on the day of scheduled visit, at sites where the local laboratory is able to determine the concentration of urine albumin and urine creatinine from a single-spot urine specimen. Investigational sites unable to report these parameters will perform routine urinalysis according to the local standard of care.
s, p serum, plasma
u urine

Reason for Amendment:

Amended to allow local laboratories to perform clinical chemistry assessments in plasma and provide leucoytes results in percentage.

Section of protocol affected:

13.1 Medical emergencies and AstraZeneca contacts

Previous text:

Name	Role in the study	Address & telephone number
Dr Jeffrey Skolnik	AstraZeneca Physician responsible for the protocol at central R&D site	1800 Concord Pike PO Box 15437 Wilmington DE 19850-5437 USA +1 302 885 7686 (desk) +1 302 897 8379 (cell) Fax +1 302 886 2622 Jeffrey.Skolnik@astrazeneca.com
Dr Marta Bucko-Justyna	AstraZeneca Study Delivery Team Leader responsible for the protocol at central R&D site	AstraZeneca R&D | Poland Clinical Operational Hub Postepu 18, Warsaw 02-676, Poland +48 22 541 55 96 (desk) +48 600 429 094 (cell) Fax: +48 22 541 55 10 Marta.Bucko-Justyna@astrazeneca.com
24-hour emergency cover at central R&D site.	24-hour emergency cover at central R&D site.	Alderley Park Macclesfield, Cheshire, SK10 4TG UK Contact AZ UK Lt Switchboard Tel: + 44 1625 582828

Revised text:

Name	Role in the study	Address & telephone number
MD, PhD Raisa Kurliandskaya	AstraZeneca Physician responsible for the protocol at central R&D site	AstraZeneca R&D | Poland Clinical Operational Hub Postepu 18, Warsaw 02-676, Poland +48 22 5415620 (desk) +48 696 950 158 (cell) Fax +48 22 541 55 10 Raisa.Kurliandskaya@astrazeneca.com
Linda Fan	AstraZeneca Study Delivery Team Leader responsible for the protocol at central R&D site	AstraZeneca R&D | Clinical Development Lane 898, Halei Road, Shanghai, China 201203 +86 21 6030 2288 ext 2725 (desk) +86 186-2167-6071 (cell) +86 21 50278559 (fax) Linda.Fan@astrazeneca.com

24-hour emergency cover at central R&D site.	24-hour emergency cover at central R&D site.	Alderley Park Macclesfield, Cheshire, SK10 4TG UK Contact AZ UK Lt Switchboard Tel:+ 44 1625 582828

Reason for Amendment:

Personnel changes in the Study Team.

Section of protocol affected:

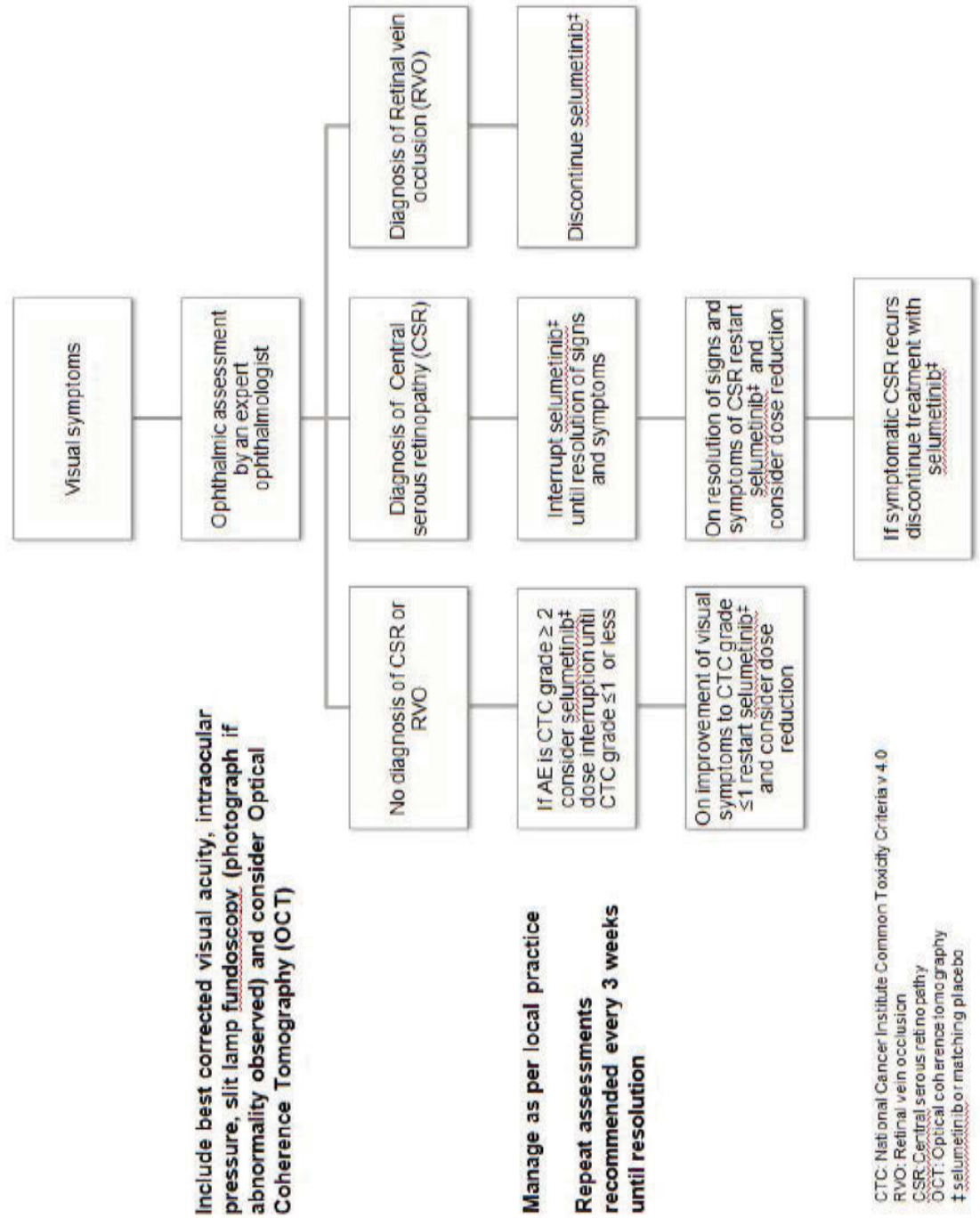
Appendix G

Guidance for Management of Adverse Events in Studies of Selumetinib

2. GUIDANCE FOR MANAGEMENT OF PATIENTS WITH VISUAL SYMPTOMS

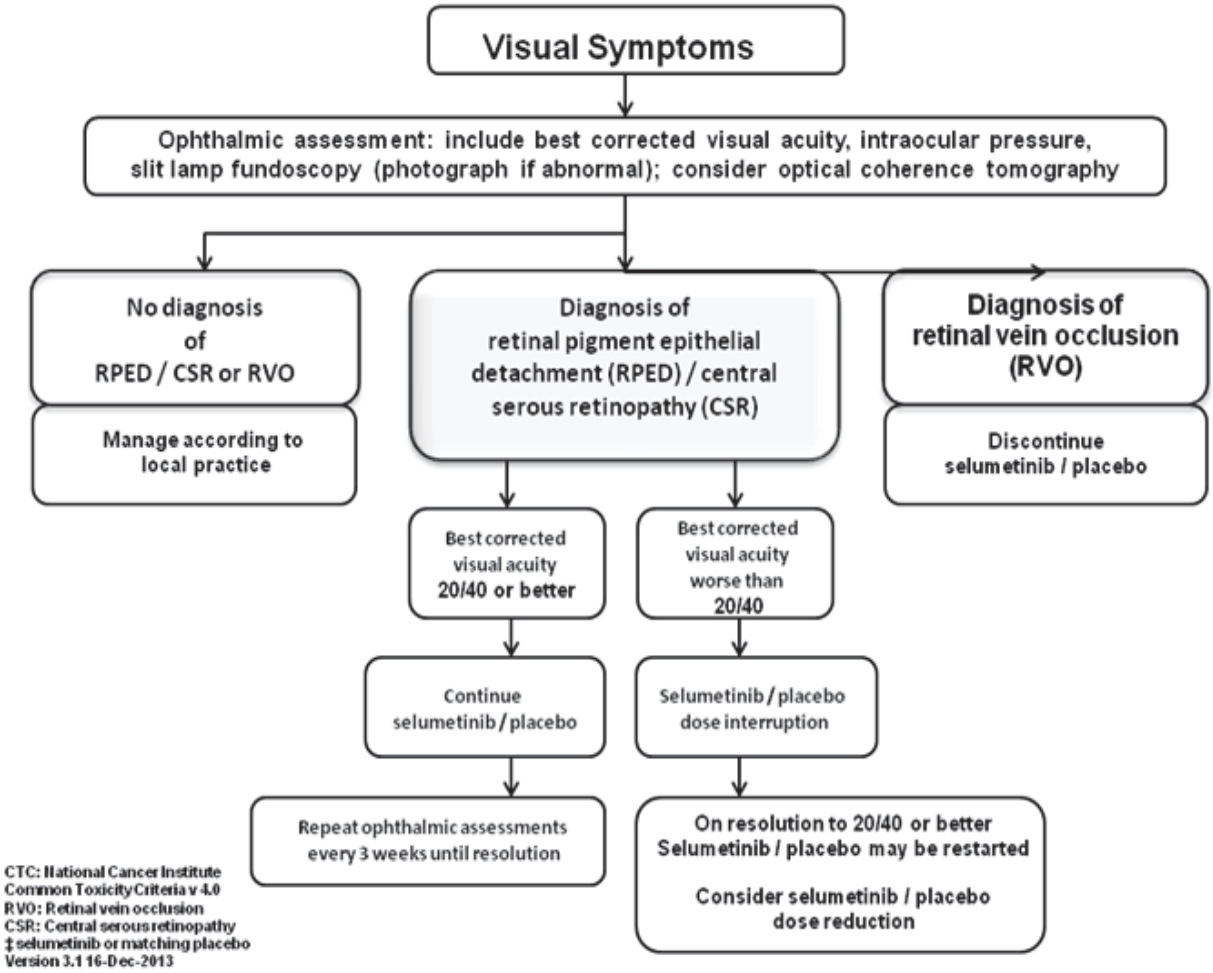
Previous text:

2. GUIDANCE FOR MANAGEMENT OF PATIENTS WITH VISUAL SYMPTOMS


Visual symptoms
Ophthalmic assessment by an expert ophthalmologist
Include best corrected visual acuity, intraocular pressure, slit lamp fundoscopy (photograph if abnormality observed) and consider Optical Coherence Tomography (OCT)
Diagnosis of Retinal vein occlusion (RVO)
Discontinue selumetinib‡
Diagnosis of Central serous retinopathy (CSR)
Interrupt selumetinib‡ until resolution of signs and symptoms
On resolution of signs and symptoms of CSR restart selumetinib‡ and consider dose reduction
If symptomatic CSR recurs discontinue treatment with selumetinib‡
No diagnosis of CSR or RVO
If AE is CTC grade ≥ 2 consider selumetinib‡ dose interruption until CTC grade ≤1 or less
On improvement of visual symptoms to CTC grade ≤1 restart selumetinib‡ and consider dose reduction
Manage as per local practice
Repeat assessments recommended every 3 weeks until resolution
CTC: National Cancer Institute Common Toxicity Criteria v 4.0
RVO: Retinal vein occlusion
CSR: Central serous retinopathy
OCT: Optical coherence tomography
‡ selumetinib or matching placebo
Version: Final 2.0 28 Sept 2012

Revised text:

2. GUIDANCE FOR MANAGEMENT OF VISUAL SYMPTOMS OR ABNORMAL FINDINGS



Reason for Amendment:

Amended to include Retinal Pigment Epithelial Detachment (RPED)

Section of protocol affected:

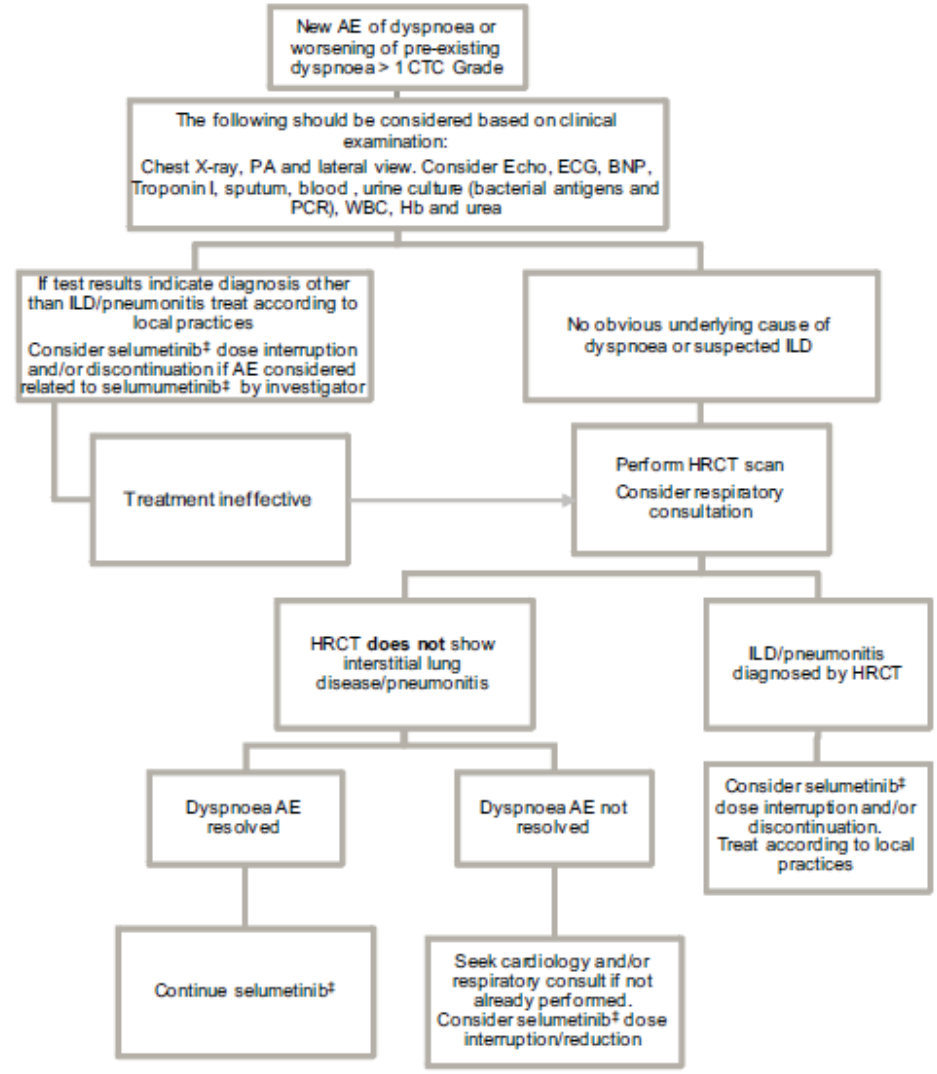
Appendix G

Guidance for Management of Adverse Events in Studies of Selumutinib

4. RECOMMENDATIONS FOR INVESTIGATIONS OF PATIENTS WITH NEW OR WORSENING DYSPNEA

Previous text:

4. RECOMMENDATIONS FOR INVESTIGATIONS OF PATIENTS WITH NEW OR WORSENING DYSPNEA

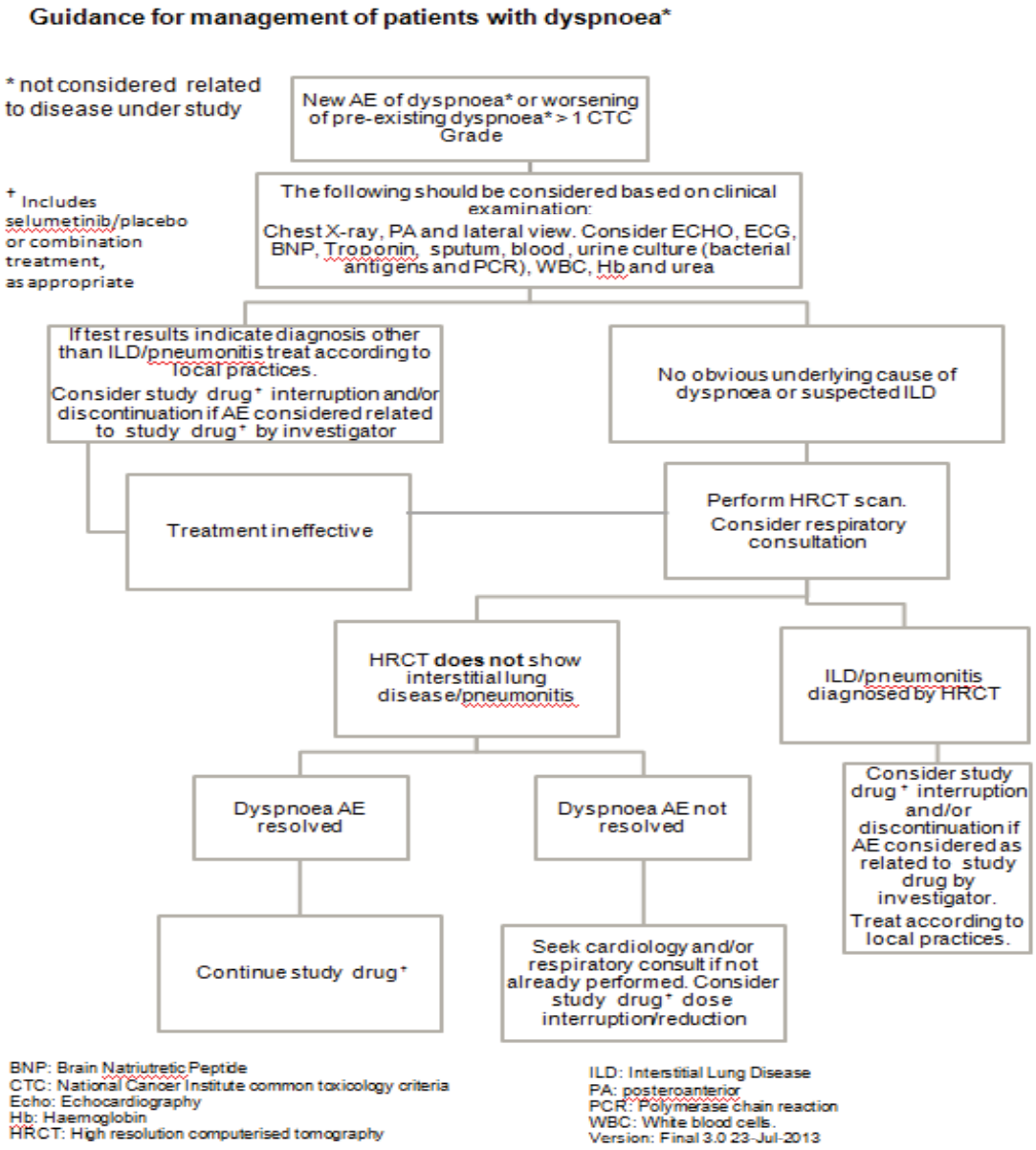


BNP: Brain Natriuretic Peptide
CTC: National Cancer Institute common toxicology criteria
Echo: Echocardiography
Hb: Haemoglobin
HRCT: High resolution computerised tomography
‡ selumetinib or matching placebo

ILD: Interstitial Lung Disease
PA: posteroanterior
PCR: Polymerase chain reaction
WBC: White blood cells
Document Version: Final 2.0 28 Sept 2012

Revised text:

4. GUIDANCE FOR MANAGEMENT OF PATIENTS WITH DYSPNOEA



Reason for Amendment:

Dyspnoea is an expected event of selumetinib. However dyspnoea could also be the symptom of underlying serious lung conditions, e.g. Interstitial Lung Disease (ILD) events. Although no causal relationship has been established between selumetinib and such ILD events, ILD is considered as an important potential risk for selumetinib. Therefore, the safety management algorithm for dyspnoea allows investigators to diagnose and treat ILD events as early as possible, should they occur.

Persons who initiated the Amendment:

PPD, Medical Science Director

PPD, Director Clinical Development

PPD, Clinical Development Manager

AstraZeneca

Clinical Study Protocol Amendment No 3 Appendix A	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	01 July 2014
Protocol Dated	20 January 2013

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study amendment

AstraZeneca Research and Development site representative	PPD	PPD

ASTRAZENECA SIGNATURE(S)

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AstraZeneca Research and Development site representative

PPD

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AstraZeneca Research and Development site representative	PPD	PPD

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

Signature: PPD PPD

AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	2
Date	3rd April 2013

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative PPD PPD

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
1	3rd April 2013		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

International Co-ordinating Investigator

PPD

Study centre(s) and number of patients planned

Approximately 228 patients with newly diagnosed differentiated thyroid cancer at high risk of primary treatment failure will be recruited from approximately 50 sites in Europe, South and/or North America.

Objectives

Primary objectives

To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in the overall study population. Complete remission is defined in Section 6.4.1.

To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

Secondary objectives

To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the overall study population. Clinical remission is defined in Section 6.4.6.

To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

Exploratory objectives

To explore subsequent thyroid cancer therapy given to patients who receive selumetinib with RAI, or placebo with RAI.

To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters.

To collect tumour, plasma and serum samples for potential future research on biomarkers relevant to DTC and response and resistance to study treatments.

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib or RAI and/or susceptibility to cancer.

Study design

This is a double-blind, randomised, placebo-controlled study comparing the efficacy of a short course (approximately 5 weeks) of selumetinib (75 mg, orally twice daily) with adjuvant RAI, to placebo with RAI.

Following recovery from surgery (1 or 2-stage total thyroidectomy), and screening to determine study eligibility, patients will be randomised and will take their assigned study treatment (selumetinib or placebo) twice daily for a period of approximately 5 weeks. Study treatment will begin approximately 4 weeks prior to the planned day of single dose RAI therapy, and will be continuous until 5 days following RAI therapy. Patients will be required to adhere to a standardised low iodine diet prior to their RAI therapy. For each of the 2 days immediately prior to their planned RAI therapy, patients will receive a 0.9 mg intramuscular (IM) recombinant human TSH injection (rhTSH, Thyrogen), in order to stimulate iodide uptake (patients or clinicians choosing to prepare for RAI ablation by withdrawal of thyroid hormone treatment will be ineligible for this study). Following the 2 consecutive days of rhTSH injections, patients will receive their planned RAI therapy as a fixed single 100 mCi (3.7 GBq) dose of ^{131}I the immediate next day. Study treatment will be taken as normal on the day of RAI therapy, and will be discontinued 5 days following the patient's RAI therapy.

Following RAI therapy, each patient will be followed up for a period of 18 months until the primary endpoint assessment of complete remission. The biochemical analysis contributing to the 18 month primary endpoint of complete remission will be performed by standardised central methodology, and the radiological imaging for structural disease at the primary endpoint will be subject to a blinded independent central review. Additional thyroid cancer therapy (eg, surgery or RAI treatment) must only be given during the 18 month primary endpoint follow up period according to the pre-specified study re-treatment criteria (refer to Section 5.9). Patients who do receive re-treatment in the 18 months following their initial RAI

therapy, will not have any 18 month primary endpoint assessments performed; they will remain in the study and enter standard of care follow up according to local practice.

Following the primary endpoint assessments (or re-treatment), all randomised patients will be further followed-up at 3 years after their initial RAI treatment, in order to further assess both the clinical status of patients, and the safety profile of selumetinib and RAI beyond the primary analysis (refer to Section 6.4.8).

Target patient population

Patients with histologically or cytologically confirmed follicular cell derived differentiated thyroid cancer (including papillary thyroid cancer and all variants, follicular thyroid cancer and all variants, and poorly differentiated thyroid cancer), who are determined to be at high risk of primary treatment failure, as defined by any one of the following staging categories post-surgery:

- Primary tumour greater than 4 cm
- Primary tumour of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)
- N1a or N1b disease with at least 1 lymph node ≥ 1 cm
- N1a or N1b disease involving 5 or more lymph nodes (of any size)

Patients with known distant metastatic disease will be excluded from this study.

Investigational product, dosage and mode of administration

Selumetinib Hyd-Sulfate (75 mg) will be administered orally twice daily as capsules (blue). The Hyd Sulfate formulation will be used in this study, and unless otherwise specified is the formulation referenced throughout this document.

Comparator, dosage and mode of administration

Placebo (to match selumetinib) will be administered orally twice daily.

Duration of treatment

The duration of study treatment (selumetinib/placebo) will be approximately 5 weeks in total (Day 36 will typically be the last day of study treatment, but this may be extended to a maximum of 43 days to allow the planned RAI to be postponed by up to 1 week if absolutely necessary).

Outcome variable(s):

Efficacy

The primary outcome variable for this study is the rate of complete remission at 18 months post-RAI treatment. Patients will be defined to be in complete remission if all of the following criteria can be demonstrated:

1. Serum thyroglobulin (Tg) levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer[a] by neck US, as assessed by investigator site review.

3. No confirmed radiological evidence of thyroid cancer[a], as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

[a]Confirmation of evidence of structural DTC will be either histopathological (from a biopsy/FNA; as criterion 4 above), or RAI-avid disease (refer to Section 6.4.4.2). In this disease setting, structural abnormalities that are not RAI-avid and do not have confirmed histopathology consistent with DTC (ie are not biopsy proven) are considered benign in the absence of biochemical DTC.

A secondary outcome variable will be the rate of clinical remission at 18 months post-RAI treatment, where clinical remission is defined on the basis of Tg, US and WBS assessments alone, without the additional radiological data.

Safety

AEs/SAEs, physical examination results, lab values, ECG, vital signs.

All randomised patients will be followed for safety monitoring for 3 years following their RAI adjuvant treatment, in order to monitor for selumetinib and RAI-associated side effects.

PK

Where sample collection and PK analysis allow, derived PK parameters for selumetinib and N-desmethyl selumetinib will be produced which may include, but not be restricted to, C_{max} and AUC. Exploratory variables will be analysed outside the clinical study report (CSR).

Statistical methods

Approximately 228 patients will be randomised in a 2:1 ratio in this study. The primary analysis will be performed when patients have been followed for 18 months following their RAI treatment. There will be two primary analysis populations: the first will comprise all randomised patients (overall population); the second will comprise the sub-group of randomised patients with tumours known to be mutation positive for *BRAF* or *NRAS*. The primary endpoint of complete remission rate will be analyzed using a logistic regression model with covariates histology status (papillary, follicular, poorly differentiated), mutation status (overall population only, *BRAF/NRAS* positive, *BRAF/NRAS* negative) and age, provided there are enough data points for a meaningful analysis. There will be two primary analysis populations: the first will comprise all randomised patients; the second will comprise the sub-group of randomised patients with tumours known to be mutation positive for *BRAF* or *NRAS*. To control the type I error rate for the study and account for the correlation between the two primary endpoints, the Dunnett and Tamhane step-up procedure will be used. The correlation between the primary endpoint comparisons will be calculated as $\sqrt{w}$, where w is the proportion of the overall population who are in the mutation positive sub-group. The associated significance level for declaring statistical significance in the mutation positive sub-group adjusting for this correlation to maintain an overall 5% type I error rate whilst assigning 4% to the overall population will then be derived.

Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumetinib-containing arms, respectively, the study will have 80% power to demonstrate a statistically significant difference at the 4% (2-sided) significance level.

Assuming the true complete remission rates in the mutation-positive sub-group are 30% and 62% for the placebo and selumetinib-containing arms, respectively, the study will have 80% power to demonstrate a statistically significant difference at the 1% (2-sided) significance level.

All secondary endpoints will be analysed at the time of the primary analysis. Exploratory biomarker analysis may be analysed after the time of the primary analysis and reported separately to the CSR (apart from the somatic genetic data required for analysis of the second primary endpoint).

All randomised patients will continue to be followed until the final study visit (3 years after their RAI treatment). At this time, data on clinical status, incidence of re-treatment and long-term safety will be summarised.

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LIST OF TABLES

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LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
^{124}I	Iodine-124
^{131}I	Iodine-131 (radioactive iodine; RAI)
AE	Adverse event (see definition in Section 6.5.1)
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatise
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
AUC	Area under the plasma concentration-time curve from zero to infinity
BD	Twice daily (dosing)
bid	*bis in die* – twice a day
BNP	B-type natriuretic peptide
BP	Blood pressure
Bpm	Beats per minute
BRAF	v-raf murine sarcoma viral oncogene homolog B1
cm	centimetres
C_{max}	Maximum plasma concentration
CRF	Case report form (electronic/paper)
CR	Clinical remission
CR	Complete remission
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
DAE	Discontinuation of investigational product due to adverse event
DNA	Deoxyribonucleic acid
DTC	Differentiated thyroid cancer
D-TC-FCO	Differentiated thyroid carcinoma of follicular cell origin

Abbreviation or special term	Explanation
DUS	Disease under study
EBRT	External beam radiation therapy
EC	Ethics committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ERK	Extracellular signal-regulated kinases
ETA	European Thyroid Association
FDG-PET	2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography
FNA	Fine needle aspiration
FSH	Follicle stimulating hormone
FTC	Follicular thyroid cancer
G1	Gap 1 phase of the cell cycle
GCP	Good clinical practice
g/dL	grams per decilitre
GMP	Good manufacturing practice
hr	hour
I	Iodine
IATA	International Air Transport Association
IB	Investigator brochure
ICH	International Conference on Harmonisation
ICH M3	The European Medicines Agency's International Conference on Harmonisation Topic M3 – "Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals"
IM	Intramuscular
INR	International normalised ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational product
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravascular
IVRS	Interactive voice response system

Abbreviation or special term	Explanation
IWRS	Interactive web response system
kg	kilograms
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LH	Luteinizing hormone
LIMS	Laboratory information management system
LLOQ	Lower limit of quantification
LSLV	Last patient last visit
LT4	Synthetic levothyroxine
LV	Left ventricular
LVEF	Left ventricular ejection fraction
M0, M1, Mx	Distant metastasis status (TNM cancer staging system)
MAPK	Mitogen-activated protein kinase
mCi	millicuries
MedDRA	Medical dictionary for regulatory activities
MEK	MAPK/ERK kinase
MI	Myocardial infarction
µg/L	micrograms per litre
µm	micrometers
mIU/L	milli-International units per litre
mg	milligrams
mg/day	milligrams per day
mL	millilitres
mL/min	millilitres per minute
mm	millimetres
mm^3	cubic millimetres
ms	milliseconds
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
N0, N1, Nx etc	Lymph node disease stage (TNM cancer staging system)
N/A	Not applicable
ng/mL	nanograms per milliliter

Abbreviation or special term	Explanation
NIS	Sodium iodide symporter
NOEL	No observed effect level
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase, receptor, type 1
NYHA	New York Heart Association
OAE	Other significant adverse event (see definition in Section 6.5)
PDTC	Poorly differentiated thyroid carcinomas
PET	Positron emission tomography
PFS	Progression-free survival
PGx	Pharmacogenetic research
PI	Principal investigator
PK	Pharmacokinetics
PRO	Patient reported outcomes
PTC	Papillary thyroid cancer
RAI	Radioactive iodine (^{131}I)
RET	Ret proto-oncogene
Rb	Retinoblastoma protein
RECIST	Response Evaluation Criteria In Solid Tumours
rhTSH	Recombinant human thyroid stimulating hormone
SAE	Serious adverse event (see definition in Section 6.5.2).
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBE-CD	Sulphobutylether β-cyclodextrin
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standard uptake value
T0, T1, Tx etc	Primary tumour disease stage (TNM cancer staging system)
T4	Free thyroxine
Tg	Thyroglobulin
TgAb	Thyroglobulin antibody
TNM	Tumour, nodes, metastasis cancer staging system
TPGS	D-α tocopheryl polyethylene glycol 1000 succinate

Abbreviation or special term	Explanation
TPO	Thyroid peroxidase
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	Ultrasound
WBDC	Web based data capture
WBS	Whole body scintigraphy (also whole body scan)
WHO	World Health Organisation
Wk	Week

1. INTRODUCTION

1.1 Background

1.1.1 Thyroid Cancer

There are approximately 56,500 new cases of thyroid cancer diagnosed in the USA per year, and approximately 34,000 new cases diagnosed in Europe per year. Thyroid cancers are classified according to their histopathological characteristics into 4 main variants: papillary thyroid cancer (PTC, the most common), follicular thyroid cancer, medullary thyroid cancer and anaplastic (undifferentiated) thyroid cancer. The papillary and follicular types together can be classified as differentiated thyroid cancer (DTC), and make up approximately 95% of thyroid cancers. All DTC (including PTC) begins in the follicular cells of the thyroid gland and is termed "of follicular cell origin." Other, rarer variants of thyroid cancer of follicular cell origin include Hürthle cell carcinoma and poorly differentiated thyroid cancer (PDTC). DTC is generally indolent and has a natural history which is measured in decades if treated appropriately (up to 95% 10 year survival). However there are very limited options for patients who ultimately fail radioactive iodine therapy and develop distant refractory metastases, and most of these patients will succumb to their disease (Durante et al 2006).

1.1.2 Radioactive iodine treatment

In addition to primary thyroid surgery, radioactive iodine (RAI, ^{131}I) is the mainstay of therapy for patients with thyroid cancer of follicular origin. It is a targeted therapeutic approach that exploits the expression of the sodium iodide symporter (NIS) to deliver radiation selectively to thyroid cells, which is used as adjuvant therapy after thyroidectomy, and to treat recurrent and metastatic disease.

Most patients with thyroid cancer of follicular origin have differentiated carcinomas which retain at least to some extent the biological properties of normal thyroid cells, including expression of NIS. Presence of this transporter is required for iodine uptake (Riesco-Eizaguirre et al 2006).

Following diagnosis, surgical resection of the thyroid gland with or without removal of the local lymph nodes is performed. Following surgical resection, a set of clinical-pathologic data (such as age at diagnosis, specific histological type, size of the primary tumour, extent of lymph node metastases, presence of distant metastases, gross extrathyroidal extension and completeness of resection) can be used to estimate the risk of recurrence and the risk of disease specific mortality. After surgery, radioactive iodine can be used for the following purposes:

For diagnostic scanning to improve initial staging and extent of disease assessment.

For ablation of the normal thyroid remnant (usually less than 2-3% of normal tissue remains after total thyroidectomy). This treatment facilitates follow-up by achieving an undetectable level of serum thyroglobulin and a subsequent negative diagnostic whole body RAI scan.

As adjuvant therapy, in an attempt to destroy microscopic residual disease in patients at intermediate to high risk of recurrence.

As primary therapy in patients with unresectable RAI-avid loco-regional disease or distant metastases.

Uptake of RAI by tumour tissue is a prerequisite for administration of RAI treatment and for its efficacy. Once patients develop distant metastatic disease, RAI uptake is observed in only two thirds of cases and less frequently in patients with aggressive disease (Durante et al 2006, Mazzaferri and Kloos 2001, Nemec et al 1979, Samaan et al 1985). Patients with no uptake in metastatic foci are considered refractory to RAI, which is then no longer indicated.

1.1.3 Risk stratified remission rates following RAI treatment

Several different risk stratification systems have been published for DTC. The Union Internationale Contre le Cancer/American Joint Committee on Cancer (AJCC) staging system is the most commonly used, but it was developed to predict the risk of death rather than recurrence. To overcome this limitation, the American Thyroid Association (ATA) published guidelines to grade the risk of recurrence into 3 categories (low, intermediate, and high) based on tumour-related parameters (pathological tumour-node-metastasis and histological variant) integrated with other clinical features, including the result of the first post-therapy RAI whole-body scan and serum Tg measurement. Although the ATA risk stratification system has been shown to better predict short-term clinically relevant endpoints of persistent and recurrent disease than the AJCC system, it does not adequately predict longer-term outcomes because the risk of persistent or recurrent disease changes following initial therapy. In addition, the ATA intermediate risk category includes a wide variety of potential risk factors that can have a significant influence on both short term and long-term outcomes (any tumour size, N1a/N1b node status, vascular invasion, extrathyroidal extension, aggressive histology).

Recent evidence suggests that the likelihood of achieving remission varies depending on the size of the primary tumour, extent of invasion, or lymph node status as defined by number and size of affected nodes (refer to Table 1, Tuttle, unpublished sub-analysis of data from Tuttle et al 2010 and Vaisman et al 2012).

Table 1 Remission rates in 2 independent data sets of risk-categorised patients with differentiated thyroid cancer - based on tumour size and lymph node status

TNM status	Description	Remission rate[a] MSKCC[b] n=588 patients	Remission rate[a] Brazil[c] n=506 patients
T1	Tumour diameter 2 cm or smaller	40%	59%
T2	Tumour diameter 2 - 4 cm	47%	52%
T3	Tumour diameter > 4 cm or with minimal extrathyroidal extension	25%	37%
T4	Tumour of any size extending to invade subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia or encasing carotid artery or mediastinal vessels	13%	17%
N0	No metastatic nodes identified	62%	54%
N1a	Metastatic nodes in central neck (pretracheal, paratracheal, or prelaryngeal)	31%	30%
N1b	Metastatic nodes in lateral neck or superior mediastinum	16%	12%

[a] Remission rate within a 2 year follow up period
[b] unpublished sub-analysis of data from Tuttle et al 2010
[c] unpublished sub-analysis of data from Vaisman et al 2012

As can be seen patients with either T3 disease or N1a disease have remission rates that approximate 30%, while patients with T4 disease or N1b disease have remission rates that approximate 15%. From a clinical perspective, these findings are not surprising since T3 disease is very commonly associated with N1a disease, and T4 disease is often associated with N1b disease. Therefore, the similarity in remission rates in T3 and N1a disease, and in T4 and N1b disease, is consistent with observations in clinical practice.

It is important to note that in addition to the location of the lymph node metastases (N1a vs. N1b), the extent of lymph node metastases (size and number of involved nodes) is also a critical factor in assessing the risk of recurrence and risk of failing initial therapy (Randolph et al, 2012, Ricarte-Filho et al 2012). The complete remission rates from the MSKCC and Brazilian cohorts are based on patients with clinically significant, structurally evident N1a and/or N1b disease that required therapeutic neck dissections for clinically apparent metastatic disease (prophylactic neck dissections to remove sub-clinical disease were not performed in either the MSKCC or Brazilian cohorts). For example, in a MSKCC series of 246 papillary thyroid cancer patients who presented with lymph node metastases at the time of diagnosis, a median of 6 metastatic lymph nodes were identified with a median maximal diameter of 1.3 cm (Ricarte-Filho et al 2012). Furthermore, multiple studies have demonstrated that small volume lymph node metastases which are usually identified as incidental findings in the fibroadipose tissue surrounding the thyroid, or as a result of prophylactic central neck dissections, are associated with a low risk of recurrence (Randolph et al, 2012, Ricarte-Filho et al 2012), and these may not even require RAI adjuvant therapy (and therefore would not be

appropriate subjects for the proposed study). Therefore, to prevent patients with lower risk N1a or N1b small volume metastatic disease from enrolling into this study, a requirement is that subjects must have N1a or N1b disease involving 5 or more lymph nodes (of any size) or at least 1 lymph node ≥ 1 cm in the largest diameter.

Since only approximately 30% of patients presenting with any of the following features are expected to achieve clinical remission following total thyroidectomy and RAI remnant ablation, they are at high risk of failing their primary treatment:

- Primary tumour greater than 4 cm
- Primary tumours of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)
- N1a or N1b disease with at least 1 lymph node ≥ 1 cm
- N1a or N1b disease involving 5 or more lymph nodes (of any size)

Total thyroidectomy and RAI ablation is therefore very effective at inducing remission in low risk patients, however approximately 70% of patients with the above characteristics do not enter remission, and have an incomplete response to initial therapy with biochemical and/or structural evidence of persistent disease.

1.1.4 The benefits of achieving remission

Thyroid cancer deaths are exceedingly rare if remission is achieved, and studies have shown that nearly all deaths ultimately occur in the group of patients who do not achieve remission. For example, two recent studies reported disease-specific deaths in 6% and 8% of the patients who did not achieve remission compared to 0% in patients who achieved remission with median follow-up times of 7 and 10 years respectively (Tuttle RM, unpublished sub-analysis of data from Tuttle et al 2010, Vaisman et al 2012). This mortality rate continues to rise with longer periods of follow up with nearly all deaths from thyroid cancer being seen in the cohort of patients that failed to achieve remission.

The importance of a successful initial therapy is demonstrated by the excellent prognosis that even high-risk patients have if therapy results in negative imaging and negative thyroglobulin levels after stimulation by TSH. The majority of patients who achieve remission do not relapse; recurrence rates are typically 1% to 4% over median follow-up periods of 5 to 10 years for patients who achieve remission (Castagna et al 2011, Tuttle et al 2010, Vaisman et al 2012).

In patients that achieve remission, there are important clinical and psychological benefits. Patients that achieve remission are re-classified as low risk patients and require much less frequent follow-up. Thyroglobulin testing and imaging assessments are reduced in frequency, and less aggressive TSH suppressive therapy is required. This in turn reduces the longer-term risks of osteoporosis and atrial fibrillation that are known complications of supra-

physiological dosing of levothyroxine, and reduces the anxiousness and fatigue that can result from the mildly hyperthyroid state caused by TSH suppression.

If remission is not achieved with initial therapy, many patients will be subjected to additional therapies (eg, more RAI, surgery, external beam irradiation), in an effort to control disease progression and achieve a cure. Therapeutic RAI is associated with a cumulative dose-related risk of early and late-onset complications such as salivary gland damage, dental caries, nasolacrimal duct obstruction, and decreased fertility (Cooper et al 2009). Furthermore, a dose-dependent relationship is also seen between cumulative administered RAI activity and the subsequent occurrence of secondary malignancies (Rubino et al 2003, Sawka et al 2009). All of these risks and symptoms constitute significant quality of life issues for the patient. The inconvenience of repeating a low iodine diet, the associated radiation safety precautions and missed days of work are additional factors the patient must consider. Additional surgery carries associated risks related to anesthesia, nerve damage (resulting in hoarseness, permanent tracheotomy in rare occasions, drooping eye lid, loss of control of shoulder muscles and loss of sensation in the neck), increased scarring in the neck (resulting in discomfort and difficulty swallowing), and damage to the parathyroid glands (resulting in hypocalcemia and a lifetime need for vitamin D and calcium supplementation and frequent blood tests). Thus avoidance of further therapy is beneficial to the patient.

Unfortunately, additional therapy is often less effective, particularly in patients with persistent structural disease (Vaisman et al, 2011). Further RAI can be given to patients that have persistent biochemical evidence of disease, and although repeat RAI is often less effective than the initial RAI treatment (especially for patients with persistent structural disease), it can be effective at driving some patients with persistent biochemical disease into remission. Thus, strategies designed to improve the tumouricidal effect of the initial RAI dose should result in higher remission and cure rates.

An intervention that enhances the effectiveness of initial therapeutic RAI in higher risk patients (the target population for this study), should result in higher remission rates and remove the need for further therapy, and would thus be of clear benefit to patients.

1.1.5 Selumetinib

Selumetinib is a potent, selective, noncompetitive inhibitor of MEK, licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma. Selumetinib was discovered by Array Biopharma and had the designation ARRY 142886. Other laboratory code names used during the development of this molecule are AR00142886 and AR-142886-X (where X refers to a sequential lot number). Array BioPharma was responsible for the first-into-human study; the remainder of the clinical development programme for oncology indications is the responsibility of AstraZeneca. AZD6244 has now been assigned the international non-proprietary name selumetinib.

1.1.5.1 MEK and NIS expression

Papillary thyroid cancer (PTC), which is the most common form of the disease, is characterised by a set of genetic alterations, all of which result in the activation of

RAF/MEK/ERK signalling. Of these genetic lesions the most common is the typical V600E mutant of *BRAF* also found in other cancers, most notably melanoma. The other genetic lesions occur in receptor tyrosine kinases (RET and NTRK1), and in *RAS* (*N* and *HRAS*). In total these mutations in effectors of ERK signalling account for approximately 70% of papillary thyroid cancer (Kimura et al 2003, Soares et al 2003). *BRAF* itself is seen in at least 38% of PTC, and is also found in poorly differentiated and anaplastic thyroid carcinomas with a prevalence of 12% and 50%, respectively (Nikiforova et al 2003, Ricarte-Filho et al 2009). These genetic mutations are mutually exclusive and suggest the importance of RAF/MEK/ERK signalling in papillary thyroid cancer.

With regard to the impact on efficacy of RAI therapy, one of the primary effects of activation of the RAF/MEK/ERK signalling pathway is a significant and sustained down regulation of the sodium iodide symporter (NIS) which is responsible for the uptake of iodine into thyroid cells and is required for the uptake of therapeutic ^{131}I into thyroid cancer cells. Studies have demonstrated that the expression of NIS (and other genes typical of differentiated thyroid cells) is suppressed by activation of RAF/MEK/ERK signalling in mouse models of the disease (Franco A et al. 2011). In mice engineered to express V600E *BRAF* in thyroid cells, expression of NIS and other thyroid differentiation markers is reduced (Knauf et al 2005). These mice develop papillary thyroid cancers with dedifferentiated features. Further data using a mouse model of thyroid-specific inducible expression of V600E *BRAF*, show that V600E *BRAF* activation suppresses expression of NIS, thyroid peroxidase (TPO) and thyroglobulin (Tg), and blocks ^{124}I uptake, all of which are re-established once expression of oncogenic *BRAF* is turned off. Treatment of mice expressing the induced V600E *BRAF* with a MEK inhibitor also re-established NIS expression and ^{124}I uptake in the poorly differentiated thyroid carcinomas (PDTC) (Chakravarty D et al 2011). Constitutive activation of MAPK signalling also inhibits the expression of thyroid peroxidase and thyroglobulin in BRAF-induced murine thyroid cancers. Genetic or pharmacological blockade of the pathway restores their expression, and consequently the ability to incorporate iodine into tyrosine (iodine organification), which is associated with greater retention time of ^{131}I in cancer cells (Chakravarty D et al 2011). Other MAPK activating alterations common to thyroid cancer can also cause de-differentiation. Over-expression of either the G12V *HRAS* mutant or *RET/PTC* in thyroid cancer cells suppresses NIS, thyroglobulin and thyroid peroxidase expression, which is restored with MEK inhibitor treatment (Knauf et al 2003, De Vita et al, 2005). These experiments provide a pre-clinical proof of concept that inhibition of ERK signalling by MEK inhibitors can reverse the suppression of NIS, TG and TPO expression and re-establish iodine incorporation into PTC.

NIS expression in clinical thyroid cancer samples

Analysis of clinical tumour samples for NIS expression indicates a relative loss of NIS expression (and the expression of other thyroid specific genes) relative to normal thyroid tissue (Durante et al 2007; Espadinha et al 2009). Furthermore, NIS expression is lower in *BRAF* mutant tumours than in those without *BRAF* mutation (Durante et al 2007; Morai et al 2011; Romei et al 2008). In a well differentiated rat thyroid cell line model, expression of RET/PTC, mutant HRAS, or constitutively active MEK1, blocked TSH-induced expression of Tg and NIS; an effect that was reversed by MEK inhibition. These data are consistent with

the hypothesis that activation of MEK, regardless of the upstream activating mutation is a key factor in the loss of thyroid differentiation specific gene expression including NIS (Knauf et al 2003).

In summary, this data predicts that both an unselected and genetically selected population may benefit from treatment with a MEK inhibitor and RAI. This study will thus assess two populations for the primary endpoint of complete remission rate at 18 months; the genetic 'all comer' population, and also a population of patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that other patients may also benefit.

1.1.5.2 Clinical data in thyroid cancer

The preclinical data generated to date suggests the clinical hypothesis that MAPK pathway inhibition in patients with RAI-refractory tumours will result in reacquisition of RAI uptake and renewed susceptibility to therapeutic ^{131}I. To test this hypothesis, an investigator-sponsored selumetinib pilot study has been performed at MSKCC for patients with RAI-refractory recurrent or metastatic differentiated thyroid carcinoma of follicular cell origin entitled, "Reacquisition Of RAI Uptake Of RAI-Refractory Metastatic Thyroid Cancers By Pre-treatment With The Selective MEK Inhibitor Selumetinib: A Pilot Study" (Ho et al 2012). In this study, the RAI avidity of thyroid tumours was quantified by lesional dosimetry with ^{124}I PET imaging in patients, before and after 4 weeks of treatment with selumetinib. For patients whose tumours reacquired the ability to take up RAI, ^{131}I treatment was administered, and tumour response was assessed both radiographically and with measurement of the serum tumour marker thyroglobulin (Tg).

20 patients were treated with selumetinib in this pilot study. Of the 20 patients, 9 patients had tumours with the V600E *BRAF* mutation, 5 patients had tumours with *NRAS* mutations at codon 61, 3 patients had tumours with *RET/PTC* rearrangements, and the remaining 3 patients were wild-type for these alterations. Twelve of the 20 patients in the study demonstrated increased tumoural ^{124}I uptake, and 8 of these 12 patients achieved sufficient iodine reuptake to warrant treatment with ^{131}I. Interestingly, 5 of these patients were found to have *NRAS* mutations, one a *BRAF* mutation, one a *RET/PTC* rearrangement and one patient was wild-type. Further genotyping and cytogenetic analysis is ongoing to discover other potential oncogenic drivers that may have promoted susceptibility to this therapeutic strategy. The increased iodine incorporation as quantified on the ^{124}I scans translated to clinical efficacy with RAI therapy. Reduction in tumour size by RECIST criteria was achieved in all RAI-treated patients, with 5 confirmed partial responses and 3 patients with stable disease. Substantial decreases in serum thyroglobulin following RAI therapy were achieved in all 8 RAI-treated patients. The mean percent reduction in serum thyroglobulin achieved "post-RAI" (2 months after RAI treatment) compared to "pre-RAI" (within 3 weeks before RAI treatment) was 89%.

Data from the pilot study also suggests that pre-treatment with selumetinib selectively increased RAI uptake in tumoural lesions compared to non-thyroidal tissue (salivary gland).

This pilot study demonstrates that MAPK pathway inhibition can modulate RAI uptake in the most difficult clinical scenario: patients with resistance to RAI therapy. Most patients in the pilot clinical study described above had many metastatic lesions, some of which were refractory to RAI at baseline, and some of which were partially RAI avid at baseline. Importantly, selumetinib not only restored RAI uptake in previously refractory lesions, but also increased RAI uptake in most partially-avid lesions (typically by more than 100% compared to the baseline value; 3 to 7 fold increases in maximum SUVs in such lesions were consistently observed). This provides a strong rationale to develop this strategy in the adjuvant setting for RAI naïve patients, with the goal of further enhancing what is more likely to be RAI-susceptible disease for patients at high risk of primary treatment failure.

In addition to the pilot study described above, a phase II study of 100 mg bid selumetinib (previous mix-and-drink formulation) in 39 patients with RAI-refractory differentiated metastatic thyroid cancer has also been completed (Hayes et al 2012). This study involved continuous monotherapy dosing of selumetinib and no RAI treatment. The results demonstrated few clinical responses (one partial response in 32 evaluable patients), but demonstrated a 66% stable disease rate; median PFS in this poor-prognosis cohort was 33 weeks in patients with mutations in *BRAF* V600E, and 32 weeks in all-comers. Although this study was conducted with the mix and drink formulation (from which selumetinib exposure may be lower), the efficacy of selumetinib as monotherapy in this population was disappointing.

Taken together, these data suggest a strong rationale for investigating selumetinib with RAI in patients with DTC. Given the known prevalence of MEK pathway activation in patients with DTC, and both the pre-clinical and clinical data seen when selumetinib is added to RAI, increasing iodine uptake, specifically with respect to selumetinib's ability to upregulate NIS expression, adding selumetinib to standard of care RAI treatment has the potential to provide important clinical benefit. This benefit may extend to all patients regardless of their genotype, or it may be greater in those patients with tumours driven by mutations in the MEK pathway. This study will allow these hypotheses to be tested.

1.1.5.3 Safety profile of selumetinib

Array BioPharma was responsible for the first study of selumetinib into patients. The remainder of the oncology clinical development programme is the responsibility of AstraZeneca. Selumetinib is currently in phase II development, and has been used as both monotherapy and in combination with other anti-cancer agents, in a variety of adult solid tumour settings (eg, pancreatic cancer, colorectal cancer, melanoma and NSCLC), and paediatric cancer patients.

The formulation taken into the phase I clinical programme by Array Biopharma was an extemporaneous preparation of an oral suspension of selumetinib as the free-base in an aqueous solution of sulphobutylether β-cyclodextrin (SBE-CD, Captisol®), referred to as the free-base suspension formulation (mix and drink). The AstraZeneca phase II monotherapy

clinical programme also utilised this formulation. Subsequent formulation development resulted in a capsule formulation of selumetinib as the hydrogen sulphate salt (AZD6244 Hyd-Sulfate), which will be used in this study. The maximum tolerated dose (MTD) for the suspension formulation was determined to be 100 mg twice daily, whereas for the capsule, the MTD was determined to be 75 mg twice daily. The emerging safety and tolerability profile of the capsule formulation is broadly consistent with that of the suspension formulation, although a higher frequency of fatigue and nausea has been reported with the capsule formulation compared to the suspension formulation in the phase II monotherapy studies.

As of April 2012, over 1200 patients have received selumetinib as monotherapy or in combination with other anti-cancer agents in clinical studies (AstraZeneca and non AstraZeneca-sponsored studies, including investigator-sponsored studies).

Two phase I studies (D1532C00005, D1532C00020) were performed with the Hyd-Sulfate formulation. Comparison of the frequencies from Study D1532C00005 and the AZ-sponsored phase II monotherapy studies described below, shows that there are higher percentages of patients reporting the most frequent AEs such as fatigue, dermatitis acneiform, diarrhoea, nausea and peripheral oedema with the Hyd-Sulfate formulation. This may be due to the higher plasma exposures achieved with the capsule formulation, but may also be in part as a consequence of the more heavily pre-treated patient population in study D1532C00005 having lower tolerances to developing toxicity.

- The frequencies of common AEs observed in Study D1532C00020 were generally more similar to that of Study D1532C00003 (free-base suspension formulation in a phase II population), which may mean that some of the differences in frequencies observed just reflect variations in the study population as the selumetinib safety profile is established.

Two hundred and sixty nine (269) patients received selumetinib free base suspension 100 mg twice daily in 4 completed phase II monotherapy studies (D1532C00003, D1532C00008, D1532C00011, and D1532C00012).

- Rashes (including the preferred terms dermatitis acneiform, rash, rash maculopapular, rash macular, rash papular, acne, and folliculitis) were reported in approximately 70% of patients receiving treatment with selumetinib, and dermatitis acneiform was the most common AE term overall (54%). Other commonly reported AEs were diarrhoea (49%), nausea (33%) and vomiting (24%). Adverse events of peripheral oedema, periorbital oedema, and facial oedema were reported in 31%, 9%, and 4% of patients, respectively. The AEs of fatigue or asthenia were reported in approximately 30% of patients in this phase II population. Dyspnoea exertional or dyspnoea was reported in 13% of patients and, in individual studies, dyspnoea exertional was reported at a higher incidence in the selumetinib groups than in the comparator chemotherapy groups.

- Serious AEs were reported in 24% of patients receiving selumetinib monotherapy. The most frequently reported serious AEs were vomiting (1.5%), diarrhoea,

erysipelas, and pulmonary embolism (in 1.1% patients each). Serious AEs of infections (bacterial sepsis, sepsis, infection, and bacterial arthritis) were reported in 2.2% of patients. The most frequently related reported treatment-related SAE was vomiting (3 patients).

- In Study D1532C00003, small increases in blood pressure were observed after 1 week on selumetinib, with mean increases of 7.4 mmHg (systolic, SBP) and 5.3 mmHg (diastolic, DBP) at Week 8, compared with mean increases of 1.1 mmHg (SBP) and 0.5 mmHg (DBP) in the temozolomide comparator arm. The AE of hypertension was reported in 18 patients (6.7%) receiving selumetinib in phase II monotherapy studies; 6 of these patients had hypertension at entry to the study, and a further 5 patients had documented risk factors for hypertension.

- Reversible asymptomatic reduction in left ventricular ejection fraction (LVEF) to below 55% has been reported in a small proportion of patients with advanced cancers in the monotherapy and randomised placebo controlled studies in combination with standard chemotherapies, with both formulations of selumetinib. In both placebo controlled studies no patient treated with selumetinib had severe LVEF impairment (< 35%) or symptomatic heart failure. Evidence of reversibility on continuing treatment with selumetinib has been demonstrated in some patients. LVEF scheduled assessments were only included in one phase II study (D1532C00003) and in the selumetinib group to evaluate a possible cardiac aetiology of the peripheral oedema reported in earlier studies. The median change in LVEF at Week 4 was 1.2 percentage points, and the individual change from baseline ranged from –20 to +19 percentage points. Adverse events of ejection fraction decreased, left ventricular dysfunction, or ventricular dysfunction were reported in a total of 5 patients (3.3%) receiving selumetinib (including 1 patient who had switched from temozolomide treatment after disease progression) versus 1 patient (1%) in the comparator group.

- Review of clinical laboratory parameters in phase II monotherapy studies identified a trend toward increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels after starting treatment with selumetinib. An increase in serum phosphate was observed in some patients after initiation of selumetinib, compared with patients randomised to comparator treatments.There was a trend toward a small mean decrease in albumin relative to the comparator. No other reports of selumetinib-related changes in laboratory parameters were considered to be of clinical relevance at this time. There was no evidence of myelosuppression or renal impairment.

- Adverse events related to visual function have been reported across the programme with selumetinib. Most often there were no specific clinical findings reported from patients that underwent ophthalmological evaluation after reporting the AE of visual disturbance. AEs consistent with central serous retinopathy have been reported in a

small number of patients receiving treatment with selumetinib, generally in combination with other anti-cancer agents.

- There have been reports of pneumonitis-type events in a small number of patients receiving treatment with selumetinib. An association with selumetinib has not been established. An algorithm for investigation of dyspneoa is provided in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

- Weakness of neck extensor muscles in conjunction with creatine phosphokinase (CPK) increases (reversible on treatment interruption) have been reported in 3 out of 54 patients with uveal melanoma receiving selumetinib 75 mg twice daily in one non-AstraZeneca sponsored study. Increases in CPK levels have been recorded in a small number of patients receiving treatment with selumetinib. CPK elevations are present in some patients with muscle symptoms, although asymptomatic elevations have also been reported. A relationship between selumetinib and elevated CPK levels or myopathy has not been established.

In the DTC pilot study described in Section 1.1.5.2 (Ho et al 2012), where 20 metastatic thyroid cancer patients were treated with a 4 week course of selumetinib 75 mg twice daily, all events attributed to selumetinib were Grade 1 or 2, and included fatigue (80%), maculo-papular rash (70%), acneiform rash (25%), elevation in AST (70%; all Grade 1), elevation in ALT (45%; all Grade 1), diarrhea (45%), nausea (40%), limb edema (30%), oral mucositis (35%), constipation (20%), hypoalbuminemia (15%), decreased white blood cell count (15%), face edema (10%), scalp pain (10%), decreased platelet count (1 patient; Grade 1), eye disorder (1 patient; Grade 1 consisting of visual halos and slight blurriness that resolved after therapy stopped), hypertension (1 patient; Grade 1), periorbital edema (1 patient; Grade 1), and vomiting (1 patient, Grade 1). One patient who was treated with RAI was subsequently diagnosed with myelodysplastic syndrome 51 weeks after RAI administration which subsequently evolved into acute leukaemia (this was determined to be unrelated to selumetinib and likely related to cumulative RAI toxicity as well as previous external beam radiation therapy). All adverse events were readily managed with supportive mediations and were reversible upon discontinuation of selumetinib. None of the 20 patients required dose delays or reductions due to selumetinib toxicity.

In the only other study to specifically investigate selumetinib in differentiated thyroid cancer patients (the phase II study of 100 mg bid selumetinib, previous mix-and-drink formulation) in 39 patients with RAI-refractory differentiated metastatic thyroid cancer (Hayes et al 2012). In these patients with RAI-refractory disease, common drug-related AEs included rash (77%), fatigue (49%), diarrhea (49%), and peripheral oedema (36%). Grade 3 and 4 AEs were consistent with those across the selumetinib program and also included rash (18%), fatigue (8%), diarrhea (5%) and peripheral oedema (5%). Twelve patients required dose reductions for reported AEs across the length of the study (the duration of treatment was greater than 16 weeks for 69% of patients). Six patients (15%) discontinued treatment due to adverse events.

A study of selumetinib in combination with radiation in patients with non-small cell lung cancer has recently been opened but no safety or efficacy results are yet available from this study.

Selumetinib is not mutagenic or clastogenic in vitro but produced increases in micronucleated immature erythrocytes in mouse bone marrow micronucleus studies. Investigatory studies show that this is predominantly via an aneugenic mechanism which is consistent with disruption of normal spindle function as a consequence of the known pharmacological action of a MEK inhibitor. With selumetinib Hyd-Sulfate, a NOEL of 24 mg/kg/day (for 2 days) was established for induction of micronuclei, with plasma exposures significantly above those observed in cancer patients at the maximum tolerated dose of 75 mg twice daily. This suggests that selumetinib will have little potential to cause aneugenicity in dividing cell populations in patients at the proposed clinical dose. Thus, any additional aueugenic risk from a 5 week course (maximum 43 days) of twice daily 75 mg selumetinib dosing in this potentially curative patient setting, is considered to be negligible in comparison with the known and more substantial risk from radiation exposure following a therapeutic dose of ^{131}I (100 mCi) that patients will receive as part of standard of care.

In summary, selumetinib has been shown to have an acceptable profile of side effects, in an extensive safety database for a compound at this stage of development.

Further details regarding the safety profile of selumetinib can be found in the Investigator Brochure.

1.2 Research hypothesis

Pre-treatment with selumetinib enhances the uptake of radioactive iodine in differentiated thyroid cancer, resulting in a greater incidence of complete remission after adjuvant RAI therapy in patients at high risk of primary treatment failure.

1.3 Rationale for conducting this study

Unfortunately a significant proportion of thyroid cancer patients are not cured by their initial surgery and RAI therapy. This is often due to the inability of their cancer cells to adequately incorporate RAI (due to reduced expression of NIS). In such cases, repeated administration of RAI may be given (for RAI avid disease) with the aim of inducing remission and curing their disease. This outcome however is not guaranteed, and patients who subsequently develop refractory metastatic disease have a much poorer prognosis and may eventually succumb to their disease; at least one third of patients who develop metastatic disease have no or very low uptake and are thus not amenable to further RAI treatment. There is thus an urgent need for a medicine that can enhance the effectiveness of initial RAI treatment and increase the probability of achieving remission, thereby preventing more patients from developing distant metastatic disease.

1.4 Benefit/risk and ethical assessment

It is clear from the Investigator-sponsored study (Ho et al 2012), that a short course of selumetinib prior to RAI therapy, is effective in enhancing RAI uptake, reducing tumour marker (Tg) levels, and reducing tumour size in heavily pre-treated patients with documented RAI-refractory disease. Most patients in the pilot clinical study had numerous metastatic lesions, some of which were refractory to RAI at baseline and some of which were partially RAI avid at baseline. Importantly, selumetinib pre-treatment not only restored RAI uptake in previously refractory lesions, but also increased RAI uptake in the majority of partially avid lesions (typically by more than 100% compared to the baseline value; 3- to 7-fold increases in maximum SUVs in such lesions were consistently observed). This pilot data not only supports the preclinical hypothesis that inhibiting the MAPK pathway can convert non-RAI avid lesions to RAI avid tumours, but also demonstrates that iodine uptake in previously iodine sensitive lesions can be significantly increased with selumetinib. This observation broadens the potential clinical applicability of this approach beyond just RAI-refractory thyroid cancer, to the use of selumetinib and RAI as part of upfront adjuvant treatment of RAI-naïve and susceptible DTC.

The potential benefit to patients in this study is therefore high, with an increased chance of complete remission. The toxicity risk from a short course (approximately 5 weeks) of selumetinib treatment has been carefully considered for this potentially curative population; the side effect profile of selumetinib in the short timeframe (maximum 6 weeks of exposure) is considered to be predictable, manageable and reversible (mainly rash and fatigue). The long term risk of secondary malignancies associated with RAI is considered low from a single 100 mCi dose, as these are rare and more typically develop following cumulative RAI treatments and exposure. Patients under the age of 18 years will be excluded to minimise any risk of increased radioactivity exposure in a younger population. The side effect profile of both selumetinib and RAI will be monitored over the entire 3 year study duration for each patient.

2. STUDY OBJECTIVES

2.1 Primary objectives

- To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in the overall study population. Complete remission is defined in Section 6.4.1.

- To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

2.2 Secondary objectives

1. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the overall study population. Clinical remission is defined in Section 6.4.6.

2. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

3. To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

4. To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

2.3 Exploratory objectives

1. To explore subsequent thyroid cancer therapy given to patients who receive selumetinib with RAI, or placebo with RAI.

2. To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters.

3. To collect tumour, plasma and serum samples for potential future research on biomarkers relevant to DTC and response and resistance to study treatments.

4. To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib or RAI and/or susceptibility to cancer.

The exploratory analysis will be reported separately from the CSR.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a double-blind, randomised, placebo-controlled study to assess the efficacy and safety of a short course (approximately 5 weeks) of selumetinib (75 mg, orally twice daily) in combination with adjuvant RAI therapy compared to placebo and adjuvant RAI therapy, in patients with differentiated thyroid cancer at high risk of primary treatment failure.

Approximately 228 patients will be randomised 2:1 selumetinib to placebo.

This will be a multi-centre, international study; it is anticipated that approximately 50 centres will recruit patients in South and/or North America and Europe.

3.1.1 Treatment Plan

Following randomisation, patients will take their assigned study treatment (selumetinib or placebo) for a period of approximately 5 weeks, twice daily. Study treatment will begin approximately 4 weeks prior to the planned day of RAI therapy. Refer to Table 2 for an example study treatment plan. The following treatment criteria must be adhered to:

1. Day 1 of study treatment must occur:
   - no earlier than 6 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy), and
   - no later than 16 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).
2. It is essential that patients remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator until the patient has been on study treatment for a minimum of 7 consecutive days beforehand.
3. Study treatment with selumetinib or placebo will typically last for 36 days, but must be for no longer than 43 days (this allows the planned RAI to be postponed by up to 1 week if absolutely necessary).
4. Patients will be required to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI treatment. Refer to Section 5.1.1 and the example diet in Appendix F for further details.
5. For each of the 2 days immediately prior to their planned RAI therapy, patients will receive a recombinant human TSH injection (rhTSH, Thyrogen), in order to stimulate iodine uptake (refer to Section 5.5.4 for details).
6. Following the 2 days of rhTSH injections, patients will receive their planned RAI therapy the immediate next day (refer to Section 5.5.4 for further RAI dosing information).
7. Twice daily dosing of selumetinib/placebo will continue for 5 days following RAI therapy (Day 36 will typically be the last day of study treatment, but this can extend to Day 43 if necessary).

Table 2 Example study treatment plan

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Day 1 X	Day 2 X	Day3 X	Day 4 X	Day 5 X	Day 6 X	Day 7 X
Day 8 X	Day 9 X	Day 10 X	Day 11 X	Day 12 X	Day 13 X	Day 14 X
Day 15 X	Day 16 X	Day 17 X	Day 18 X	Day 19 X	Day 20 X	Day 21 X
Day 22 X	Day 23 X	Day 24 X Low I diet	Day 25 X Low I diet	Day 26 X Low I diet	Day 27 X Low I diet	Day 28 X Low I diet
Day 29 X Low I diet **Thyrogen**	Day 30 X Low I diet **Thyrogen**	Day 31 X Low I diet **RAI**	Day 32 X Low I diet	Day 33 X	Day 34 X	Day 35 X
Day 36 X **last day of study treatment**		Day 38 (Day 36-41) WBS scan (3-10 days after RAI dose)				

X: Study treatment administration (selumetinib or placebo, twice daily)
RAI: radioactive iodine therapy (^{131}I) refer to Section 5.5.4.2 for details
This suggested treatment plan is an example only. The treatments may be planned for different days as long as all criteria in Section 3.1.1 are met.

3.1.2 Follow-up plan

Following completion of RAI therapy and planned discontinuation of study treatment (randomised selumetinib or placebo); patients will be followed up as follows:

1. 3-10 days after RAI therapy, patients will undergo a post-therapy whole body RAI (^{131}I) nuclear medicine scan to determine where the RAI has localized in the body (refer to Section 6.4.4.2 for further detail).

2. Patients will be monitored for TSH and thyroxine (T4) levels as per local standard of care (refer to Section 6.4.3.3 for further detail). Note that T4 levels will not be collected in the study database.

3. At 9 months (±3 months) following RAI treatment, patients will be assessed for:

   (a) TSH-suppressed Tg and Tg antibody levels (TgAb). Refer to Section 5.9.1.1 for further details.

(b) Neck ultrasound (US). Refer to Section 5.9.1.2 for further details.

It is important that these assessments are not performed earlier than 6 months after RAI treatment.

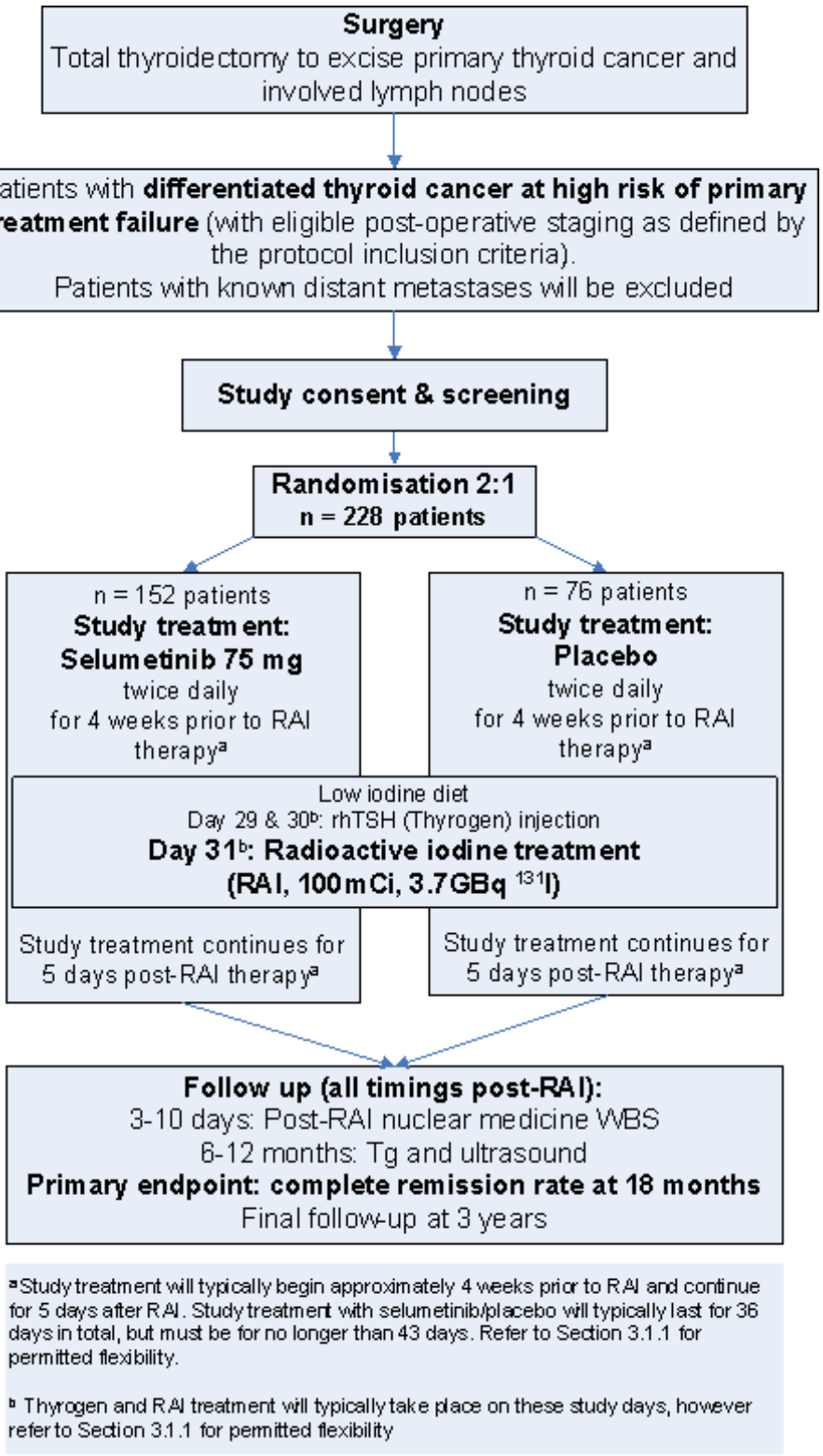
4. Patients will be assessed for their complete remission status at the primary endpoint 18 months following their RAI treatment. A staged approach to the primary endpoint assessments will be used in this study in order to determine remission status (presence or absence of thyroid cancer), such that each patient may not require all assessments. Refer to Section 6.4, Table 4 and Figure 3 for further details. The primary endpoint assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within an 8 week period.

   Further thyroid cancer therapy (eg, additional surgery, RAI re-treatment, external beam radiotherapy or systemic therapy) should only be given during the initial 18 month follow-up period according to the re-treatment criteria in Section 5.9. Any patient that is re-treated in the 18 month period following their RAI therapy will not require any primary endpoint assessments performing (they will be determined not to be in complete remission for the purpose of the study and will enter standard of care follow up, remaining in the study until the 3 year follow up).

5. Following the primary endpoint assessments (or re-treatment), all randomised patients will be further followed-up at 3 years following their RAI treatment. It is the responsibility of the study investigator to ensure they conduct follow-up as described in this protocol if patients transfer to non-study hospitals, or if patients are discharged for routine follow up at other institutions (eg, family doctor or local non-specialist hospital).

Assessments planned at each visit are detailed in Table 3, Table 4 and Section 6.

Figure 1 Study flow chart



[a] Study treatment will typically begin approximately 4 weeks prior to RAI and continue for 5 days after RAI. Study treatment with selumetinib/placebo will typically last for 36 days in total, but must be for no longer than 43 days. Refer to Section 3.1.1 for permitted flexibility.

[b] Thyrogen and RAI treatment will typically take place on these study days, however refer to Section 3.1.1 for permitted flexibility

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Informed consent	X												
Physical examination	X		X	X (Day 29 or 30)			X						6.5.6
Additional screening procedures	X												6.2
Provision of archival tumour[b]		X											6.10.1.1
Plasma/serum sample for exploratory analysis[b]		X (pre-dose)											6.10.2
Pregnancy test	X				X					X[a]			6.5.9.1
Optional genetic consent & sample (whole blood)		X (pre-dose)											6.9
Adverse events[c]	X →	→	→	→	→	→	→	→	→	→	→	→	6.5.3
Concomitant medications	X →	→	→	→	→	→	→	→	→	→	→	→	5.6
Telephone follow up for safety[d]								X			X		6.5.3

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Vital signs (including height at screening), weight	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.8
Clinical chemistry	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.5
Haematology	X	X (pre-dose)	X	X (Day 29 or 30)			X			X		X	6.5.5
Urinalysis	X		X				X						6.5.5
ECG[e]	X	X		X[e] (Day 29 or 30)			X						6.5.7.2
ECHO/MUGA[f]	X						X						6.5.7.1
Ophthalmologic examination[f]	X						X						6.5.9.2
Selumetinib/placebo dosing[g] twice daily		→	→	→	→	→							5.5.2

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On - treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
PK blood samples[h]		X		X[h] (Day 29 or 30)									6.7
Low iodine diet[i]				X	X					X[a]			5.1.1
Thyrogen injection				Xx2 (Day 29 and 30)						Xx2[a]			5.5.4.1
^{131}I (RAI) treatment single 100 mCi dose					X								5.5.4.2
^{131}I 5 diagnostic dose for WBS single 5 mCi dose										X[a]			5.5.4.2
^{131}I nuclear medicine WBS scan						X[j]				X[a]			6.4.4.2
Re-treatment assessment[k]									X	X		X	5.9
Blood sample for TSH									X	X			6.4.3.3
Blood sample for suppressed Tg									X[n]	X			6.4.3.1

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to Table 4	± 2 months	± 1 month	
Blood sample for TgAb	X								X	X			6.4.3.4
Blood sample for rhTSH-stimulated Tg										X[a]			6.4.3.2
Neck ultrasound	X[l]								X	X			6.4.4.1
Neck MRI	X[l]									X[a]			6.4.4.3
Chest CT without contrast	X[l]									X[a]			6.4.4.4
Final follow-up assessment of clinical status												X	6.4.8
Biopsy/FNA for disease confirmation									X[m]	X[m]			6.4.4.5
Tumour biopsy on progression (optional)	Optional sample on disease progression (for example, if the patient is re-treated for persistent or recurrent thyroid cancer, or has further surgery). Note that both a plasma and serum sample for exploratory analysis should also be taken on disease progression.												6.10.3 6.10.2

Study Plan Table 3 Footnotes

[a] Refer to Table 4 and Section 6.4.2.

[b] Provision of these samples is mandatory in this study. Samples should also be obtained on progression (refer to Section 6.10.2).

[c] All AEs/SAEs should be collected from the day of consent until 30 days following the last dose of study treatment. From then on, all SAEs (regardless of causality), and all AEs related to either RAI, or the combination of RAI and study treatment, should be collected until the last study visit 3 years following the patient's RAI dose. The same AE collection scheme applies for any re-treated patient.

[d] The Investigator (or delegate) is required to contact the patient by telephone to follow up for any safety information (according to the collection scheme detailed in Section 6.5). For re-treated patients, safety follow-up should continue according to the protocol-scheduled visits, but may be collected by telephone if necessary at each visit (refer to Section 5.9).

[e] Single ECG assessments 1-2 hours following the first dose on Day 1 and Day 29 or Day 30 of study treatment. A single ECG assessment is also required whenever an ECHO/MUGA is performed, on any cardiorespiratory AE, and for premature discontinuation.

[f] These assessments must also be performed on symptomatology according to the relevant protocol section.

[g] Study treatment must be initiated no earlier than 6 weeks after the patient's thyroid cancer surgery, and no later than 16 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).

[h] Each patient will be asked to contribute 8 PK blood samples, one from each of the four pre defined time windows on both Day 1 and Day 29 or Day 30. The Day 29 or Day 30 PK blood samples may be taken earlier, from Day 22 onwards of study treatment if preferred, but it is essential that all PK blood samples are collected before the RAI dose is administered. (a) Pre-dose (within 15 minutes of dosing), (b) between 15 minutes and 1 hour post-dose, (c) between 1.5 and 2.5 hours post-dose, and (d) between 3 and 8 hours post-dose.

[i] All patients must adhere to a low iodine diet (an example diet is provided in Appendix F).

[j] The post-RAI WBS may be performed any time from 3-10 days following the patient's RAI dose (thus it does not have to be on the same day as the last dose of study treatment).

[k] The re-treatment assessment will establish whether the patient has received any further treatment for thyroid cancer. Refer to Section 5.9 for the study criteria for re-treatment in the initial 18 months following the patient's RAI dose.

[l] The post-operative imaging assessments must be performed no sooner than 4 weeks post-surgery, and after all other screening assessments have been performed (ie, they should not be performed for any patient that is otherwise ineligible).

[m] Only if required (refer to Section 6.4.4.5)

[n] A repeat sample for suppressed Tg may be required 2-4 weeks later, refer to Section 5.9.1.1.

For imaging data that is required to be sent to the central imaging CRO at any point in the study refer to Section 6.4.4.5.

Table 4 Study Plan for the 18 month Primary Endpoint Assessments

A staged approach to the primary endpoint assessments will be used in this study in order to determine remission status (absence of thyroid cancer), such that each patient may not require all assessments. Full details are outlined in Section 6.4.2.

	Stage 1	**Stage 2**	**Stage 3**	Protocol Section
Time window	Stage 1 assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within an 8 week period.			6.4.2
Thyroid cancer re-treatment assessment[a]	X[a]			5.9
Suppressed Tg	X			6.4.3.1
TSH	X			6.4.3.3
TgAb[b]	X[b]	X[b]		6.4.3.4
Neck US[f]	X			6.4.4.1
Biopsy or FNA[d]	X[d]			6.4.4.5
Haematology	X			6.5.5
Low iodine diet[e]		X[e]		5.1.1
Thyrogen injection[c]		X x 2[c]		5.5.4.1
Stimulated Tg[c]		X[c]		6.4.3.2
Pregnancy test		X		6.5.9.1
Diagnostic 5mCi ^{131}I dose[c]		X[c]		5.5.4.2
WBS (nuclear medicine scan)[c, f]		X[c]		6.4.4.2
Neck MRI with contrast[f]			X	6.4.4.3
Chest CT without contrast[f]			X	6.4.4.4
Selumetinib/RAI-related AE/SAEs	———	———	———▶	6.5.3

Footnotes for Table 4: Study Plan for the 18 month Primary Endpoint Assessments

[a] Patients that have been re-treated for thyroid cancer between their initial RAI dose and the primary endpoint assessments 18 months later (refer to Section 5.9 for re-treatment criteria), will not have any primary endpoint assessments performed, they will remain in the study and enter standard of care follow up according to local practice. They should still be followed up for safety information at 18 m, 27 m and 3 years following their initial RAI dose.

[b] For decision making purposes at any time in the study, standardised central analysis results must be used. If the stage 1 blood sample is positive for TgAb, but the stage 2 blood sample is negative for TgAb, then a third blood sample 10 days later (± 3 days) is required to confirm absence of TgAb.

[c] Patients will receive 2 Thyrogen injections on consecutive days (day 1 and 2), followed by a diagnostic dose (5mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5.

[d] Only if required to prove absence of disease for suspicious lesions (refer to Section 6.4.4.5).

[e] Patients will be required to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI treatment. Refer to Section 5.1.1 and the example diet in Appendix F for further details.

[f] For imaging data that is required to be sent to the central imaging CRO refer to Section 6.4.4.5.

3.2 Rationale for study design, doses and control group

This study is designed to determine the efficacy of a 5-week course of selumetinib or placebo, and adjuvant RAI therapy, by assessing the rate of complete remission at 18 months post-RAI therapy.

The dose and duration of selumetinib treatment in this study (75 mg twice daily for 5 weeks) is selected to be consistent with the pilot study, which has previously demonstrated enhanced RAI uptake following selumetinib treatment, reduction in Tg levels, and reduced tumour size following RAI therapy, in patients with RAI-refractory metastatic thyroid cancer (Ho et al 2012). In addition to the effects of selumetinib on the sodium iodine transporter (refer to Section 1.1.5.1), selumetinib may also increase levels of thyroid peroxidase and thyroglobulin in any remaining thyroid cells. These proteins are required to organify and retain iodide in thyroid cells, thus facilitating greater retention of ^{131}I, and a higher dose of radiation to cancer cells. For this reason, patients will remain on selumetinib treatment for 5 days after receiving the therapeutic dose of RAI.

Since RAI is the standard of care for this patient population, the selumetinib/RAI treatment group will be compared to a placebo/RAI control group for all study endpoints.

The population who will participate in this study will be patients with differentiated thyroid cancer at high risk of primary treatment failure that would routinely require RAI adjuvant therapy as standard of care. This risk-stratified population has been selected because it is known that they are at an increased risk of failing to achieve remission following standard initial therapy, and therefore require more effective treatment strategies (refer to Section 1.1.3). This study is intended to be an adjuvant therapy trial for patients without known structural persistent disease; patients with known distant metastases at screening will be excluded in order to minimise heterogeneity of the efficacy recorded.

The second primary efficacy endpoint will be assessed in patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that these patients are not likely to be the only population to benefit. Incorporation of a genetically predefined study population enables this hypothesis to be examined (mutation analysis of samples to identify the genetically predefined study population will be performed post-randomisation, and prior to data base lock for the primary endpoint data analysis).

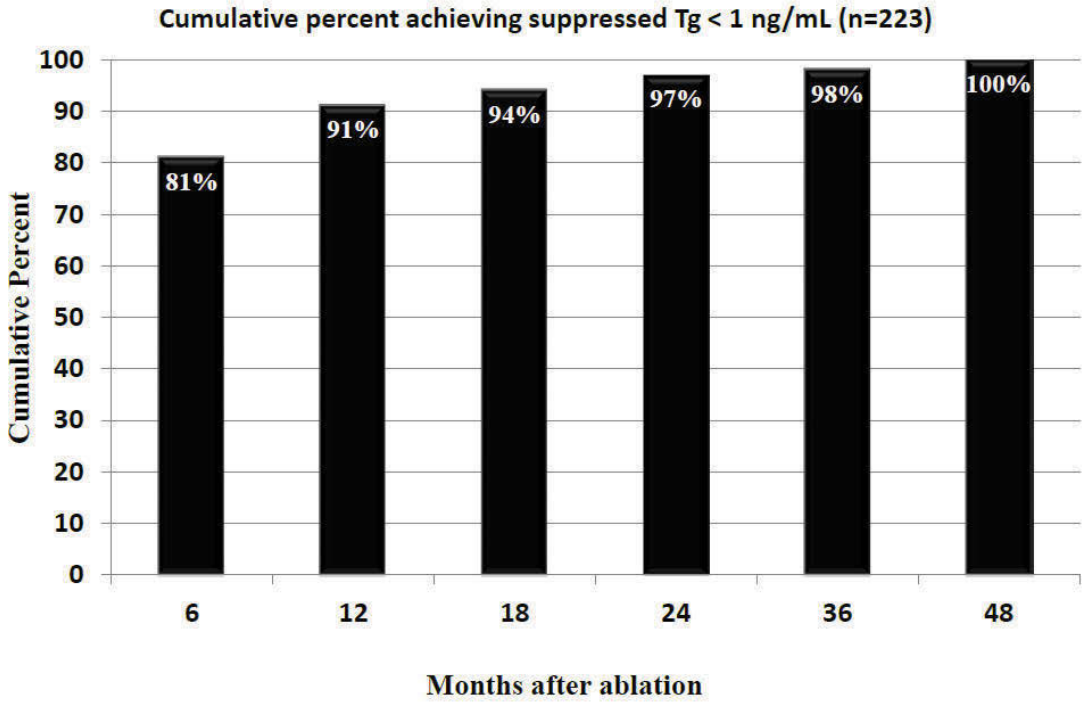
Enhancing RAI uptake into thyroid cancer cells has the potential to increase the incidence of complete remission following RAI treatment. It has been shown that the incidence of complete remission following initial RAI treatment correlates with long-term outcome, and if complete remission has not been achieved, further treatment is frequently administered (Castagna et al 2011, Tuttle et al 2010).

A study has retrospectively evaluated the time to nadir Tg in 299 patients who did not receive additional therapy after total thyroidectomy and RAI (Padovani et al 2012). This patient

population includes both patients with no evidence of disease (remission) and patients with low level disease who are being observed (median follow up time is 7 years). Figure 2 illustrates that 94% of the 223 patients with no evidence of disease achieved a suppressed Tg level of < 1 ng/mL (the biochemical component of remission) by 18 months after initial RAI therapy. Therefore, it is expected that most patients who are likely to achieve remission in both arms will have done so by this time (for the purpose of this study both biochemical and structural absence of disease will be assessed). Longer follow-up would not be expected to change the conclusions regarding an efficacy difference between the two study arms. In patients with similar characteristics to those planned in this study, a similar pattern and extent of Tg decline is also seen (Tuttle RM, unpublished sub-analysis of data from Padovani et al 2012). Previous studies have used time-points ranging from 8 to 24 months to assess remission rates after primary treatment of surgery and RAI (Castagna et al 2011, Tuttle et al 2010, Vaisman et al 2012).

Taking all the data into consideration, the incidence of complete remission at 18 months following initial RAI therapy has been selected as the primary endpoint for the proposed study. Each randomised patient will be followed beyond their 18 month primary endpoint assessment, until 3 years after their RAI treatment, in order to further assess both the clinical status of patients, and the safety profile of selumetinib and RAI beyond the primary analysis (refer to Section 6.4.8).

Figure 2 **Time course to achieving a suppressed Tg<1 ng/mL in patients receiving total thyroidectomy and RAI therapy**



4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, (eg, patient screening log), of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures. The main study consent will include mandatory consent to provide a sample of archival tumour material.

2. Males and females aged 18 years or above.

3. Patients with histologically or cytologically confirmed follicular cell derived differentiated thyroid cancer including papillary thyroid cancer and all variants, follicular thyroid cancer and all variants, and poorly differentiated thyroid cancer.

4. Note: Patients with a diagnosis of Hürthle cell carcinoma should be excluded. These are defined as having an invasive tumour composed of >75% of oncocytic (Hürthle) cells lacking the nuclear features of papillary carcinoma, tumor necrosis and marked mitotic activity. Patients with oncocytic (Hürthle cell variants) of papillary thyroid carcinoma defined as a tumour composed of a majority of oncocytic (Hürthle) cells having the nuclear features of papillary carcinoma are eligible to participate.

5. Patients presenting with any one of the following staging categories post-surgery:

   (a) Primary tumour greater than 4 cm

   (b) Primary tumour of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)

   (c) N1a or N1b disease with at least 1 lymph node ≥ 1 cm

   (d) N1a or N1b disease involving 5 or more lymph nodes (of any size)

   Note: Patients with known metastatic disease at screening will be ineligible for this study as per the exclusion criteria.

6. Patients must have had a one or two-stage total thyroidectomy with therapeutic neck dissection of any clinically apparent metastatic lymph nodes (levels I to VII of the lateral and central neck). All known tumour must have been resected.

Note, the optimal surgical procedure is based on the findings from preoperative ultrasound, to identify the extent of lymph node metastases and thereby facilitate compartment-oriented neck dissection for complete surgical removal of all gross disease. Prophylactic neck dissection is not required or encouraged, but may be performed at the discretion of the treating surgeon. As the surgical procedure(s) will have been performed before study consent, any patient for whom a total thyroidectomy cannot be verified must be excluded from the study (note that patients having undergone a robotic or endoscopic thyroidectomy, or any other novel or remote access surgical technique must also be excluded). For patients who have had a two-stage thyroidectomy, the second surgical procedure must have taken place no later than 12 weeks after the first procedure, otherwise the patient is not eligible.

7. Patients must have all of the following post-operative assessments performed no sooner than 4 weeks post-surgery (post their last surgery if it was a 2-stage thyroidectomy) and the results from each must verify the absence of macroscopic disease:

   (a) Neck US exam

   (b) Neck MRI with contrast

   (c) Chest CT without contrast

   Refer to Section 6.3 for further details. These assessments must be performed within the 28 day screening period (but ideally after all other screening assessments have been performed, ie, they should not be performed for any patient that is otherwise ineligible).

8. Patients must be suitable for radioactive iodine therapy.

9. Patients must be suitable for TSH suppression with a goal of ≤0.5 mIU/L TSH for the duration of the study (this may exclude some patients with cardiac conditions or osteoporosis).

10. Patients must be willing and able to start study treatment within 16 weeks of their thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy). Note that study treatment must not be initiated within 6 weeks of the patient's last surgery.

11. WHO or ECOG Performance Status 0 or 1.

12. Females must:

   (a) be using adequate contraceptive measures (refer to Section 5.1.2),

(b) not be breast feeding (breast feeding must be discontinued in order to participate in this study),

(c) have a negative pregnancy test prior to the start of dosing if they are of child-bearing potential,

(d) or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

(i) Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.

(ii) Women under 50 years old will be considered postmenopausal if they have been amenorrheic for at least 12 months following cessation of exogenous hormonal treatments, and with LH and FSH levels in the post-menopausal range for the institution.

(iii) Documentation of irreversible surgical sterilisation by hysterectomy and/orbilateral oophorectomy and/or bilateral salpingectomy but not tubal ligation.

13. Male patients with sexual partners who are pregnant or who could become pregnant (ie, women of child-bearing potential) must agree to use acceptable methods of contraception until 12 weeks after completing study therapy, or longer if required for standard RAI administration restrictions and in accordance with local labels, to avoid pregnancy and/or potential adverse effects.

14. Adequate organ function as defined by:

(a) ANC ≥ 1.5x109/L (1500 per mm3)

(b) Platelets ≥ 100 x 109/L (100,000 per mm3)

(c) Hemoglobin ≥ 9 g/dL

(d) ALT/SGOT and AST/SGPT < 2.5 X upper limit of normal (ULN).

(e) Bilirubin ≤ 1.5 X ULN (with the exception that patients with elevated unconjugated bilirubin due to a pre-existing diagnosis of Gilbert's syndrome are eligible for the study)

(f) Serum creatinine clearance > 50mL/min by either Cockcroft-Gault formula (see Appendix E) or 24hr urine collection analysis.

15. Patients must be able to swallow selumetinib/placebo capsules for the duration of the study treatment period. This may exclude some patients with swallowing

dysfunction due to the specific technique required for their thyroid surgery. Functional assessment of swallowing ability may be made by the treating Investigator.

4.1.1 Genetics research study (optional blood sample)

1. For inclusion in the optional genetics research study patients must provide optional genetics research informed consent.

2. If a patient declines to participate in the genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

4.1.2 Biomarkers research study on tumour progression biopsy

For inclusion in the optional progression tumour sample study, patients must provide optional consent for this sample to be obtained.

If a patient declines to provide consent to obtain optional tumour sample on progression, there will be no penalty or loss of benefit to the patient, and the patient will not be excluded from any other aspect of the main study.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Known distant metastatic disease at study entry. Investigators are not required to specifically screen patients for distant metastasis beyond their normal Standard of Care practices and the protocol-specific post-operative imaging assessments, but any patient with known distant metastatic disease at screening must be excluded.

2. Diagnosis of anaplastic thyroid cancer, medullary thyroid cancer, or Hürthle cell carcinoma (refer to inclusion criterion 4 for further details on Hürthle cell eligibility).

3. Presence of anti-Tg antibodies at screening (as determined by standardised central methodology, refer to Section 6.4.3.4).

4. Previous treatment with ^{131}I (RAI) or external beam radiation therapy (EBRT) at any time in the past.

5. Any unresolved toxicity ≥ CTCAE Grade 2 from previous anti-cancer therapy including the patient's recent thyroid cancer surgery.

6. Having received an investigational drug during the last 4 weeks prior to first dose of study treatment.

7. Recombinant human TSH (rhTSH, Thyrogen):

(a) Patients with known hypersensitivity to rhTSH will be excluded.

(b) Patients not willing to use rhTSH prior to their RAI treatment will also be excluded (ie, patients or clinicians choosing withdrawal of thyroid hormone treatment prior to their RAI treatment will be ineligible for this study).

8. Patients requiring medication with high content in iodide (amiodarone), or patients receiving IV iodine containing contrast as part of radiographic procedure within the last 3 months prior to the planned RAI treatment (unless a urine measurement demonstrates that urinary iodide level has returned to normal range earlier than 3 months following administration of a contrast agent).

9. Patients with clinically significant cardiovascular disease as defined by the following:

(a) Uncontrolled hypertension (BP ≥150/95 despite optimal therapy)

(b) LVEF < 55% measured by echocardiography (or MUGA)

(c) Symptomatic heart failure (NYHA grade II-IV), prior or current cardiomyopathy, or severe valvular heart disease

(d) Uncontrolled angina (Canadian Cardiovascular Society grade II-IV despite medical therapy)

(e) Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest

(f) Acute coronary syndrome within 6 months prior to starting treatment

(g) Mean QTc interval >470 ms

10. Patients with the following ophthalmological findings/conditions:

(a) Intraocular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intraocular pressure)

(b) Current or past history of central serous retinopathy or retinal vein occlusion

11. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to agents used in the study.

12. Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

13. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

14. Pregnant women will be ineligible (breast feeding should be discontinued if the mother is treated with study therapy).

15. Male or female patients of reproductive potential who are not employing an effective method of contraception (refer to Section 5.1.2).

16. Refractory nausea and vomiting, chronic gastrointestinal diseases, or significant bowel resection that in the Investigator's opinion would preclude adequate absorption of study therapy.

17. History of another primary malignancy within 5 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ and the disease under study.

18. Clinical judgement by the investigator that the patient should not participate in the study.

19. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

20. Previous treatment with any MEK or BRAF inhibitor.

21. Previous enrolment or treatment in the present study.

4.2.1 Genetics research study (optional blood sample)

1. Exclusion criteria for participation in the optional genetics research component of the study:

(a) Previous allogeneic bone marrow transplant

(b) Whole blood transfusion within 120 days of the date of genetic sample collection (except for leukocyte depleted blood transfusion, which is allowed)

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

5.1.1 Low-iodine diet

Published data and opinion regarding the necessity for a low iodine diet prior to RAI therapy or a diagnostic whole body scan is variable. For the purpose of this study a low iodine diet will be mandated in order to standardise patient care and study data as best as possible. Compliance to the low iodine diet will not be recorded or assessed, and all randomised patients will receive RAI treatment as planned. Refer to Table 2 and the Study Plan (Table 3) for further details. An example low iodine diet is provided as Appendix F to this protocol.

A low iodine diet is necessary at two occasions in the study:

Prior to RAI adjuvant treatment

All patients must be willing to adhere to the low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI therapy.

Prior to the primary endpoint Stage 2 assessments

All patients must be willing to adhere to the low iodine diet for a period of 1 week before the diagnostic ^{131}I dose used prior to the primary endpoint WBS assessment (^{131}I nuclear medicine scan), until the diagnostic WBS assessment is completed. This is only relevant for patients who pass Stage 1 primary endpoint assessments (refer to Section 6.4.2).

5.1.2 Other study restrictions

The following restrictions also apply while the patient is receiving selumetinib or placebo:

1. Female patients of child-bearing potential will be required to use reliable methods of contraception until 4 weeks after the last dose of selumetinib/placebo or longer if required for standard RAI administration restrictions and in accordance with local labels. Male patients will be required to use reliable methods of contraception until 12 weeks after the last dose of the last study treatment, or longer if required for standard RAI administration restrictions and in accordance with local labels. Reliable methods of contraception should be used consistently and correctly. Acceptable methods include implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception), some IUDs and vasectomised partner. Sexual abstinence is also an acceptable method of contraception according to ICHM3.

2. Fasting restrictions for the study are described in Section 5.5.2.

3. Patients should avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.

4. Patients should avoid large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study treatment period.

5. Selumetinib capsules contain D-α- Tocopheryl polyethylene glycol 1000 succinate (TPGS, a water-soluble form of vitamin E) as an excipient. Patients should not therefore take vitamin E supplements or multivitamin supplements which provide a total daily dose in excess of 100% of the recommended daily allowance for vitamin E. The maximum dose of vitamin E patients may receive from selumetinib is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided. High doses of vitamin E have been reported to potentiate the anticoagulant activity of coumadins such as warfarin. Patients who are taking coumadin anticoagulants should increase the frequency of assessment of anticoagulation, such as INR measurements, upon initiation of dosing with study treatment.

6. Permitted and excluded antiemetic medications in this study are described in Section 5.6.

7. Permitted and excluded medications for management of skin toxicities (eg, rash) are described in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib." All patients will be given prophylactic provision of emollient cream to take home and to start using when starting study treatment.

8. Unless patients require re-treatment, they should not be enrolled in other studies evaluating novel therapies for thyroid cancer for the entire study duration.

5.2 Patient enrolment, randomisation and initiation of investigational product

The Principal Investigator or delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 4.1 and 4.2

3. Call IVRS/IWRS to assign the eligible patient a unique enrolment number (beginning with 'E#'), and randomisation code (subject number). Randomisation codes will start at 001 and go up.

Randomisation codes will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for randomisation.

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused.

If a patient withdraws from the study after they have been enrolled or have received study treatment then they cannot re-enter the study.

5.2.1 Procedures for randomisation

Patients who satisfy all the entry criteria will be centrally assigned by the IVRS/IWRS, according to the randomisation scheme generated by the Biostatistics Group, AstraZeneca, to selumetinib or placebo in a ratio of 2:1.

Every effort should be made to minimise the time between randomisation and starting treatment. Patients must not be randomised unless all eligibility criteria have been met.

IVRS/IWRS will be used for allocation of enrolment number, allocation of randomisation number, study medication assignment, discontinuation from study treatment, emergency code breaks and study drug shipment confirmation.

5.3 Procedures for handling patients incorrectly enrolled, randomised or initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are incorrectly enrolled but are not yet randomised or initiated on treatment should be withdrawn from the study.

Where patients that do not meet the inclusion and/or exclusion criteria, are enrolled in error, or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the AstraZeneca Physician immediately.

The AstraZeneca Physician must ensure all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The active and placebo capsules will appear identical and presented in the same packaging to ensure blinding of the medication. Medication will be labelled using a unique material pack code which is linked to the randomisation scheme. IVRS/IWRS will allocate randomisation numbers sequentially when sites call IVRS/IWRS to randomise an eligible patient. IVRS/IWRS will allocate the medication pack code to be dispensed to the patient.

All patients must remain blinded until after the 18 month primary endpoint data analysis has been conducted for the study; most patients will thus remain blinded for longer periods of time than their initial 18 month follow up period. Any patient that is re-treated prior to the 18 month primary endpoint time-point (refer to guidelines in Section 5.9), must not be unblinded until after the primary analysis of 18 month primary endpoint data from all patients in the study.

The personnel analyzing the PK samples will be unblinded to treatment allocation in order to organise the appropriate sample analysis. The treatment allocation information will be kept in a secure location until the end of the study.

Once the 18 month primary endpoint data analysis has been conducted for the study, patients may be unblinded for the remaining study follow up.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Procedures for emergency unblinding will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Selumetinib	25 mg Hyd-Sulfate capsule	AstraZeneca
Placebo to match selumetinib	Capsule	AstraZeneca

5.5.2 Doses and treatment regimens

Patients will be randomised on a 2:1 basis, via IVRS/IWRS, to receive either selumetinib 75 mg twice daily, or matching placebo.

Patients will be instructed to take 3 capsules orally on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing), twice a day approximately 12 hours apart according to the Study Plan. Capsules should be taken with water only. On clinic days when PK samples are scheduled to be taken, dosing should be delayed until arrival at the clinic and until the pre-dose PK sample has been taken.

Selumetinib/placebo will be supplied in bottles of 60 capsules of 25 mg strength. At Randomization visit, selumetinib/placebo for the entire treatment period will be dispensed (5

bottles). Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Day 1 of study treatment must occur within 16 weeks of the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).

5.5.3 Management of study treatment related toxicity

The immediate management of any adverse event should be according to standard clinical practice for that event. Subsequent management of treatment related adverse events should be guided by the Investigators' assessment of causality.

5.5.3.1 Selumetinib dose interruption or reduction

It is essential that patients remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator until the patient has been on study treatment for a minimum of 7 consecutive days (as long as the total duration of study treatment does not exceed 43 days, this allows the planned RAI to be postponed by up to 1 week if absolutely necessary).

For all adverse events reported in this study that are considered at least partly causal to administration of selumetinib, the following dose modification guidance should be applied.

Study treatment with selumetinib/placebo should be temporarily interrupted if one of the following AEs are observed (and considered causal to study treatment), **despite optimal supportive care** (ie, supportive treatment may be given prior to withholding study treatment):

- Any intolerable adverse event regardless of Grade
- Any adverse events ≥ CTCAE Grade 3

On improvement of the adverse event to Grade 1 (Grade 2 for rash) or baseline, study treatment may be restarted at the original dose or may be reduced at the discretion of the investigator. One dose reduction of study treatment to 50 mg twice daily is permitted before permanent discontinuation.

- If a further episode of the same AE subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the AE.
- If a different AE subsequently requires dose interruption, selumetinib may be restarted at the same dose or at the next dose level down on improvement of the AE.
- Selumetinib should not be re-escalated to an earlier dose level on improvement of an AE.

- The schedule of assessments described in Table 3 should continue relative to Day 1 in the event of selumetinib dose interruption or reduction.

Therefore, the dose reduction/adjustment algorithm in the study allows for 2 steps only:

75 mg twice daily (initial dose)
↓
50 mg twice daily
↓
permanent discontinuation

All dose delays, reductions and adjustments will be recorded in the appropriate electronic Case Report Form (eCRF).

The guidance above should also be followed for dose interruptions or reductions for adverse events of rashes or diarrhoea. Guidance for interruption or reduction of treatment with selumetinib may be considered for particular events, as indicated in the algorithms provided as a separate study aid in the "Guidance for Management of Specific Adverse Events in Studies of Selumetinib" (refer to Section 5.5.3.2).

5.5.3.2 Management and investigation of specific selumetinib related AEs

Recommendations for the management or investigation of the following specific AEs is provided in Appendix G: Guidance for Management of Adverse Events in Studies of Selumetinib.

- Rash: early initiation of treatment for rash is strongly recommended to minimise the duration and severity of the adverse event. All patients should be given prophylactic provision of emollient cream to take home and to start using when starting study treatment as indicated in the algorithm for management and investigation of rash included in Appendix G.

- Visual disturbances: symptoms, including blurred vision, have been reported during treatment with selumetinib. Events consistent with central serous retinopathy have been reported in a small number of patients receiving treatment with selumetinib, generally in combination with other novel targeted anti-cancer agents. AEs of central serous retinopathy and retinal vein occlusion have been reported in studies of other MEK inhibitors (Lemech & Arkenau 2012). Investigation to determine the underlying cause of visual disturbance is recommended.

- Diarrhoea: early initiation of treatment for diarrhoea is strongly recommended to minimise the duration and severity of the adverse event. Treatment provision will be according to Investigator discretion according to local practice and regulations.

- Dyspnoea: new or worsening dyspnoea has been reported during treatment with selumetinib; investigation to determine the underlying cause is recommended.

5.5.4 Additional study drugs

5.5.4.1 Thyrogen (rhTSH, thyrotropin alfa for injection)

Thyrogen use prior to the RAI ablative dose

Effective use of RAI therapy requires stimulation by TSH in order to maximise RAI uptake by thyroid cells. Recombinant human TSH (rhTSH or Thyrogen) will be used to stimulate iodide uptake according to the manufacturer's recommendation (0.9 mg intra-muscular injection for 2 days immediately prior to the RAI treatment according to the Study Plan Table 3). rhTSH is approved for use in routine clinical care as a diagnostic tool to stimulated serum thyroglobulin and RAI uptake for diagnostic scanning and as an adjunct to RAI ablation in many countries. This allows patients to avoid the hypothyroidism state, since they can maintain their routine thyroid hormone supplementation. Patients or clinicians choosing withdrawal of thyroid hormone treatment for this purpose will be ineligible for this study. All randomised study patients will receive Thyrogen twice prior to their RAI treatment dose.

Thyrogen use for the primary endpoint assessments (18 months post-RAI)

For those patients that progress to Stage 2 of the primary endpoint assessments (refer to Section 6.4.2), Thyrogen will be used to stimulate iodide uptake immediately prior to administering the diagnostic ^{131}I dose for the primary endpoint WBS assessment. Patients will receive a 0.9 mg intra-muscular Thyrogen injection for two consecutive days. Refer to Section 6.4.2.2 for further details.

5.5.4.2 Radioactive iodine (RAI)

All RAI for the study will be locally provided at each site.

Therapeutic RAI dose (^{131}I)

A single oral RAI dose of 100 mCi (3.7 GBq) ^{131}I (+/- 10% at the time of administration) will be administered to all patients according to the Study Plan Table 3, according to standard practice at each site.

Diagnostic WBS dose (^{131}I)

For those patients that progress to Stage 2 of the primary endpoint assessments (refer to Section 6.4.2), a single oral RAI dose of 5 mCi (185 MBq) ^{131}I (+/- 10% at the time of administration) will be administered for the primary endpoint WBS (nuclear medicine scan) 18 months following the ablative treatment dose of RAI. Refer to the Study Plan Table 3, and Section 6.4.4.2 for further details.

5.5.4.3 Thyroid hormone supplementation (TSH suppression)

Routine thyroid hormone supplementation (levothyroxine, LT4) is required during the study as per standard clinical practice. The purpose of this is both to correct resulting hypothyroidism using a dosage appropriate to achieve normal blood levels of thyroid hormone, and to inhibit TSH-dependant growth of residual thyroid cancer cells. Thyroid

hormone supplementation will be adjusted in individual patients with the aim of achieving suppressed TSH levels of <0.5 mIU/L for the duration of the study.

5.5.5 Study drug labelling

Each bottle of selumetinib and matching placebo capsules will be labelled by Pharmaceutical Development Supply Chain, AstraZeneca or its designee.

All labels will comply with good manufacturing practice (GMP) regulations, and will state that the drug is for clinical use only or that it is the investigational drug and is to be used by qualified investigators only and should be kept out of reach of children. The labels will have blank spaces for the site personnel to complete the following at the time of drug dispensing: enrolment code, visit number and dispensing date.

Label text will be translated into local language.

Each bottle of selumetinib/placebo capsules will have a tear-off portion that will be removed at the time of dispensing and attached to the Drug Label Accountability Log.

5.5.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

5.6 Concomitant medications

The use of antiemetic medication for the prevention of nausea caused by administration of radioactive iodine is permitted in this study according to local clinical practice (with the exception of aprepitant which is an excluded medication in this study, due to the potential for modification of selumetinib exposure via CYP3A4). The administration of any antiemetic medication must be recorded in the appropriate sections of the Case Report Form.

All patients will be given prophylactic provision of emollient cream to take home and to start using when starting study treatment as indicated in the algorithm for management and investigation of rash included in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

The following treatments/drugs are restricted in this study:

- No other anti-cancer agents, or investigational drugs should be administered whilst patients are receiving study medication or are in follow-up in this study (unless the patient withdraws from the study, or meets the re-treatment criteria in Section 5.9).
- Patients who are taking coumarin anticoagulants should increase the frequency of assessment of anticoagulation, such as INR measurements, during the study treatment period with selumetinib/placebo.

- The maximum dose of vitamin E patients may receive from selumetinib is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided in patients receiving the capsule formulation.

- Throughout the study, patients should avoid changes to, or the addition of all other concomitant medications, in particular any that may affect the metabolism of selumetinib (eg, CYP1A2 or 3A4 inhibitors/inducers), unless considered clinically indicated.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

All concomitant medications will be recorded on the CRF until 30 days after the last dose of study treatment, and after this time a study-specific record must be kept of any further treatment for thyroid cancer (including surgery), or treatment for RAI-related AEs/SAEs until the last study visit for all patients (refer to Section 5.9).

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Where appropriate facilities and procedures for drug destruction exist, and prior approval from the site monitor has been received, site personnel will account for all unused drugs and for appropriate destruction.

Where such facilities do not exist study site personnel/study monitor will return all unused drugs to AstraZeneca or its designee according to country rules.

The AstraZeneca monitors will ensure that all drug-handling procedures at sites are appropriate, and that all certificates of delivery and return are completed and signed by the site, AstraZeneca, or its delegate, as appropriate. In addition, the monitor will check that the certificate of destruction has been signed by the site, if study drug destruction is performed at the site.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Risk to patients as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- A female patient becoming pregnant

5.8.1 Procedures for premature discontinuation of a patient from investigational product

A patient that decides to prematurely discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.5.3 and 6.5.4), and all study drugs should be returned by the patient. In this situation, a treatment discontinuation visit will be conducted as soon as possible after the patient received the last dose of study drug (selumetinb/placebo). A single 12-lead ECG is also required at premature discontinuation of treatment.

If a patient is withdrawn from the study (ie, withdraws consent for follow-up procedures), see Section 5.10.

Collection of all AEs/SAEs will continue until 30 days after the last dose of study drug (selumetinib/placebo) for prematurely withdrawn patients. As long as the patient does not withdraw consent, follow up in this study will continue as planned.

Any patient with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (±7days) after discontinuation.

5.9 Criteria for further thyroid cancer therapy during the study

5.9.1 Re-treatment prior to the 18 month primary endpoint assessments

It is acknowledged that there is variability in thyroid cancer re-treatment clinical practice. The study-specific criteria below are designed to standardise re-treatment prior to the primary endpoint assessments for the purpose of this study as best as possible. Thus, further thyroid cancer therapy (eg, additional surgery or RAI treatment) prior to the primary analysis of complete remission at 18 months post-RAI, must not be administered unless any of the following criteria are met.

Patients meeting the following re-treatment criteria do not have to be re-treated, they can instead be followed expectantly without re-treatment at the discretion of the treating Investigator.

5.9.1.1 Biochemical disease re-treatment criteria

The first scheduled post-RAI follow up for serum Tg will be assessed 9 months after the RAI dose (± 3 months). Tg assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (**but not before 6 months**).

All biochemical sample analysis for study re-treatment criteria must be performed by standardised central laboratory methodology (for further details refer to the Laboratory Manual).

Patients must not be re-treated for thyroid cancer unless any of the following biochemical criteria are met:

1. If a serum Tg level ≥ 5 ng/mL on central analysis is measured **during TSH suppression**, then a repeat Tg sample must be assessed by central analysis 2-4 weeks later. The patient must not be re-treated unless both centrally analysed samples demonstrate the suppressed Tg level to be 5 ng/mL or higher.

2. If a serum Tg level ≥ 10 ng/mL is measured **following TSH stimulation**, the patient may be re-treated (a repeat sample for confirmation is not necessary). Note, a stimulated Tg assessment is not part of the study-specific follow up plan for patients prior to the 18 month primary endpoint assessments (thus it is not recommended or required, and is not included in the Study Plan). However, if a stimulated Tg assessment is performed due to local practice, this re-treatment criterion applies.

3. If an increase (delta change) in serum Tg level of 3 ng/mL or more is determined between two Tg assessments taken 2-4 weeks apart (due to a repeat sample), the patient may be re-treated.

Thus, in the absence of structurally identifiable disease, patients in this study should have continued observation without additional thyroid cancer treatment (eg, additional RAI, surgery) until the study primary endpoint (18 months after RAI treatment), if the serum Tg level remains below 5 ng/mL during TSH suppression, below 10 ng/mL following TSH stimulation (if assessed), and is either stable/declining, or rising less than 3 ng/mL between samples 2-4 weeks apart.

Note: If a patient has Tg levels below the above re-treatment criteria, but TgAb are detected (ie, the patient is TgAb positive; refer to Section 6.4.3.4), the patient should not be re-treated unless new structural disease is detected according to Section 5.9.1.2 (ie, it is recommended that patients are not re-treated on the basis of new antibodies alone, in the absence of structural disease).

Unscheduled samples and local analysis

It is acknowledged that Investigators may wish to also perform their own local biochemical analysis according to local standard of care. In general, unscheduled samples that are taken

either outside of the visit window specified, or in addition to the scheduled study samples, should not be sent for standardised central analysis. Only if such unscheduled local analysis leads the Investigator to wish to administer further therapy for thyroid cancer, should a sample ideally be sent for central analysis and the above criteria applied before the patient is re-treated.

5.9.1.2 Structural disease re-treatment criteria

The first post-RAI ultrasound follow up will be assessed 9 months after the RAI dose (± 3 months). Ultrasound assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (but not before 6 months).

Patients must not be re-treated for thyroid cancer unless any of the following structural criteria are met:

1. In the absence of any biochemical evidence of thyroid cancer, structural DTC should be confirmed prior to re-treatment, by positive histology/cytology from a biopsy/FNA of ultrasonographically suspicious lesions or lymph nodes ≥ 5 mm in the smallest diameter (refer to Section 6.4.4.5).

2. Identification of new distant metastases (these do not need to be confirmed by biopsy). Assessment of potential distant metastases is not required, but may be performed if clinically indicated at the discretion of the treating Investigator.

5.9.1.3 Patient management on study (up to the primary analysis at 18 months post-RAI)

At the required follow up visits, the following questions should be answered for each subject:

1. Does the patient have a suppressed Tg ≥ 5 ng/mL, a TSH stimulated Tg ≥ 10 ng/mL or a rising Tg level (increase of 3 ng/mL or more) according to the guidelines in Section 5.9.1.1?

2. Does the patient have new loco-regional structural thyroid cancer according to the guidelines in Section 5.9.1.2?

3. Does the patient have new distant metastatic lesions according to the guidelines in Section 5.9.1.2?

If the answer is yes to any of the questions, the patient is unlikely to enter remission and may be re-treated for thyroid cancer (but does not have to be).

Full details of any thyroid cancer re-treatment must be recorded on the appropriate eCRF.

Any re-treated patients will remain in the study and should enter standard of care follow up according to local practice until 3 years after their initial RAI therapy (refer to Section 6.4.8). Patients who are re-treated prior to the primary endpoint at 18 months post-RAI do not require primary endpoint disease assessments performing, however these patients should continue to

follow all protocol-scheduled visits for safety (AE/SAE follow-up) as described in the Study Plan Table 3 and in Section 6.5. Patients do not need to attend these follow up visits in person (telephone contact is permitted), however when local follow-up visits coincide with protocol-specified visits, these should ideally be in person where possible.

If the answer is no to all questions, the patient should continue the study follow-up as per protocol without additional thyroid cancer re-treatment.

5.9.2 Re-treatment after the 18 month primary endpoint assessments

Following completion of all assessments for complete remission at the primary endpoint 18 months post-RAI, patients may receive re-treatment for thyroid cancer as per clinically indicated according to local standard of care. Any re-treated patients will remain in the study and should enter standard of care follow up according to local practice until 3 years after their initial RAI therapy (refer to Section 6.4.8).

Full details of any thyroid cancer re-treatment must be recorded on the appropriate eCRF.

5.10 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and follow-up assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.5.3 and 6.5.4); any remaining study drug should be returned by the patient.

5.11 Replacement of patients

There will be no replacement of randomised patients in this study for any reason.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

6.2 Data collection at enrolment

The following data will be collected & procedures performed for each patient:

1. Informed consent (to include consent for archival tumour sample provision)

2. Demography (date of birth, sex, race)

3. Histological/cytological confirmation of thyroid cancer, including post-operative disease staging

4. Medical and surgical history

5. Concomitant medications and previous anti-cancer therapy

6. Assessment of WHO or ECOG performance status (refer to Section 6.2.1)

7. Collection of AEs will start after signing the consent form

8. Physical examination

9. Vital signs (resting blood pressure (BP), pulse rate), weight and height

10. Single ECG

11. Blood samples for clinical chemistry and haematology

12. Blood sample for determination of interfering Tg antibodies (central standardised analysis)

13. Urinalysis (at sites where the local laboratory is able to determine the required parameters, see Section 6.5.5)

14. Pregnancy test for female pre-menopausal patients

15. Full ophthalmologic examination, including slit-lamp fundoscopy and intraocular pressure examination

16. ECHO or MUGA

17. The following imaging assessments must be performed within the 28 day screening period but only after all other screening procedures have confirmed eligibility status (refer to Section 6.3):

    (a) Neck ultrasound (US)

    (b) Neck MRI with contrast

    (c) Chest CT scan without contrast

18. Overall assessment of patient eligibility for the study

19. Upon confirmation of patients' eligibility, patients will be invited to attend the randomisation visit. Patients must not be randomised unless all eligibility criteria have been met.

20. Call interactive voice response system (IVRS)/interactive web response system (IWRS) to randomise the patient

6.2.1 Performance status definitions

Performance status will be assessed at screening according to either the WHO or ECOG criteria as follows:

0 = Fully active, able to carry out all pre-disease performance/activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

6.3 Post-operative imaging assessments for eligibility

The post-operative imaging assessments of US, neck MRI and chest CT are performed during screening to determine study eligibility. These assessments must determine the absence of macroscopic persistent disease post-surgery for a patient to be eligible prior to randomisation. The post-operative imaging assessments must be scheduled once all other screening assessments and eligibility criteria have been verified.

The screening chest CT procedure must be performed **without iodine containing contrast agent**.

Eligibility will be determined by the local investigational site.

Acquisition guidelines for the post-operative imaging assessments will be provided separately to this protocol.

In addition to information recorded on the eCRF for US, the post-operative images for chest CT and neck MRI must be collected and sent to the central imaging CRO.

6.4 Efficacy

6.4.1 Complete remission

The primary endpoint for this study is **complete remission rate at 18 months** (following RAI treatment).

Definition of complete remission:

Patients will be defined to be in complete remission if all of the following criteria can be demonstrated:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer[a] on neck US, as assessed by investigator site review.

3. No confirmed radiological evidence of thyroid cancer[a], as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

There are two main components to complete remission: biochemical remission and structural remission. Biochemical remission is measured by Tg and structural remission is assessed by the imaging assessments US, MRI, CT and WBS in conjunction with biopsy/FNA.

A staged approach will be taken for performing assessments contributing to the primary endpoint, to avoid unnecessary assessments for individual patients who received further therapy prior to the primary assessment, and for those patients not in biochemical remission (as determined by serum Tg levels in the absence of interfering Tg antibodies).

[a]Confirmation of evidence of structural DTC will be either histopathological (from a biopsy/FNA; as criterion 4 above), or RAI-avid disease (refer to Section 6.4.4.2). In this disease setting, structural abnormalities that are not RAI-avid and do not have confirmed histopathology consistent with DTC (ie are not biopsy proven) are considered benign in the absence of biochemical DTC.

6.4.2 Staged approach to primary endpoint assessments

Full details of the staged approach to the primary endpoint assessments are outlined below.

There will be 3 stages of assessments. Patients that have been re-treated for thyroid cancer will not have any primary endpoint assessments performed. All patients who have not been re-treated for thyroid cancer will have stage 1 assessments performed. The decision on whether to proceed to stage 2 and 3 assessments for patients that have not been re-treated will be based on centrally analysed biochemical data (Tg and TgAb data).

Sites will receive results from standardised central laboratory analysis of the biochemical data and make a decision to proceed based on these results. Patients identified as not in

biochemical remission will not be required to have all imaging assessments described in Section 6.4.1 performed.

For patients that have imaging assessments performed, the appropriate data will be sent to the imaging CRO for blinded independent central review to identify presence or absence of structural disease. Note: results from the central imaging review will not be reported to clinical sites.

Briefly:

In stage 1, suppressed Tg will be determined together with neck US assessment for all patients who did not require re-treatment for thyroid cancer during the first 18 months of follow up (refer to Section 6.4.2.1).

In stage 2, rhTSH stimulated Tg and diagnostic WBS will be performed (refer to Section6.4.2.2).

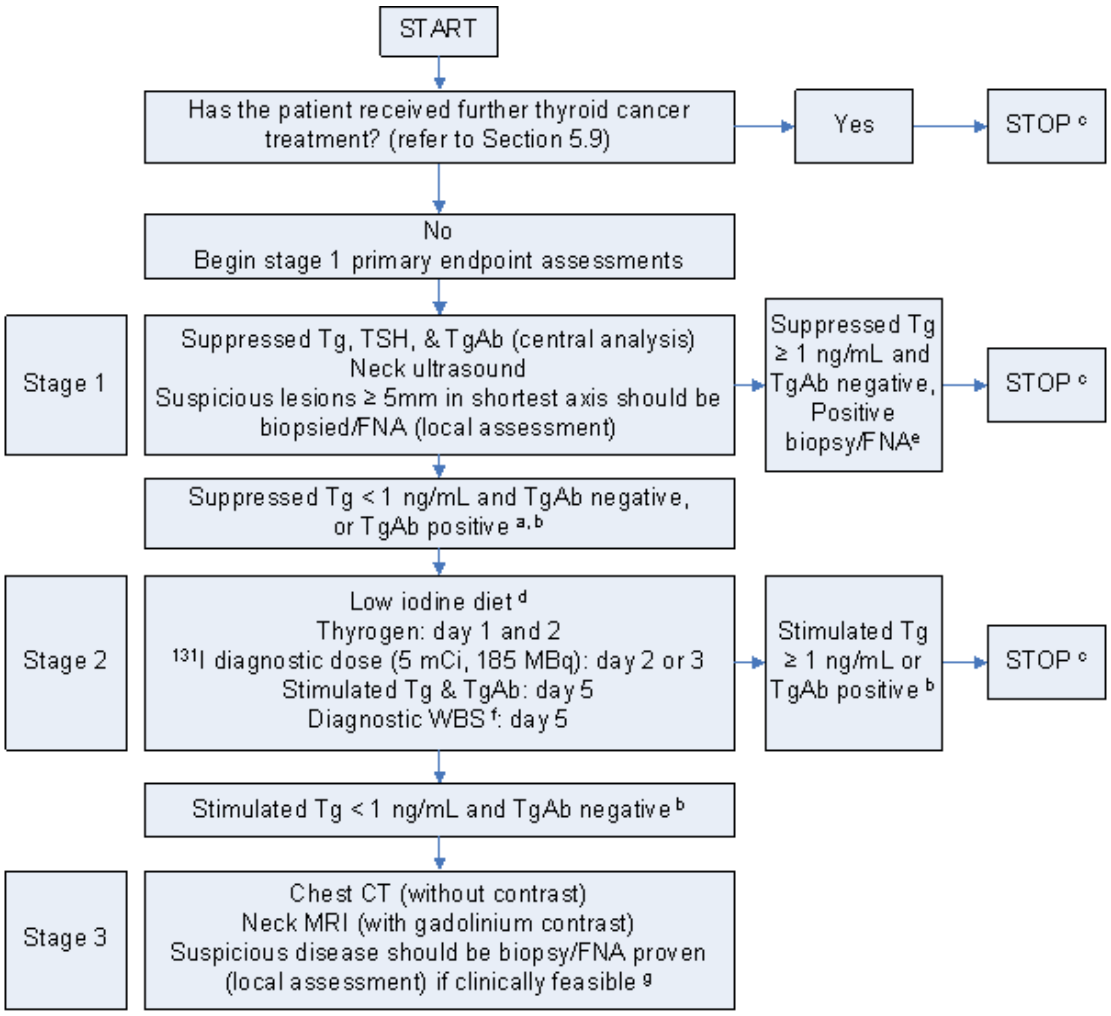
In stage 3, additional radiological imaging (chest CT and neck MRI) will be performed (refer to Section 6.4.2.3).

Stage 1 assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments (all 3 stages if required) must be completed within an 8 week period (refer also to Table 4).

Refer to the flowchart Figure 3 for a visual representation of the staged approach for primary endpoint assessments.

Refer to Section 6.4.5 for the process of determining complete remission from the primary endpoint assessment data.

Figure 3 Flow chart for staged primary endpoint assessments



[a] Patients should progress to stage 2 assessments based on biochemical data only (regardless of US results). Any TgAb positive patients should progress to stage 2 regardless of their suppressed Tg result.
[b] If both stage 1 and stage 2 blood samples are positive for TgAb, then the stimulated Tg result will be deemed to be uninterpretable, and for the purpose of this study the patient will be classified as not in complete remission. No further primary endpoint assessments are required. The patient will remain in the study for follow up until 3 years following their initial RAI treatment. If the stage 1 and stage 2 samples are discordant for TgAb status, then a third blood sample 10 days later (± 3 days) is required to confirm TgAb status.
[c] For the purpose of this study, patient will be classified as not in complete remission. The patient should remain in the study for follow up until the final study visit 3 years following their initial RAI treatment, and enter standard of care treatment/follow up according to local clinical practice.
[d] Low iodine diet is required from 1 week before the diagnostic dose of ^{131}I is administered, until completion of the WBS assessment. Refer to Appendix F.
[e] If a patient has a biopsy/FNA result available that confirms the presence of structural DTC then no further assessments are required. If a biopsy/FNA was taken, but the result is not yet available, then the patient should not delay moving to stage 2 assessments (even if the biopsy/FNA is subsequently confirmed to be positive for structural DTC).
[f] For study endpoint purposes the WBS will evaluated by blinded independent central review. Even if local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).
[g] For the size criteria for biopsy/FNA from MRI/CT assessments, refer to Sections 6.4.4.3 and 6.4.4.4 respectively.

6.4.2.1 Primary endpoint assessments Stage 1

Patients that have been re-treated for thyroid cancer between their initial RAI dose and the primary endpoint assessments 18 months later (refer to Section 5.9 for re-treatment criteria), will not have any primary endpoint assessments performed. For the purpose of the primary endpoint, such re-treated patients will be determined not to be in complete remission.

In stage 1, all patients that have not previously been re-treated for thyroid cancer will have:

- Suppressed Tg level determined by standardised central laboratory analysis.
- TSH and TgAb (using the same blood draw for suppressed Tg) determined by standardised central laboratory analysis. Refer to Section 6.4.3.
- Neck US assessment for structural disease to be assessed by investigator site review. Refer to Section 6.4.4.1.

Suspicious lesions identified by US ≥ 5 mm in the shortest diameter should be biopsied or aspirated by fine needle. All biopsy/FNA samples will be assessed locally at each site. Lesions identified by US < 5 mm in the shortest diameter do not require a biopsy.

All neck US and biopsy/FNA samples will be assessed locally at each site. The relevant US information with any biopsy findings will be provided to the imaging CRO as part of the blinded independent central review.

When to proceed to stage 2 assessments

All patients in the following situations should proceed to stage 2 assessments:

1. Patients with suppressed Tg < 1 ng/mL. These patients should proceed to stage 2 regardless of the TgAb or US results.
2. Patients who are TgAb positive in stage 1 (regardless of the suppressed Tg level, and US results).
3. Patients who fulfil either of the 2 above criteria, and have a biopsy/FNA result pending (ie, Investigators should not wait for the biopsy/FNA result before performing stage 2 assessments).

When not to proceed to stage 2 assessments

All patients in the following situations will be classified not in complete remission and should not proceed to stage 2 assessments:

1. Patients who have suppressed Tg level ≥ 1 ng/mL in the absence of TgAb (unequivocal biochemical disease).

2. Patients with a positive biopsy/FNA that confirms the presence of structural DTC. Note that if the biopsy/FNA results are not yet available, the patient should not delay proceeding to stage 2 assessments.

Patients who demonstrate presence of disease and do not proceed to stage 2 assessments will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, **and will continue to be followed in this study** until 3 years following their initial RAI dose (refer to Section 6.4.6).

6.4.2.2 Primary endpoint assessments Stage 2

In stage 2, patients will have:

- rhTSH stimulated Tg level determined by standardised central laboratory analysis.
- TgAb (from the same blood draw for rhTSH stimulated Tg) determined by standardised central laboratory analysis. TSH will not be analysed from this sample. A repeat (third) sample for TgAb analysis may be required 10 days ± 3 days later if the stage 1 and 2 TgAb status is discordant (refer to Table 5).
- Diagnostic nuclear medicine ^{131}I scan (WBS) to be evaluated by blinded independent central review.

These assessments will require the patient to follow a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose, until the diagnostic WBS assessment is completed (refer to Section 5.1.1 and Appendix F). Patients will also receive two Thyrogen injections (refer to Section 5.5.4.1) on consecutive days (day 1 and 2), followed by a diagnostic dose (5 mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5.

When to proceed to stage 3 assessments

Patients should proceed to stage 3 assessments in the absence of biochemical disease. Patients with stimulated Tg < 1 ng/mL and TgAb negative (for the definition of TgAb negativity refer to Section 6.4.3.4) should proceed to stage 3 **regardless of the WBS results**.

- Note that if the stage 1 and 2 blood samples are discordant for TgAb, a repeat (third) blood sample for central analysis is required 10 days (±3 days) later. Only if the third sample is negative for TgAb will the stimulated Tg level from stage 2 be considered to be interpretable and valid for decision making. Refer also to Table 5.
- Note also that for study purposes the WBS will evaluated by blinded independent central review, and even if local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).

When not to proceed to stage 3 assessments

All patients in the following situations will be classified not in complete remission and should not proceed to stage 3 assessments:

1. Patients who have stimulated Tg level ≥ 1 ng/mL in the absence of TgAb (unequivocal biochemical disease by standardised central laboratory analysis).

2. Patients confirmed to be TgAb positive (regardless of all other data):

   (a) When both the stage 1 and 2 blood samples are TgAb positive (refer to Section 6.4.3.4).

   (b) When the repeat (third) blood sample confirms positive TgAb following a discordant TgAb status from stage 1 and 2.

In these situations the stimulated Tg value will be deemed to be uninterpretable, and the patient will be deemed not to be in complete remission because absence of biochemical disease cannot be proven.

These patients will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, and will continue to be followed in this study until 3 years following their initial RAI dose (refer to Section 6.4.6).

Note that for study purposes the WBS will evaluated by blinded independent central review. If local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).

Table 5 Criteria for biochemical decision making (based on standardised central analysis results)

Scenario	Stage 1		Stage 2		Repeat 3rd TgAb sample[b]	Biochemical remission?
	Suppressed Tg	TgAb[a]	Stimulated Tg	TgAb[a]		
1	≥ 1ng/mL	Negative	Not required	Not required	Not required	No. Stop.[c]
2	< 1 ng/mL	Negative	< 1 ng/mL	negative	Not required	Yes. Proceed to stage 3
3	< 1 ng/mL	Negative	≥ 1 ng/mL	negative	Not required	No. Stop.[c]
4	Any	Positive	< 1 ng/mL	negative	negative	Yes. Proceed to stage 3
5	Any	Positive	< 1 ng/mL	negative	positive	No. Stop.[c]
6	< 1 ng/mL	Negative	< 1 ng/mL	positive[d]	negative	Yes. Proceed to stage 3
7	< 1 ng/mL	Negative	< 1 ng/mL	positive	positive	No. Stop.[c]
8	Any	Positive	Any	positive	Not required	No. Stop.[c]

[a] Standardised central methodology will be used to define TgAb negative/positive status, refer to Section 6.4.3.4.
[b] When the TgAb results from stage 1 and 2 are discordant, a repeat (third) blood sample for TgAb is required 10 days (± 3 days) after the stage 2 blood sample.
[c] For the purpose of the study, the patient will be deemed not to be in complete remission and no further stage 3 assessments are required. These patients will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, and will continue to be followed in this study until 3 years following their initial RAI dose (refer to Section 6.4.6).
[d] Although this stimulated Tg blood sample is positive for TgAb, the patient will be declared to be in biochemical remission if the other two TgAb samples are both negative by standardised central analysis. It is not feasible to repeat a second stimulated Tg assessment.

6.4.2.3 Primary endpoint assessments Stage 3

In stage 3, patients with biochemically-negative disease will have:

- Neck MRI with gadolinium contrast to be evaluated by blinded independent central review.
- Chest CT without contrast to be evaluated by blinded independent central review.
- If clinically indicated, a biopsy/FNA should be performed as follows:
  - For any suspicious lymph nodes on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter.
  - For any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter should be biopsied/FNA.

6.4.3 Blood sample assessments for efficacy

All protocol-scheduled samples for serum Tg (suppressed and stimulated), TSH and TgAb assessment, will be sent for central laboratory analysis using standardised methodology. All decision making for study purposes will be based on the standardised central analysis results; values obtained from different assay methods may be different and cannot be used interchangeably.

Full details of the sample collection, shipment and analytical methodology is provided in the Laboratory Manual.

Unscheduled samples and local analysis:

Investigators may also perform local biochemical analysis for these parameters as per standard site practice if desired, however this data will not be used for study-related decision making. If local analysis is performed, Investigators must ensure that the maximum permissible blood volumes for individual patients at their institutions are not exceeded.

In the case that an investigator performs additional assessment of Tg (and TSH, TgAb) outside of the protocol scheduled visits, such samples should not be sent for central laboratory analysis. Only if such unscheduled local analysis leads the Investigator to wish to administer further therapy for thyroid cancer, should an additional sample ideally be sent for central analysis and the protocol-specified re-treatment criteria applied (Section 5.9.1.1) before the patient is re-treated.

6.4.3.1 Suppressed Tg

Prior to the 18 month primary endpoint assessments:

A blood sample for TSH-suppressed serum Tg is required at 9 months after the RAI dose (± 3 months) in order to assess whether thyroid cancer re-treatment is clinically indicated;

refer to the thyroid cancer re-treatment guidelines in Section 5.9.1.1. Tg assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (but not before 6 months). A second blood sample 2-4 weeks later may also be required to verify the biochemical re-treatment criteria (refer to Section 5.9).

Stage 1 primary endpoint assessments:

For all patients that have not been re-treated for thyroid cancer prior to the primary endpoint assessments 18 months following their RAI dose, a blood sample to centrally analyse the TSH-suppressed serum Tg level will be taken.

Anytime that a Tg blood sample is taken, the same sample will also be centrally analysed for TSH and TgAb (refer to Sections 6.4.3.3 and 6.4.3.4 respectively).

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

6.4.3.2 Stimulated Tg

Prior to the 18 month primary endpoint assessments:

Prior to the 18 month primary endpoint assessments, stimulated Tg levels are not recommended and not included as part of the patient follow up for this study.

Stage 2 primary endpoint assessments:

Serum Tg measured during TSH suppression is not sufficiently sensitive to confirm that a patient is free of thyroid cancer. For this reason, rhTSH (Thyrogen) stimulated serum Tg level will also be assessed at the primary endpoint, only for patients proceeding to stage 2 of the primary endpoint assessments.

For patients that require stimulated Tg assessment, 0.9 mg of rhTSH will be administered IM for 2 consecutive days (refer to Section 5.5.4.1), with the blood sample taken for stimulated Tg central analysis on day 5.

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

Each time that a blood sample is taken for central stimulated Tg analysis, the same sample will also be centrally analysed for TgAb (refer to Sections 6.4.3.4 respectively).

6.4.3.3 TSH

Thyroid hormone supplementation will be adjusted in individual patients with the aim of achieving suppressed TSH levels of 0.5 mIU/L or less for the duration of the study. Each time that a suppressed Tg sample is taken, TSH should also be assessed (by central standardised methodology).

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

6.4.3.4 Tg antibody (TgAb)

Each time that a blood sample is taken for central Tg analysis, the same sample will also be centrally analysed using standardised methodology for TgAb. Full details of the sample collection, shipment and analytical methodology to be used will be provided in the Laboratory Manual.

TgAb cut-off for decision making

For decision making purposes at any time in the study, standardised central analysis results must be used. The cut-off value for positive/negative TgAb status according to the standardised central methodology will be provided to sites prior to the start of recruitment.

At screening:

Patients with TgAbs present at screening will be ineligible for the study (refer to the exclusion criterion in Section 4.2, screening samples must be sent for standardised central analysis).

Prior to the 18 month primary endpoint assessments:

If TgAbs are detected in the follow-up Tg blood sample (at 9 months ±3 months), the patient should not be re-treated unless new structural disease is detected according to Section 5.9.1.2 (ie, it is strongly recommended that patients are not re-treated on the basis of new antibodies alone, in the absence of structural disease). Refer to Section 5.9.

Primary endpoint assessments (Stage 1 and 2)

The TgAb status of the stage 1 blood sample will not be taken into consideration alone. The following rules will apply (refer also to Table 5):

1. If both stage 1 and stage 2 blood samples are negative for TgAb, then the Tg results will be valid for decision making.

2. If both stage 1 and stage 2 blood samples are positive for TgAb, then the stimulated Tg result will be deemed to be uninterpretable, and for the purpose of this study the patient will be classified as not in complete remission. No further primary endpoint assessments are required.

3. If the stage 1 and 2 blood samples are discordant for TgAb status, then a repeat (third) blood sample is required 10 days later (± 3 days). Only if the repeat sample is confirmed negative for TgAb, will the stimulated Tg level in stage 2 be considered to be interpretable and valid for decision making.

6.4.4 Imaging assessments for efficacy

6.4.4.1 Neck ultrasound (US)

Neck US assessments will take place at the times indicated in the Study Plan Table 3. Refer also to Section 6.4.2 and Table 4 for further details of US assessment at the primary endpoint.

Any suspicious lymph nodes or lesions in the neck ≥ 5 mm in the smallest diameter identified by US during the study should be biopsied/FNA.

Note: for a lesion to be suspicious it must be new or enlarged compared to the previously obtained imaging data, and be consistent with the biological characteristics of DTC.

Biopsy/FNA samples, where performed, will be assessed at each site. Needle washout may be analysed locally for Tg according to local standard practice. The totality of the information obtained from a biopsy/FNA (including washout Tg data where analysed), will be assessed locally to determine presence or absence of thyroid cancer in the sample.

US definition of structural DTC

Any soft tissue or lymph node lesions that are new or enlarged compared to previous ultrasound assessment (either post operatively and/or at 9 months) that are consistent with the biological characteristics of DTC and fulfil the following criteria will be considered as structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is subsequently shown to be RAI avid/positive on central review of WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on US that is non-RAI avid on the subsequent WBS, will be considered benign even in the absence of a biopsy.

The assessment of neck US and biopsy/FNA sample will be made by investigator site review.

The local ultrasound information will be recorded in the eCRF (with FNA/biopsy results if performed) and provided to the central imaging CRO if necessary as supporting clinical data (refer to Section 6.4.4.6).

Guidelines for standardised acquisition, defining suspicious lesions and reporting of US assessments required for this study will be provided to each study site.

6.4.4.2 Whole body diagnostic ^{131}I nuclear medicine scan (WBS)

Pre-RAI treatment

There is no pre-ablation WBS in this study. This is a fixed RAI dose study (100mCi, 3.7GBq) with Thyrogen stimulation. Study-specific post-operative imaging will be used to ensure that enrolled patients do not have overt macronodular disease remaining in the neck or distant metastatic disease in the lungs.

Post-RAI treatment

All randomised patients will have a WBS performed 3-10 days following their RAI treatment dose to assess where the administered ^{131}I has localised.

It is acknowledged that this assessment may identify a small number of patients with distant metastatic disease that was not previously identified (patients with known metastatic disease at study entry will be excluded). Such patients will continue in the study and should not be withdrawn; they will continue to be followed according to the protocol and will be included in both the Intention To Treat (ITT) efficacy and safety analysis sets for the study.

Primary endpoint (stage 2)

If required according to Section 6.4.2, the diagnostic WBS to assess the primary endpoint will be performed following a diagnostic dose of 5 mCi ^{131}I (refer to Section 5.5.4.2). Patients will receive 2 Thyrogen injections on consecutive days (day 1 and 2), followed by a diagnostic dose (5 mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5. Patients will be required to adhere to a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose, until the diagnostic WBS assessment is completed.

Standardised acquisition and submission guidelines for every WBS procedure will be provided separately to this protocol.

WBS definition of structural DTC

The WBS evaluation will be made by blinded, independent central review.

If the central review determines no visible ^{131}I uptake then the WBS for that patient will be considered normal/negative (no disease). Areas considered to be anatomically normal (for example uptake in the salivary glands, stomach, gastrointestinal, urinary tract and bladder) will not be considered disease.

If the central review determines there is a low level of visible uptake in the thyroid bed:

- Uptake must be < 0.1% to be considered normal/negative (no disease).
- If uptake in the thyroid bed region is ≥ 0.1%, the patient will be deemed not to be in remission due to the presence of iodine-avid DTC.

The % uptake in the thyroid bed (using the region-of-interest method drawn over the thyroid bed) will be measured and calculated by the local Investigator site and entered into the eCRF, to be made available to the central reviewer.

If an abnormality identified by US is subsequently shown to be RAI avid on WBS, the WBS data takes precedent over a negative biopsy/FNA.

6.4.4.3 Neck MRI

Post-operative (screening)

This baseline assessment is performed to determine study eligibility according to Section 4.1). The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Primary endpoint (stage 3)

Neck MRI to define the primary endpoint will be performed in stage 3 of the assessments in patients deemed to be biochemically-negative for thyroid cancer. Refer to Section 6.4.2.3 and Figure 3.

The neck MRI must be performed using T1 weighted image sequences with and without gadolinium contrast agent, and T2 weighted image sequences.

If clinically indicated, any suspicious lymph nodes on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter, should be biopsied/aspirated by fine needle.

MRI definition of structural DTC

New lesions (nodal or non-nodal) or significantly enlarged lymph node lesions compared to previous post operative (screening) MRI which are consistent with the biological characteristics of DTC and fulfil either of the following criteria will be considered to represent structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is shown to be RAI avid/positive on WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on MRI that is non-RAI avid on the WBS, will be considered benign even in the absence of a biopsy.

This assessment will be made by blinded, independent central review.

6.4.4.4 Chest CT

In this study all chest CT procedures should be performed without iodine containing contrast agent.

Post-operative (screening)

This baseline assessment is performed to determine study eligibility according to Section 4.1). The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Primary endpoint (stage 3)

Chest CT to define the primary endpoint will be performed in stage 3 of the assessments in patients deemed to be biochemically-negative for thyroid cancer. Refer to Section 6.4.2.3 and Figure 3.

If clinically indicated, any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter should be biopsied/FNA.

CT definition of structural DTC

New lesions (nodal or non-nodal) or significantly enlarged lymph node lesions compared to previous post operative (screening) CT which are consistent with the biological characteristics of DTC and fulfil either of the following criteria will be considered to represent structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is shown to be RAI avid/positive on WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on CT that is non-RAI avid on the WBS, will be considered benign even in the absence of a biopsy.

This assessment will be made by blinded, independent central review

6.4.4.5 Biopsy or fine needle aspirate (FNA)

A biopsy or FNA should be performed in the following situations:

- **US:** For any suspicious lymph nodes or lesions in the neck ≥ 5 mm in the smallest diameter identified by US during the study.
- **MRI:** If clinically indicated, for lymph nodes suspicious on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter.

- **CT**: If clinically indicated, for any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter.

Note: for a lesion to be suspicious it must be new or enlarged compared to the previously obtained imaging data, and be consistent with the biological characteristics of DTC.

All biopsy/FNA samples taken during the study will be assessed at each site according to local standard practice. Needle washout may be analysed locally for Tg according to local standard practice (this is not a mandatory requirement). The totality of the information obtained from a biopsy/FNA (including washout Tg data where analysed), will be assessed locally to determine presence or absence of thyroid cancer in the sample. This information will be provided to the central imaging CRO.

Refer to Section 6.10.3 for details regarding tumour sample acquisition on disease progression.

6.4.4.6 Information to be sent to the central imaging CRO

The following information will be sent to the central imaging CRO (further details are provided in the imaging charter/guidelines for this study).

1. Post-operative screening assessments (refer to Section 6.3): images for chest CT and neck MRI. This data must be sent for all patients as soon as possible after each patient is randomised.

2. Post-RAI WBS images taken 3-10 days after each patient's RAI dose. This data must be sent for all patients as soon as possible after each patient has their post-RAI WBS assessment.

3. Primary endpoints assessments stage 1: site ultrasound and biopsy information. The required data must be entered into the clinical database for each patient as soon as possible after completion of the assessment (NOTE: this information is not sent to the central imaging CRO, but instead must be entered into the database directly using eCRF).

4. Primary endpoint assessments stage 2: diagnostic WBS images. This data must be sent for all patients as soon as possible after completion of the assessment.

5. Primary endpoint assessments stage 3: chest CT and neck MRI images and biopsy information (if performed). This data must be sent for all patients as soon as possible after completion of the assessments. Biopsy data must be entered into the clinical database for each patient as soon as possible after completion of the assessment.

6.4.5 Derivation of primary endpoint of complete remission

The complete remission status of each patient will be determined programmatically by AstraZeneca, by incorporating data on re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, and structural disease assessment from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in complete remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer, all available imaging data will be sent to the imaging CRO. Determination of presence or absence of structural thyroid cancer will be made by the imaging CRO only for biochemically negative patients. A list of biochemically negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

The imaging CRO will assess the WBS, MRI and CT and also review the site assessment of neck US to provide an overall assessment: presence or absence of structural thyroid cancer, or not evaluable based on all of the available information. For the derivation of the complete remission endpoint, patients that are not evaluable for structural disease assessment will be considered as not achieving complete remission, regardless of the result of other assessments.

AstraZeneca will programmatically combine information on further therapy, biochemical data, and the determination of structural disease from the central imaging CRO, to determine the complete remission status of each patient as shown in Table 6.

The dates on which assessments were performed will be incorporated into the derivation of the primary endpoint to ensure patients are assessed within a time window around the scheduled 18 month post-RAI treatment. The first assessment must be started at 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within a 8 week period. If a patient has assessments/scans that fall outside of these time windows, the patient will be considered not to be in complete remission, regardless of the assessment of disease status.

Table 6 Programmatic derivation of complete remission status

Scenario	Further thyroid cancer therapy[a] (re-treatment)	Biochemical data[b]		Structural disease assessment[c]	Complete remission
		Stimulated Tg[b]	TgAb[b]		
1	Yes	N/A	N/A	N/A	No
2	No	< 1 ng/mL	Negative[d]	Absence of disease	Yes
3	No	≥ 1ng/mL	Any	Any	No
4	No	Any	Positive[d]	Any	No
5	No	Any	Any	Presence of disease	No
6	No	NE	Any	Any	No
7	No	Any	NE	Any	No
8	No	Any	Any	NE	No

[a] As assessed by investigator at site.
[b] As assessed by standardised central laboratory analysis.
[c] As assessed by blinded, independent central review.
[d] If the stage 1 and 2 blood samples are discordant for TgAb status, then a third blood sample 10 days later (± 3 days) is required. Only if the third sample is negative for TgAb will the overall TgAb result be considered negative for the primary endpoint assessments. Refer also to Table 5.
N/A primary endpoint assessments are not required for patients that have received further treatment for thyroid cancer in the previous 18 months.
NE Not evaluable (for example due to missing samples or assessments).

6.4.6 Clinical remission

The secondary efficacy endpoint for this study is **clinical remission rate at 18 months** (following RAI treatment). This is designed to more typically reflect clinical practice. As such, the definition of clinical remission will exclude the additional radiological assessments performed for the purpose of complete remission in this study.

Definition of clinical remission:

Patients will be defined to be in clinical remission if all of the following criteria can be demonstrated:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer on neck US, as assessed by investigator site review.

3. No evidence of thyroid cancer on diagnostic WBS, as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed to clarify equivocal US findings, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

6.4.7 Derivation of clinical remission status

The clinical remission status of each patient will be determined programmatically by AstraZeneca, by incorporating data on re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, structural disease assessment based on US by investigator site review and structural disease assessment based on WBS from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in clinical remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer:

A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the investigator based on US.

A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the central imaging CRO based on WBS for only biochemically negative patients. Information on US will not be reviewed as part of this assessment. A list of biochemically

negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

AstraZeneca will programmatically combine information on further therapy, biochemical data, determination of structural disease from the investigator site assessment of US and determination of structural disease from the central imaging CRO of WBS, to determine the clinical remission status of each patient.

Full details of the programmatic derivation of clinical remission will be provided in the SAP.

6.4.8 Final study follow up at 3 years

The final study follow-up will take place 3 years post-RAI for each patient, and will include:

1. The clinical status of each patient, for example: remission, persistent disease, recurrent disease, survival status.

2. The incidence of further therapy (re-treatment) for thyroid cancer, for example, additional RAI or surgery.

3. Final assessment of selumetinib or RAI-related AEs and SAEs.

Note, following the primary endpoint assessments until the final study visit at 3 years following each patient's initial RAI treatment, each patient will enter standard of care treatment or follow up according to local practice. No study-specific assessments will be performed, and locally performed assessments and data will not typically be collected as routine in the clinical study database (except for safety data, refer to Section 6.5.3). The patient's clinical status at the final study follow up will be collected (along with any relevant supporting local assessment data). For example, remission status will be defined by the Investigator on the eCRF based on the relevant local standard of care assessments (eg, locally assessed Tg and no evidence of thyroid cancer on locally assessed US).

6.5 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.5.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.5.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.5.3 Recording of adverse events

All adverse events will be graded according to NCI CTCAE Version 4.

Time period for collection of adverse events

All AEs/SAEs will be collected from informed consent until 30 days following the last dose of study treatment (selumetinib or placebo).

After this time:

- all SAEs regardless of causality will be collected until the final study follow-up (3 years post-RAI for each patient, refer to Section 6.4.8)
- only AEs considered causal to RAI or the combination of RAI and study treatment will be collected until the final study follow-up (3 years post-RAI for each patient, refer to Section 6.4.8).

Follow-up of unresolved adverse events

Any AE or laboratory change occurring during the study treatment period should be followed up by the investigator for as long as medically indicated (resolution or stabilisation), and follow up information recorded in the eCRF.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade information
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no) and/or RAI (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study treatment
- Treatments patient received for AE
- Outcome
- Whether event constitutes an SAE.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (if applicable)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.5.2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The Investigator will assess causal relationship between Investigational Product and RAI and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication, study procedures and additional study drug (eg, RAI). Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient, or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation, will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs etc should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

After the 30 day follow up visit, AEs associated with RAI or the combination of study treatment and RAI, should continue to be collected by AE reporting, these would include abnormalities, for example, white blood cell count or Hb reductions.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law,' for further instructions. All patients with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (± 7 days) later for follow-up.

6.5.3.1 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.5.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.5.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (Table 3). For samples taken after Day 1 during the study treatment period, the sample may be taken any time of day (ie, it does not matter whether it is pre-dose or post-dose). Day 1 samples should be taken pre-dose.

The following laboratory variables will be measured:

Table 7 Laboratory safety assessments

Clinical chemistry	Haematology	Urinalysis [a]
s-Albumin	Erythrocyte count	u-Albumin
s-ALT	Haemoglobin	u-Creatinine
s-AST	Platelet count	
s-ALP	Leucocyte cell count	
s-Total Calcium	Leucocyte differential count (absolute count):	
s-Creatinine	Neutrophils	
s-Gamma glutamyl transferase (γGT)	Eosinophils	
s-Glucose	Basophils	
s-Magnesium	Lymphocytes	
s-Phosphate	Monocytes	
s-Potassium		
s-Sodium		
s-Total protein		
s-Total bilirubin		
s-Urea nitrogen		
s-Creatine kinase		

[a] A single-spot urine specimen will be collected on the day of scheduled visit, at sites where the local laboratory is able to determine the concentration of urine albumin and urine creatinine from a single-spot urine specimen. Investigational sites unable to report these parameters will perform routine urinalysis according to the local standard of care.

s serum
u urine

All laboratory safety assessments will be analysed by the local laboratory.

Clinical chemistry, haematology and urinalysis testing will be repeated as clinically indicated as part of the routine management of the patient on the occurrence of AEs.

For blood volume see Table 9.

6.5.6 Physical examination

A complete physical examination will be performed at the times indicated in the Study Plan Table 3.

6.5.7 Cardiac monitoring

Note: troponin assessment in this study is only required for cardiac AE follow up as clinically indicated.

6.5.7.1 ECHO or MUGA

An ECHO or MUGA assessment (according to site preference) will be conducted at the timepoints indicated in the Study Plan (Table 3). A further assessment should be performed as part of the assessment package for any cardiorespiratory adverse event with no obvious diagnosis. Medical management of the event should follow local clinical practice. Selumetinib interruption should be considered until resolution of the event or until return to baseline.

LVEF can be measured in many different ways but echography is the preferred choice when possible. The same modality should be used as baseline for any ECHO/MUGA follow up. Recommendations include having complete high quality standardized 2-D with Doppler echocardiographic examinations performed by an experienced sonographer (preferably with the same operator performing all studies for a given patient), according to a specified protocol including evaluation of both systolic and diastolic left ventricular function. Ejection fraction determinations should be assessed quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.

6.5.7.2 Resting 12-lead ECG

ECGs will be analysed locally at each site. Patients should be supine and at rest 10 minutes prior to recording the ECG.

Parameters including heart rate, duration of QRS complex, PR and QT intervals will be collected. R-R interval and QTcF will be calculated by AstraZeneca from the data provided.

The investigator should review the paper copy of the ECGs on each study day and may refer to a local cardiologist if appropriate.

Any symptoms from the patient should be registered as a comment and if AE criteria are met, recorded as an AE.

At screening all patients will have a single 12-lead ECG performed. The screening ECG can be conducted up to 28 days prior to randomisation.

During the treatment phase of the study, patients will have single 12-lead ECGs assessments at the following timepoints:

- 1-2 hours after the first dose of study treatment on Day 1

- 1-2 hours after the first dose of study treatment on Day 29 or 30
- At the 30-day follow up visit following completion of study treatment
- Single ECGs must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event
- A single 12-lead ECG is also required at premature discontinuation of treatment

6.5.8 Vital signs

Resting blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size. Vital sign assessments, including weight, will be performed at the times indicated in the Study Plan Table 3. Pulse and blood pressure must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event. Height will be assessed at Visit 1 only.

Any changes in vital signs should be recorded as an AE if applicable.

6.5.9 Other safety assessments

6.5.9.1 Pregnancy test

A serum or urine pregnancy test (according to local practice) will be performed at the times indicated in the Study Plan Table 3. Following the RAI treatment, monitoring for pregnancy will be performed according to standard clinical practice at each centre.

6.5.9.2 Ophthalmologic examination

An ophthalmologic examination (best corrected visual acuity, intraocular pressure, slit lamp fundoscopy) should be performed at the timepoints indicated in the Study Plan (Table 3), and if a patient experiences a visual symptoms (including blurring of vision) with additional tests if clinically indicated e.g. consider OCT scans.

Patients who have a retinal abnormality prior to discontinuation of selumetinib/placebo should have a follow up eye examination performed within 30 days after discontinuation of selumetinib/placebo in order to document reversibility.

An algorithm for management and investigation of visual symptoms is provided in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

6.6 Patient reported outcomes (PRO) – not applicable

Patient reported outcomes will not be collected in this study.

6.7 Pharmacokinetics

6.7.1 PK samples required

Blood samples (2 mL) for determination of plasma concentrations of selumetinib and N-desmethyl selumetinib will be collected from every patient according to the time points below. Other metabolites (eg, selumetinib amide) may also be determined in the PK analysis. Each patient will be asked to contribute 8 blood samples, one from each of the pre defined time windows below on both Day 1 and Day 29 or Day 30. The Day 29 or Day 30 PK blood samples may be taken earlier, from Day 22 onwards of study treatment if preferred, but it is essential that all PK blood samples are collected on a visit day **prior** to the RAI dose being administered.

- Pre-dose (within 15 minutes of dosing)
- Between 15 minutes and 1 hour post-dose
- Between 1.5 and 2.5 hours post-dose
- Between 3 and 8 hours post-dose

Depending on emerging data/information, the timings and number of the PK samples may be altered, but the maximum total blood volumes given in Table 9 will not be exceeded. The actual sample date and time of all PK samples must be recorded in the eCRF.

Samples will be collected, labelled, stored and shipped as detailed in Laboratory Manual.

6.7.2 Determination of drug concentration

Samples for determination of selumetinib and N-desmethyl selumetinib concentrations in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Other metabolites (eg, selumetinib amide) may also be determined in the PK analysis. Full details of the bioanalytical method used will be described in a separate bioanalytical report.

For each placebo patient, samples will only be analysed on a ‘for cause’ basis, for example, if no quantifiable concentrations were observed in a patient’s samples when the drug was expected to be present.

All samples still within the known stability of the analytes of interest (ie, selumetinib, N-desmethyl selumetinib and its metabolites) at the time of receipt by the bioanalytical laboratory will be analysed.

6.8 Pharmacodynamics – not applicable

Pharmacodynamic samples will not be taken during this study.

6.9 Pharmacogenetics

6.9.1 Genetic blood sample at study entry

An optional blood sample for genetic research will be obtained from eligible patients at Visit 1 or 2 ideally. If for any reason the sample is not drawn at Visit 1 or 2, it may be taken at any visit **before the RAI dose is administered** (radioactive samples for this purpose will not be accepted). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. Only one sample should be collected per patient for this purpose. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volumes see Section 7.1.

6.10 Biomarker analysis

6.10.1 *BRAF* and *NRAS* patient population

Archival tumour sample from every patient will be analysed for *BRAF* and *NRAS* mutational status centrally using standardised methodology. Full analytical methodology details will be provided in the CSR.

The genetic analysis of archival tumour samples to identify the *BRAF* and *NRAS* patient population will be performed retrospectively in the study (after randomisation but prior to the primary endpoint data analysis).

BRAF/NRAS positive = mutations in *BRAF/NRAS* have been detected

BRAF/NRAS negative = no mutation in *BRAF/NRAS* has been detected

BRAF/NRAS unknown = mutation status in *BRAF/NRAS* cannot be confirmed

6.10.1.1 Archival tumour sample

All patients will be required to provide consent for AstraZeneca to collect and analyse samples of their previously obtained tumour material (ie, from their recent surgery) for analysis of biomarkers relevant to DTC. Archival tumour sample provision is mandatory in this study, and each Investigator should make every effort to collect a sample from all randomised patients. It is accepted that it may not be possible to obtain all samples prior to commencement of study treatment (which should continue as planned). However, it should be established during the screening period that sufficient sample exists and is available. Samples are expected to be made available as soon as possible. Note, no replacements will be made for patients where an archival tumour sample is not provided.

These samples will be analysed for the biomarkers necessary for the definition of the second primary objective patient population (*BRAF* and *NRAS* mutational status), and may also be used for exploratory analyses on residual material. Such analyses may include (but are not restricted to):

- Mutational status of *BRAF* and *NRAS* genes, *RET* rearrangements, and other known MAPK and PI3K effector oncogenes.

- Baseline expression of pathway and thyroid differentiation specific genes such as *NIS*, *Tg*, *TPO*, and *PAX8*.

- Comprehensive genetic analysis to ensure coverage of the major mutational events in DTC.

The exploratory analyses from tumour material may include but are not limited to mRNA expression profiling, microRNA expression profiling, gene copy number analysis and protein expression by immunohistochemistry for any markers relevant to DTC, either known at the time of analysis, or identified in the future.

For the tumour samples detailed below, each site will be asked to provide one of the following for each randomised patient:

– Formalin-fixed, paraffin-embedded tumour tissue block,

or

– 20 pre-cut sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 μm thick.

Sites should ship the tumour sample as soon as it is available. If mutational status cannot be adequately determined from the initial tumour biopsy sample, and histopathological review shows it to be a poor quality sample, a second sample should be submitted for re-testing.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

If requested, unused tumour samples will be repatriated. For further details see the Laboratory Manual.

6.10.2 Collection of plasma and serum for exploratory biomarker research

All randomised patients will be required to provide a blood sample at or before randomisation, and disease progression (for example, when the patient is re-treated for persistent or recurrent thyroid cancer) for exploratory biomarker research.

All patients will be required to provide:

– 1x 10ml blood sample for preparation of serum at randomisation (any time before the first dose of study treatment for eligible patients) and disease progression.

– 1x 10ml blood sample for preparation of plasma at randomisation (any time before the first dose of study treatment for eligible patients) and disease progression.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Residual material may be used for exploratory biomarker research.

6.10.3 Collection of disease progression tumour sample

Patients will be asked to provide a tumour sample removed during the study when the patient's cancer is deemed to have progressed (for example, when the patient is re-treated for persistent or recurrent thyroid cancer, or has had further surgery). This is an optional sample.

This will enable a comparison to be made of (for example) tumour genetics and relevant signal transduction pathways between the randomisation and the disease progression tumour sample and also the evolution of the tumour biology in response to treatment with selumetinib can be explored. Such changes may reflect an evolution in phenotype of the tumour, which ultimately may guide future treatment decisions post progression on selumetinib.

Samples can be of any type (such as FNA, or tumour sample taken from a surgical procedure performed as part of the patient’s disease management plan), and will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Table 8 Biomarker summary table

Biomarker sample	Time point	Protocol Section
Archival tumour for *NRAS* and *BRAF* analysis[a]	Randomisation	6.10.1.1
Plasma sample for exploratory biomarker analysis	Randomisation and disease progression	6.10.2
Serum sample for exploratory biomarker analysis	Randomisation and disease progression	6.10.2
Disease progression tumour biopsy (optional)	Disease progression	6.10.3
Blood sample for genetic analysis (optional)	Randomisation	6.9.1

[a] Residual tissue sample material will be stored for potential retrospective biomarker analysis, which will be performed in an AstraZeneca laboratory or AstraZeneca approved laboratory.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood (maximum) that will be drawn from each patient in this study is as follows:

Table 9 Volume of blood to be drawn from each patient

Assessment		Maximum sample volume [a] (mL)	Typical number of samples (over 18+ months)	Total volume (mL)
Safety	Clinical chemistry (local analysis)	5	5	25
	Haematology (local analysis)	3	7	21
Efficacy	Tg, TSH, TgAb (central analysis)	10	4	40
PK		2	8	16
Genetics at randomisation (optional)		10	1	10
Exploratory biomarkers at randomisation, serum		10	1	10
Exploratory biomarkers at randomisation, plasma		10	1	10
Exploratory biomarkers on progression, serum		10	1	10
Exploratory biomarkers on progression, plasma		10	1	10
	Total			152

[a] All volumes presented are maximums. The actual volume requirements will be detailed in the Laboratory Manual.

7.2 Handling, storage and destruction of biological samples

Biological samples for future research may be retained at or on behalf of AstraZeneca for a maximum of 25 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report or Scientific Publication.

7.2.1 Pharmacokinetic samples

Samples will be anonymised by pooling or will be disposed of after the Bioanalytical report finalisation or six months after issuance of the draft Bioanalytical report (whichever is earlier), unless requested for future analyses. Pooled, anonymised samples may be used for analytical method development and/or validation. Anonymised samples will be retained for no more than 5 years after the CSR is finalised. Samples may also be disposed of earlier, pending further notification.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical report.

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 25 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document.'

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of any optional donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central and bioanalytical laboratories holding the samples are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

In the USA the Principal Investigator is also responsible for providing the Ethics Committee with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of

AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study.' All patients in this study will be followed for 3 years following their RAI treatment.

The study is expected to start in 2013 and to end in 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with selumetinib.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the principal investigator has signed the eCRF electronically as per eCRF instructions, the subject's data will be locked.

Medical coding will be performed using the AstraZeneca Autocoder application. The Data Management Centre Coding Team will perform coding using agreed coding conventions. AEs and medical and surgical history will be coded using the standard dictionary – Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medication will be coded using the AstraZeneca Drug Dictionary.

SAEs will be entered into a global patient safety database for regulatory reporting purposes and be reconciled with the AEs in the clinical database.

Data associated with biological samples will be transferred to the data manager as an electronic file and merged with study data as appropriate.

Data from external providers (eg, central laboratory) will be validated as appropriate to ensure that it is consistent with the clinical data and included in the final database.

Clean file will be declared for the database once all data have been received, entered, validated and all queries resolved. The database will be locked after clean file has been declared. Treatment codes will not be broken until after clean file. Following database lock, all data will be extracted as SAS (Statistical Analysis Software) data sets for the statistical analysis to be performed by AstraZeneca.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate. Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Complete remission rate at 18 months post-RAI treatment

Patients will be considered to be in complete remission if they are alive and all of the criteria in Section 6.4.1 are met at 18 months post-RAI treatment.

Complete remission rate at 18 months post-RAI treatment is defined as the proportion of patients who have achieved complete remission at this time point. The complete remission rate will be calculated using all randomized patients as the denominator.

11.1.2 Clinical remission rate at 18 months post-RAI treatment

Patients will be considered to be in clinical remission if they are alive and all of the criteria in Section 6.4.6 are met at 18 months post-RAI treatment.

Clinical remission rate at 18 months post-RAI treatment is defined as the proportion of patients who have achieved clinical remission at this time point. The clinical remission rate will be calculated using all randomized patients as the denominator.

11.1.3 Thyroid cancer recurrence

The occurrence and date of any thyroid cancer recurrence will be recorded for patients who have previously entered either complete or clinical remission (at any point during the study or follow up periods). The rate of thyroid cancer recurrence will be calculated using only patients who have achieved remission as the denominator.

11.1.4 Survival status

The survival status and survival assessment date of all patients will be recorded. Survival time will be calculated as the time from the date of randomisation to the date of death. Patients who have not died at the time of the final study follow up will be censored at the last date the patient was known to be alive.

11.1.5 Further therapy

The dates and type of any further therapy for thyroid cancer will be recorded during the study and follow up periods.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Adverse events

Adverse events will be listed for each patient and summarised by treatment received according to the System Organ Class (SOC) and preferred term assigned to the event using the MedDRA. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs Version 4. The CTC Grade will be assigned by the Investigator.

AE summaries will include all of the following:

- Any AEs occurring after commencement of study treatment and within 30 days of the last dose of study medication
- AEs related to RAI or the combination of RAI and study treatment occurring between 30 days after the last dose of study medication and the final study visit at 3 years following the initial RAI dose
- All SAEs occurring after commencement of study treatment until the final study visit at 3 years following the initial RAI dose

AEs occurring before commencement of study treatment will not be included in AE summaries but will be included and identified in the patient listings.

11.2.2 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2.3 Vital signs, laboratory data, ECGs, ECHO/MUGA, physical examination and ophthalmologic examination

For change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF (Fredericia) will be calculated programmatically by AstraZeneca using the reported ECG values (RR and QT).

QTcF = QT / RR^ (1/3) where RR is in seconds

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality. For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded

The denominator in vital signs data should include only those patients with recorded data.

11.3 Calculation or derivation of PK variables

The final PK analyses will be the responsibility of Clinical Pharmacology and Pharmacometrics, AstraZeneca.

Using appropriate PK software the available PK data will be used to derive PK parameters such as, but not restricted to, C_{max}, AUC for Selumetinib, N-desmethyl selumetinib and any other metabolites determined.

The selumetinib, N-desmethyl selumetinib and metabolite concentration-time profiles, along with the derived PK variables, will be listed for each patient per dose and dosing day and summarised appropriately, as described in the SAP.

Population PK models may be used to derive the PK parameters and will aim to characterise variability in the population by investigating the influence of covariates such as weight, age, sex, and/or concomitant medications. In addition, if the data are suitable, potential relationships between plasma selumetinib and N-desmethyl selumetinib concentrations will be investigated using a graphical approach and/or appropriate PK/PD modelling techniques. A detailed PK analysis plan will be produced prior to any such investigations and will be reported separately.

11.4 Calculation or derivation of pharmacogenetic variables

Genetic data (except *BRAF* and *NRAS* data) will be reported separately to the CSR for this study.

11.5 Calculation or derivation of biomarker variables

11.5.1 Analysis of *NRAS* and *BRAF*

Tumour samples will be collected as outlined in the study plan and assessed for *BRAF* and *NRAS* biomarkers to identify patients for this primary patient population.

11.5.2 Further biomarker research analysis

Methods of analysis for all other biomarker research may include investigation of genetic variability, gene expression profiling, protein expression profiling.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Intention to treat (ITT) analysis set

The ITT analysis set will include all randomised patients. The ITT analysis set will be used for all efficacy analyses and treatment groups will be compared on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment will be included in the ITT analysis set.

12.1.2 *BRAF/NRAS* mutation positive analysis set

For the analysis of the *BRAF* and *NRAS* mutation positive population (primary objective), only those patients from the ITT population with genetic samples that are positive for *BRAF* or *NRAS* will be included.

12.1.3 Treatment-compliant (TC) analysis set

The treatment-compliant analysis set will be a subset of the ITT population containing patients that adhered to the minimum study treatment requirements specified in Section 3.1.1, i.e. patients who take study treatment twice daily for a **minimum** of 7 consecutive days prior to RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. Patients must also have had their RAI dose.

The TC analysis set will be used as a sensitivity analysis for the primary endpoint.

12.1.4 Safety analysis set

The safety analysis set will consist of all patients who received at least one dose of randomised treatment and for whom post dose data are available. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment combination received, ie, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

12.1.5 PK analysis set

PK data will be analysed according to treatment received. This population will comprise all patients who receive study treatment as per protocol and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the AstraZeneca Study Team Physician, Pharmacokineticist and Statistician prior to any analyses being performed.

12.2 Methods of statistical analyses

A comprehensive SAP will be prepared prior to start of recruitment (first subject in).

Since there are two correlated primary comparisons of interest (selumetinib vs. placebo in the overall population and selumetinib vs. placebo in the mutation-positive population), the Dunnett and Tamhane step-up procedure will be used to control the type I error rate (Dunnett and Tamhane 1992, Fernandes & Stone 2011). This procedure is an adaptation of the Hochberg approach, which accounts for the correlation between the primary endpoint comparisons. The correlation between the primary endpoint comparisons will be calculated as √w, where w is the proportion of the overall population who are in the mutation positive sub-group. The associated significance level for declaring statistical significance in the mutation positive sub-group adjusting for this correlation to maintain an overall 5% type I error rate whilst assigning 4% to the overall population will then be derived. For example, assuming that 55% of the overall population are in the mutation-positive sub-group, the correlation is 0.74. Using Dunnett and Tamhane step-up procedure, significance would therefore be declared if both the overall and mutation positive populations are significant at the 5% two-sided level, or if either the overall population is significant at the 4% level or the mutation-positive population is significant at the 1.625% level.

12.2.1 Complete remission rate at 18 months post-RAI treatment

The endpoint of complete remission rate will be compared between selumetinib in combination with RAI, and placebo in combination with RAI in the overall population using a logistic regression model with covariates histology status (papillary, follicular, poorly differentiated), mutation status (*BRAF/NRAS* positive, *BRAF/NRAS* negative) and age, provided there are enough data points for a meaningful analysis.

The primary endpoint of complete remission rate will be compared between selumetinib in combination with RAI vs. placebo in combination with RAI in the mutation positive population using a logistic regression model with covariates histology status (papillary, follicular, poorly differentiated) and age, provided there are enough data points for a meaningful analysis.

For each covariate, if the status is missing or unknown, patients will be assigned to the status that the majority of patients are known to have, e.g. if 55% of patients with known mutation status are *BRAF/NRAS* positive and 45% are *BRAF/NRAS* negative, a patient with missing mutation status will be assigned *BRAF/NRAS* positive. If a value for the continuous covariate age is missing, the mean will be imputed.

The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood confidence interval and 2-sided p-value. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above. The complete remission rate will be estimated for each treatment arm.

Sensitivity analyses

The primary endpoint analysis will be repeated using the treatment-compliant population.

A sensitivity analysis will be performed in which patients that were identified as being in complete remission outside of the specified time windows will be included in the logistic regression analysis and classed as being in complete remission to ensure there is no evaluation time bias between arms.

Elevated TSH can be caused by poor compliance and can mean a patient is less likely to achieve remission. A sensitivity analysis will be performed in which patients with high TSH are excluded from the logistic regression. A high TSH is defined as a value >10 mIU/L recorded at any point by standardised central laboratory analysis.

The extent to which the treatment effect is consistent across the subgroups histology status, mutation status, gender, race and age will be assessed for the overall primary population and across the subgroups histology status, gender, race and age for the mutation positive primary population. The presence of a quantitative interaction will be assessed by means of an overall global interaction test. This will be performed by comparing the fit (likelihood ratio test) of a model including all covariate-by-randomised treatment interaction terms, treatment and covariate terms with a model that excludes the interaction terms. If the global interaction test is found to be statistically significant at the 10% significance level, an attempt to determine the cause and type of interaction will be made. Stepwise backward selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

For quantitative interactions identified, the presence of any qualitative interactions will be assessed using the approach of Gail and Simon (Gail & Simon 1985). For categorical covariates the test statistics, based on the appropriate degrees-of-freedom, can be taken directly from the paper. For the continuous covariate, the approach will be adapted as follows:

Identify the cut-point ($-\beta_1/\beta_3$) of the covariate where the odds ratio for the treatment effect is 1, where β_1 is the treatment parameter estimate and β_3 is the treatment-by-covariate parameter estimate. Re-analyse the data separately for the values of the covariate above and below the cut-point and use the separate chi-square values in the Simon and Gail test.

Subgroup data (histology status, mutation status, gender, race and age) will be summarised by a forest plot where the odds ratio is plotted on the log scale. For this, age will be categorised as ≤45 or >45 years. The treatment effect and confidence intervals for each level of the subgroup will be obtained from a single model that contains a treatment, factor and treatment-by-factor interaction term.

12.2.2 Clinical remission rate at 18 months post-RAI treatment

The secondary endpoint of clinical remission rate will be analysed (for both study populations) as described in Section 12.2.1.

12.2.3 Thyroid cancer recurrence

Very few thyroid cancer recurrences are expected on this study, therefore no formal analysis of thyroid cancer recurrence data will be performed; data will be listed and summarised.

12.2.4 Survival status

Very few deaths are expected on this study therefore no formal analysis of survival data will be performed; data will be listed and summarised. Kaplan-Meier plots of survival may produced if appropriate.

12.2.5 Further therapy

No formal analysis of further therapy data will be performed; data will be listed and summarised. Kaplan-Meier plots of time to further therapy may produced if appropriate.

12.2.6 Safety data analysis

Safety data will not be formally analysed. All patients who commenced study treatment will be included in the assessment of safety and will be summarised by treatment received.

12.2.7 PK data analysis

The selumetinib, N-desmethyl selumetinib and metabolite concentration-time profiles, along with the derived PK variables, will be listed for each patient per dose and dosing day and summarised appropriately.

12.2.8 Genetics

Any genetic data analysis (other than *BRAF* and *NRAS*) will be reported outside the CSR for this study.

12.2.9 Biomarker data

BRAF and *NRAS* mutation assessment of tumour biopsy will be used to identify patients for this primary patient population.

The results of any other exploratory biomarker investigations will be reported outside of the CSR.

12.2.10 Interim analyses

There are no interim analyses planned for this study.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The two primary objectives of the study are to compare the efficacy of selumetinib with RAI versus placebo with RAI, by assessment of the complete remission rate at 18 months post-RAI treatment in the overall study population, and in a sub-group of patients whose tumours have *BRAF* and *NRAS* mutations. Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumentinib-containing arms, respectively, a total of 228 patients, randomised in a 2:1 ratio (152 and 76 patients in the selumentinib and placebo-containing arms, respectively) provides 80% power to show statistical significance, based on a two-sided 4% significance level. Assuming that the prevalence of the mutation-positive sub-group described is 55%, and the true complete remission rates in the mutation-positive sub-group are 30% and 62% for the placebo and selumentinib-containing arms, respectively, the expected numbers of 84 mutation-positive patients in the selumentinib arm and 42 mutation-positive patients in the placebo arm at the time of the analysis, provides 80% power to show statistical significance, based on a two-sided 1% significance level.

12.4 Data monitoring committee

Due to the short treatment duration in this study there will not be a data monitoring committee for this study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.5.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Physician. If the Study Delivery Team physician is not available, contact the Study Delivery Team Leader.

Name	Role in the study	Address & telephone number
PPD	AstraZeneca Physician responsible for the protocol at central R&D site	PPD
PPD	AstraZeneca Study Delivery Team Leader responsible for the protocol at central R&D site	PPD
24-hour emergency cover at central R&D site.	24-hour emergency cover at central R&D site.	PPD

13.2 Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.5.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.5.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

The outcomes of any conception occurring from the date of the first dose, until 30 days after last dose, must be followed up and documented in the "Pregnancy Outcome Report" form.

Male patients must refrain from fathering a child for 12 weeks following the last dose of study treatment, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated. Restrictions from

fathering children should also take into account local recommendations following therapy with RAI.

Pregnancy of the patients' partner is not considered to be an AE. However, the outcome of all pregnancies (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

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Clinical Study Protocol Appendix B	
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Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C	
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample

containment standards are encouraged wherever possible when road or rail transport is used.

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Appendix D

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. ACTIONS REQUIRED IN CASES OF AST OR ALT ≥ 3X ULN OR TBL ≥ 2X ULN

The Investigator is responsible for, without delay, determining whether the subject meets potential Hy's law (PHL) criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN **or** TBL ≥ 2x ULN, please follow the instructions below.

- Review each laboratory report and if a subject has an increase in AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit:
  - Notify the AstraZeneca representative
  - Promptly enter the laboratory date into the laboratory CRF.

1.2 Determination and Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the subject **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP

- Inform the AZ representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

1.2.2 Potential Hy's Law Criteria met

If the subject **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- Notify the AZ representative who will then inform the central ST

The Study Physician (SP) contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data.

The Investigator:

- Follows the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigates the etiology of the event and perform diagnostic investigations as discussed with the SP
- Completes the Liver CRF Modules.
- If at any time (in consultation with the SP) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

1.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

For the purpose of this process a Hy's Law case is defined as:

Any subject with an increase in both Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum Alkaline Phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug

If there **is** an agreed alternative explanation for the AST or ALT **and TBL** elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** other explanation that would explain the AST or ALT and TBL elevations:

- Report an SAE (report term Hy's Law') according to AZ standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

– As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

2. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm

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Clinical Study Protocol Appendix E

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Appendix E
Cockcroft-Gault Formula

COCKCROFT-GAULT FORMULA

The Cockcroft-Gault formula has been provided for reference, as the protocol allows for the serum creatinine clearance to be calculated using the Cockcroft-Gault formula (see Section 4.1, Inclusion criteria):

For serum creatinine values in µmol /L:

Estimated creatinine clearance rate (eCCr) (for men) = [(140 – age) x weight (kg) x 1.23] / creatinine (µmol/L)

eCCr (for women) = [(140 – age) x weight (kg) x 1.04] / creatinine (µmol/L)

For serum creatinine values in mg/dL:

eCCr (for men) = [140 – age] x weight (kg) / [72 x creatinine (mg/dL)]

eCCr (for women) = 0.85 x ([140 – age] x weight (kg) / [72 x creatinine (mg/dL)])

Reference: Cockcroft D, Gault MD. Nephron 16: 31-41, 1976.

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Appendix F
Low Iodine Diet

LOW IODINE DIET

Published data and opinion regarding the necessity for a low iodine diet prior to RAI therapy or a diagnostic whole body scan is variable. For the purpose of this study a low iodine diet will be mandated in order to standardise patient care and study data as best as possible. Compliance to a low iodine diet will not be recorded or assessed, and all randomised patients will receive RAI treatment as planned.

A low iodine diet is necessary at two occasions in the study:

Prior to RAI adjuvant treatment

All patients must be willing to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI therapy.

Prior to the primary endpoint Stage 2 assessments

All patients must be willing to adhere to a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose used prior to the primary endpoint WBS assessment (^{131}I nuclear medicine scan), until the diagnostic WBS assessment is completed. This is only relevant for patients who progress to Stage 2 primary endpoint assessments (refer to Section 6.4.2 of the main protocol).

What is Iodine?

Iodine is a mineral. It plays an important role in several processes that take place in the body. One is the production of a hormone called thyroxine, which occurs in the thyroid gland.

Where is Iodine Found?

The amount of iodine found in food varies. Much of the iodine we get comes from iodized salt and breads. Adults need 150 micrograms of iodine a day. This appendix describes an example of a low iodine diet typically used in this treatment setting. This is a diet with less than 50 micrograms of iodine per day. A local low iodine diet may be used instead, as long as it is equivalent to this appendix.

Why is a Low Iodine Diet Necessary?

The iodine in your diet can block the uptake of radioactive iodine by the thyroid gland.

What Should You Avoid?

Read all food labels to check for iodine content. Do NOT eat or use:

- Iodized salt.
- Sea salt in any form.
- Onion salt.

- Celery salt.
- Garlic salt.
- Seasoned salt.
- Kelp (seaweed).
- Any food that has:
  - **Iodates**
  - **Iodides**
  - **Algin**
  - **Alginates**
  - **Carrageen**
  - **Agar**
- Commercial breads and bakery products, because they often contain iodate.
- Milk (except for 1 ounce a day), egg yolks, and seafood.
- Vitamins and food supplements if they have iodine. If you have any doubt, do not take them.
- Food, pills, or capsules with food dyes or that are orange, red, or brown in color. Examples include red or pink cereals or candies/sweets.
- Antiseptics, such as tincture of iodine (Betadine®) applied on a cut.
- Cough medicines (especially those with red coloring).
- Supplements such as:
  - **Ensure®**
  - **Boost®**
  - **Commercial shakes**
  - **Nutrament®**.

- Restaurant and processed foods, because they are often high in iodine content.
- Soy products such as edamame, tofu, soy burgers etc.
- All canned foods, because the lining of the can contains iodine.

Do not stop taking any of your medicines unless your doctor tells you.

Ask your doctor about drinking alcohol during a low iodine diet.

This low iodine diet does not meet the suggested daily allowance for all nutrients. You will be on it for a short time only.

Drink Plenty of Fluids

Note: Unless your doctor tells you differently, you must drink at least 8 to 10, 8-ounce cups of fluid a day. This includes the drinks in the diet guidelines and as much water as you want.

LOW IODINE DIET GUIDELINES

Breads and Cereals **Total number of servings per day:** 6-8 (1 serving equals 1 slice of bread or 1/2 cup of cooked pasta)	
Include	**Avoid**
Plain cooked barley, oats, millet, buckwheat, bulgur wheat, quinoa; unsalted unprocessed preservative-free boxed cereals such as puffed rice and shredded wheat; rice, plain macaroni, spaghetti, noodles; unsalted grits, cream of rice or cream of wheat hot cereals; unsalted rice cakes, unsalted plain crackers, English muffins, plain unsalted popcorn, homemade breads prepared without commercial dough.	All commercial breads and rolls, processed boxed cereals, salted crackers, potato chips/crisps, pretzels, bagels, Melba toast, egg noodles, packaged rice and pasta mixes.

Meat and Meat Substitutes **Total number of servings per day:** Two–three (1 serving equals 3 ounces of meat, fish, poultry, or 2 Tablespoons of unsalted peanut or almond butter)	
Include	**Avoid**
Fresh beef, veal, pork, lamb, chicken and turkey; unsalted peanut or almond butter; freshwater fish such as carp, riverbass, lake trout, and river perch; fresh egg white.	Egg yolks and whole eggs, foods made with eggs; all fast foods; all canned fish such as salmon and tuna; seafood, shellfish (clams, crabs, oysters, lobsters), or any food made with fish stock; all processed meats; liver and all organ meats; all canned, dried, salted, or cured meats such as bacon, sausage, ham, frankfurters, chipped beef, luncheon meats (salami, bologna, pastrami); spicy meats such as chili, beef jerky, liverwurst; all canned or processed poultry such as turkey or chicken roll; tofu and soy products, such as soy burgers (e.g., Boca); salted peanut butter.

Milk and Milk Products **Total number of servings per day:** Zero	
Include None allowed Exception: Only 1 ounce of milk a day in your coffee or tea.	**Avoid** All milk (except for one ounce daily) and milk products such as condensed or evaporated milk, cheese, yogurt, puddings, ice cream, custard; any cream such as heavy/double or light/single cream, whipped cream, sour cream; any foods made with cream or milk or cheese such as soup, pizza, macaroni and cheese.

Fruits **Total number of servings per day:** Five (1 serving equals 1 small piece of fruit or 3/4 cup of juice)	
Include All fresh fruit, exception: limit bananas to 1 serving per day; fresh apple sauce; all natural frozen fruits; fresh fruit juices (including bottles or cartons of fruit juice without artificial coloring or preservatives); white grape juice.	**Avoid** Cranberries, all dried fruits, all canned fruits and canned fruit juices; jarred applesauce; cranberry and grape juice, canned or bottled cherries; rhubarb.

Vegetables **Total number of servings per day:** Four (1 serving equals 1/2 cup of cooked or 1 cup raw vegetable)	
Include All fresh vegetables except spinach, fresh potatoes without skin, all plain frozen vegetables without added salt, fresh or dried lentils and peas.	**Avoid** All canned vegetables and all canned vegetable juices, fresh or dried beans such as red kidney beans, lima beans, navy beans, pinto beans; canned legumes (such as beans, peas, and lentils); canned soups; sauerkraut, celery; commercially prepared potatoes (e.g., instant mashed potatoes); frozen vegetables with added salt; spinach.

Fat **Total number of servings per day:** Suggest four to six servings a day (1 serving equals 1 teaspoon of butter or oil)	
Include Unsalted margarine or sweet butter **(not more than 1 teaspoon of each per day),** oils, vegetable shortening, plain oil and white vinegar dressing.	**Avoid** Salted nuts and seeds, mayonnaise, commercial salad dressings and salad cream, and lard.

Beverages **Total number of servings per day:** No restrictions One serving equals 12 ounces of a carbonated beverage or 1 cup (8 ounces) of any of the other beverages listed	
Include	**Avoid**
Water; bottled carbonated beverages without added coloring (such as Sprite®, 7Up®, sodium-free seltzer); brewed coffee, tea steeped from tea leaves; white tea bags; fresh lemonade or fresh orangeade.	Mineral water containing sodium; all bottled, canned, or powdered: iced tea, lemonade, instant coffee, instant tea, instant iced-tea, fruit punch, and other powdered or commercial drinks, such as Hi-C® and Kool-Aid®; tea steeped from tea bags; soy milk and rice milk (which contain sea salt); ginger ale, Coke®, Pepsi® or any other carbonated beverages with added coloring.

Desserts and sweets **Total number of servings per day:** Two (See below for serving equivalents)	
Include	**Avoid**
Each of the following equals 1 serving: • 1 cup Knox® or equivalent clear gelatin • 2 tablespoons (T) sugar • 2T honey • 2T maple syrup • 2 regular size marshmallows • 1/2 cup natural sorbets with no coloring or added salt	All bakery products such as pies, cakes, pastries, danishes, muffins, doughnuts and cookies; sweet crackers/biscuits; Jell-O® (or equivalent jelly), colored gelatins; chocolate and chocolate desserts; candy.

Miscellaneous **Total number of servings per day:** Unlimited	
Include	**Avoid**
Pepper, spices such as cinnamon; herbs such as oregano; white vinegar, and non-iodized salt (contains trace amounts of iodine, use sparingly).	All salted foods such as salted nuts, Chinese food, soy sauce, catsup, Worcestershire sauce, chili sauce, all commercial sauces, tomato sauce, all gravies, olives, pickles, relish, bouillon cubes, soup bases, iodized salt, sea salt, onion salt, garlic salt, celery salt, seasoned salt, kelp (seaweed); molasses; any food containing food coloring, iodates, iodides, iodate dough conditioners or stabilizers, algin, alginate, carrageens, agar, or nori (seaweed); all sushi; red wine vinegar, balsamic vinegar (with caramel coloring); all additives, preservatives, or artificial colorings.

EXAMPLE MENU FOR A LOW IODINE DIET

BREAKFAST

1 Fruit	½ cup orange juice
3 Breads	½ cup oatmeal (no milk) 1-2 plain unsalted cracker/crispbreads
1 Meat	1 egg white omelet
Misc.	2 teaspoons sugar
1 Beverage	1 cup brewed coffee

MID MORNING SNACK

1 Bread	2 rice cakes
1 Fat	1 teaspoon unsalted butter
1 Beverage	1 cup water

LUNCH

1 Meat	3 oz fresh turkey breast
2 Fats	2 tsp oil
2 Breads	2 slices homemade white bread
1 Vegetable	1 cup Romaine lettuce
1 Beverage	1 cup fresh lemonade

MID AFTERNOON SNACK

1 Fruit	1 fresh apple
1 Meat	2 tablespoons unsalted peanut butter

DINNER

1 Meat	3 oz roast beef
2 Breads	1 baked potato (no skin)
2 Vegetables	1 cup fresh broccoli
2 Fats	2 tsp oil (used in cooking)
1 Fruit	1 orange
1 Beverage	1 cup white tea

BEDTIME SNACK

1 Fruit	1 small pear
1 Beverage	1 cup tea made from fresh tea leaves

Clinical Study Protocol Appendix G	
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Appendix G
Guidance for Management of Adverse Events in Studies of Selumetinib

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1. GUIDANCE FOR THE MANAGEMENT OF PATIENTS WITH RASH

Recommendations to start on day 1 of treatment with selumetinib‡ and for the duration of treatment

- Use skin moisturiser (thick, alcohol-free) at bedtime
- Avoid excessive exposure to sunlight
- Use sunglasses/sunscreen (PABA-free, SPF ≥15; UVA and UVB protection) as needed
- Use of topical retinoids or benzoyl peroxide is not recommended

CTC Grade 1 rashes

Mild or moderate strength topical steroid

and/or topical antibiotic

CTC Grade 2 rashes

Moderate strength topical steroid

and oral antibiotic

CTC grade ≥3 rashes
CTC grade 2 rashes considered by the patient to be intolerable

Moderate strength topical steroid

and oral antibiotic
(consider broad spectrum/Gram negative cover if infection suspected)

Consider referral to a dermatologist: manage rash per recommendation

Interrupt selumetinib‡ until rash improves to grade 2 or less

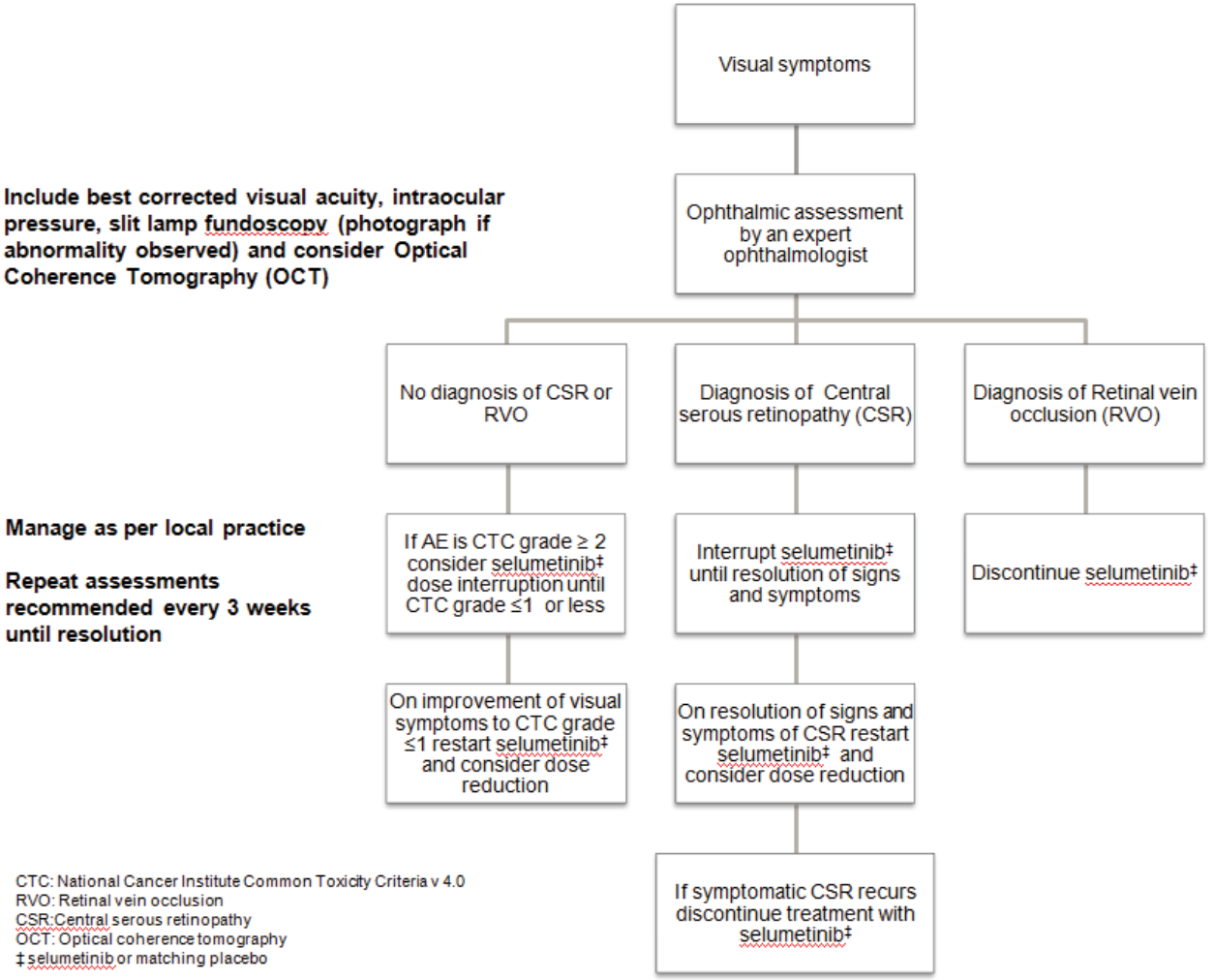
Selumetinib‡ may be restarted at original dose or reduced at the discretion of the investigator

‡ selumetinib or matching placebo
Version: Final 2.0 28Sep2012

Table 1 Example topical steroids and antibiotics (use according to local guidelines)

Topical steroids moderate strength	Triamcinolone acetonide 0.025% Fluticasone proprionate 0.05% Desonide 0.05% Aclometasone 0.05%
Topical antibiotics	Clindamycin 1 - 2% Metronidazole 1% Erythromycin 1% - 2% Silver sulphadiazine 1%
Oral antibiotics	Doxycycline 100 mg bd Minocycline 100 mg bd Oxytetracycline 500 mg bd

2. GUIDANCE FOR MANAGEMENT OF PATIENTS WITH VISUAL SYMPTOMS



3. RECOMMENDATIONS FOR DIARRHOEA MANAGEMENT

Diarrhoea may occur during treatment with selumetinib (AZD6244) and action should be taken as soon as symptoms develop. The recommendations for diarrhoea management are based on guidelines from the American Society of Clinical Oncology (J Clin Oncol 2004; 22:2918-26). These guidelines recommend that treatment-induced diarrhoea should be carefully monitored and treated aggressively to ensure that severe complications are avoided and that treatment is not delayed.

- Patients should be made aware that they may experience diarrhoea and be encouraged to record the number of stools and report possible associated symptoms
- Patients should be given loperamide (in accordance with local regulation and local practice) to take home with them and be advised to start immediately after the first episode of unformed stool.
- Patients should be given dietary advice in case of diarrhoea (eg. BRAT [bananas, rice, apple sauce, toast, plain pasta] diet; readily digestible food; avoidance of lactose-containing products, fried, fatty or spicy food) and increase fluid intake (8 to 10 glasses of clear fluids daily, including water and fluids containing salt and sugar, such as sports drinks and clear broth).
- Patients should seek advice early, from their physician or study nurse, if:

  (a) Persistent Grade 1 or 2 diarrhoea (refer to Section 3.2), or

  (b) Grade 3 or 4 diarrhoea, or

  (c) Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension.

Table 2 CTCAE (version 4) grading for diarrhoea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 1	Increase in number of stools per day (<4)	Mild increase in loose watery colostomy output compared with pre-treatment
Grade 2	Increase in number of stools per day (4-6) or nocturnal episodes	Moderate increase in loose watery colostomy output compared with pre-treatment, not interfering with normal activity
Grade 3	Increase of more than 7 stools per day or incontinence or needing support for dehydration.	Severe increase in loose watery colostomy output compared with pre-treatment and interfering with normal activity

Table 2 CTCAE (version 4) grading for diarrhoea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 4	Life-threatening consequences (eg, hemodynamic collapse)	

3.1 Initial management of uncomplicated Grade 1 or 2 diarrhoea

- Patients should immediately start loperamide after the first episode of diarrhoea (4 mg initially) and continue loperamide (2 mg every 4 hours or after each unformed stool) until they have been free from diarrhoea for at least 12 hrs
- If after 12 hours of loperamide treatment the diarrhoea is not improving or resolved, the patient should be instructed to contact the centre and to increase to high dose loperamide (2 mg every 2 hours, or 4 mg every 4 hours at night) and continue to take loperamide until they have been free from diarrhoea for at least 12 hrs. Additional treatment may be considered according to local practice.

3.2 Management of persistent (>24h) Grade 1 or 2 diarrhoea despite loperamide at high dose

The patient should be seen by the physician or study nurse for full evaluation and the following should be considered:

- Rehydration and electrolytes replacement as appropriate
- Infectious causes and aetiologies such as Clostridium difficile or viral gastroenteritis;
- Antibiotics if appropriate (for example an oral fluroquinolone for 7 days) particularly if the patient is neutropenic ($<1 \times 10^9$/L) or has a fever;
- Discontinuation of loperamide and start of octreotide (Sandostatin);

It may also be appropriate to consider:

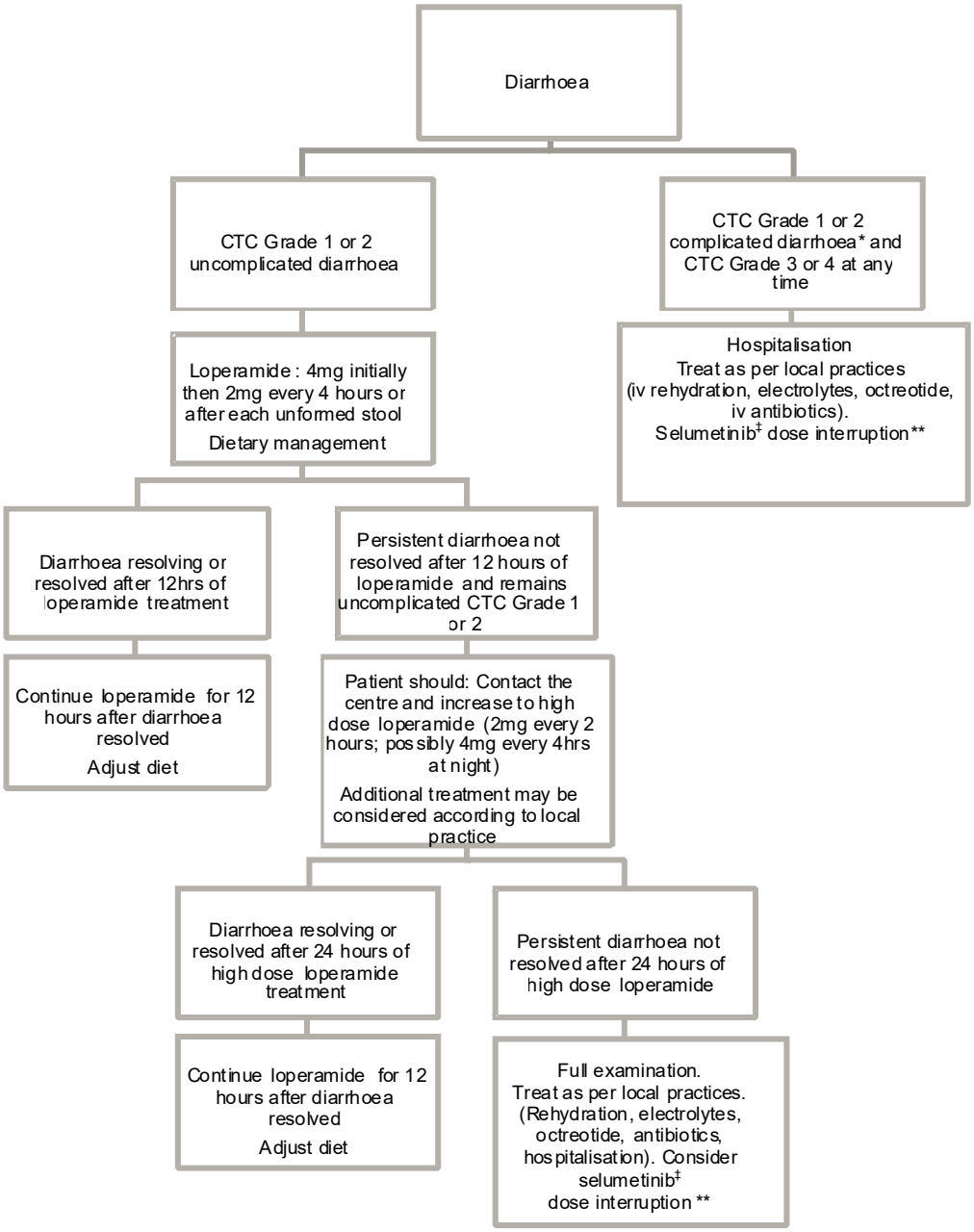
- Addition of other second-line anti-diarrhoeal agents according to local practice
- Selumetinib (or matching placebo) interruption until resolution of the diarrhoea
- Hospitalisation

3.3 Management of any grade uncontrolled or complicated diarrhoea, or Grade 3-4 diarrhoea

- Hospitalisation and full evaluation,

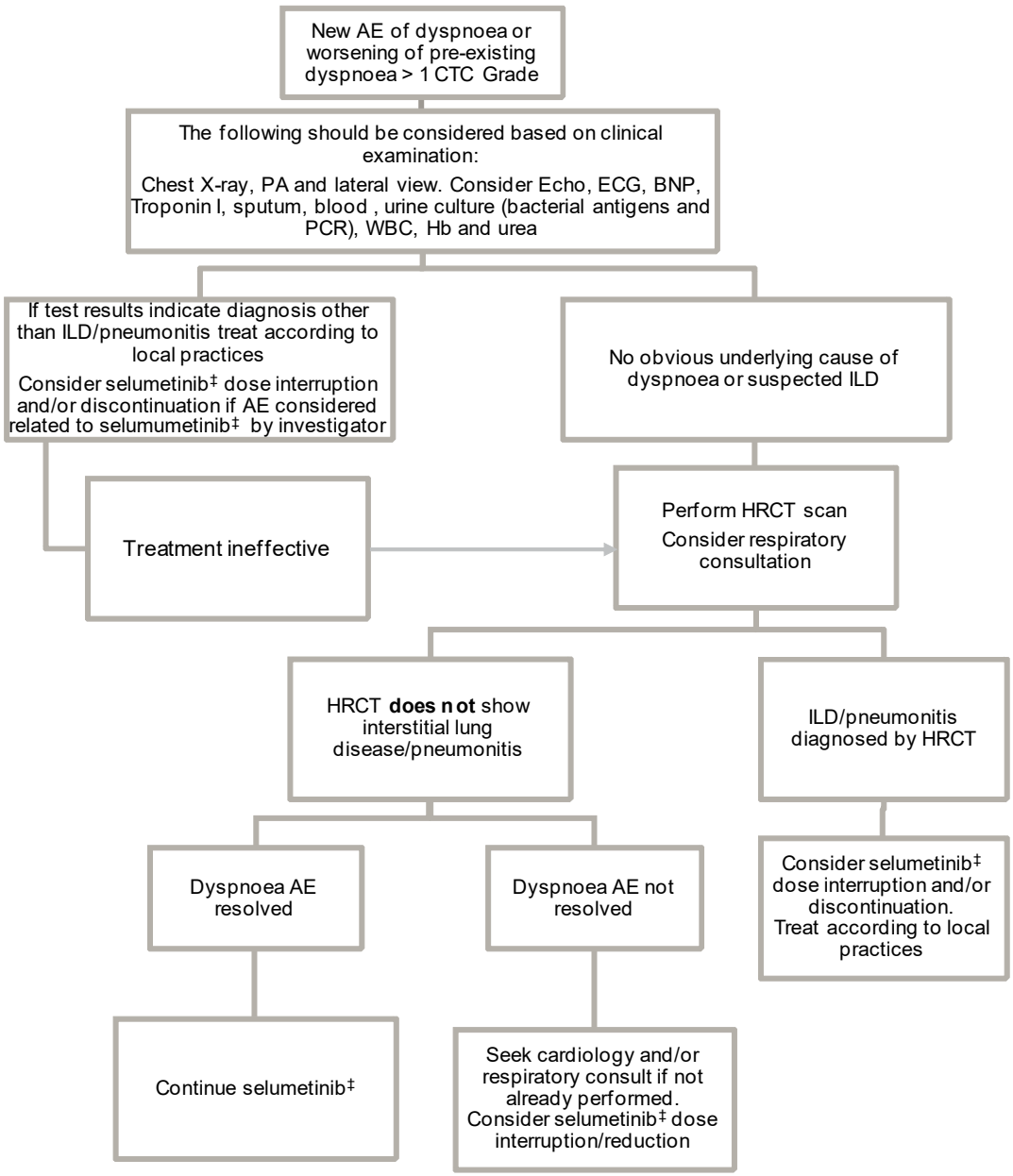
- Intravenous fluids, electrolytes and antibiotics if needed (eg. fluroquinolone)
- Interrupt selumetinib (or matching placebo) until diarrhoea and associated symptoms resolve
- Start octreotide (Sandostatin).
- In studies involving combination of selumetinib (or matching placebo) with other anti-cancer treatment, interruption or delay of the combination agent may be considered according to manufacturer's guidance or local practice.

Figure 1 Guidance for the management of patients with diarrhoea



*Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension
****Consider interruption or delay of combination anticancer agent if applicable**
‡ selumetinib or matching placebo
Document version: Final 2.0 28Sept2012

4. RECOMMENDATIONS FOR INVESTIGATIONS OF PATIENTS WITH A NEW OR WORSENING DYSPNOEA



BNP: Brain Natriuretic Peptide
CTC: National Cancer Institute common toxicology criteria
Echo: Echocardiography
Hb: Haemoglobin
HRCT: High resolution computerised tomography
‡ selumetinib or matching placebo

ILD: Interstitial Lung Disease
PA: posteroanterior
PCR: Polymerase chain reaction
WBC: White blood cells
Document Version: Final 2.0 28 Sept 2012

Revised Clinical Study Protocol

Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	3
Date	15 July 2013

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
2	15 July 2013		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

International Co-ordinating Investigator

PPD

Study centre(s) and number of patients planned

Approximately 228 patients with newly diagnosed differentiated thyroid cancer at high risk of primary treatment failure will be recruited from approximately 50 sites in Europe, South and/or North America.

Objectives

Primary objective

To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in the intention to treat (ITT) study population. Complete remission is defined in Section 6.4.1.

Secondary objectives

To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the ITT study population. Clinical remission is defined in Section 6.4.6.

To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

Exploratory objectives

To explore subsequent thyroid cancer therapy given to patients who receive selumetinib with RAI, or placebo with RAI.

To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters.

To collect tumour, plasma and serum samples for potential future research on biomarkers relevant to DTC and response and resistance to study treatments.

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib or RAI and/or susceptibility to cancer.

Study design

This is a double-blind, randomised, placebo-controlled study comparing the efficacy of a short course (approximately 5 weeks) of selumetinib (75 mg, orally twice daily) with adjuvant RAI, to placebo with RAI.

Following recovery from surgery (1 or 2-stage total thyroidectomy), and screening to determine study eligibility, patients will be randomised and will take their assigned study treatment (selumetinib or placebo) twice daily for a period of approximately 5 weeks. Study treatment will begin approximately 4 weeks prior to the planned day of single dose RAI therapy, and will be continuous until 5 days following RAI therapy. Patients will be required to adhere to a standardised low iodine diet prior to their RAI therapy. For each of the 2 days immediately prior to their planned RAI therapy, patients will receive a 0.9 mg intramuscular (IM) recombinant human TSH injection (rhTSH, Thyrogen), in order to stimulate iodide uptake (patients or clinicians choosing to prepare for RAI ablation by withdrawal of thyroid hormone treatment will be ineligible for this study). Following the 2 consecutive days of rhTSH injections, patients will receive their planned RAI therapy as a fixed single 100 mCi (3.7 GBq) dose of ^{131}I the immediate next day. Study treatment will be taken as normal on the day of RAI therapy, and will be discontinued 5 days following the patient's RAI therapy.

Following RAI therapy, each patient will be followed up for a period of 18 months until the primary endpoint assessment of complete remission. The biochemical analysis contributing to the 18 month primary endpoint of complete remission will be performed by standardised central methodology, and the radiological imaging for structural disease at the primary endpoint will be subject to a blinded independent central review. Additional thyroid cancer therapy (eg, surgery or RAI treatment) must only be given during the 18 month primary endpoint follow up period according to the pre-specified study re-treatment criteria (refer to Section 5.9). Patients who do receive re-treatment in the 18 months following their initial RAI

therapy, will not have any 18 month primary endpoint assessments performed; they will remain in the study and enter standard of care follow up according to local practice.

Following the primary endpoint assessments (or re-treatment), all randomised patients will be further followed-up at 3 years after their initial RAI treatment, in order to further assess both the clinical status of patients, and the safety profile of selumetinib and RAI beyond the primary analysis (refer to Section 6.4.8).

Target patient population

Patients with histologically or cytologically confirmed follicular cell derived differentiated thyroid cancer (including papillary thyroid cancer and all variants, follicular thyroid cancer and all variants, and poorly differentiated thyroid cancer), who are determined to be at high risk of primary treatment failure, as defined by any one of the following staging categories post-surgery:

- Primary tumour greater than 4 cm
- Primary tumour of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)
- N1a or N1b disease with at least 1 lymph node ≥ 1 cm
- N1a or N1b disease involving 5 or more lymph nodes (of any size)

Patients with known distant metastatic disease will be excluded from this study.

Investigational product, dosage and mode of administration

Selumetinib Hyd-Sulfate (75 mg) will be administered orally twice daily as capsules (blue). The Hyd Sulfate formulation will be used in this study, and unless otherwise specified is the formulation referenced throughout this document.

Comparator, dosage and mode of administration

Placebo (to match selumetinib) will be administered orally twice daily.

Duration of treatment

The duration of study treatment (selumetinib/placebo) will be approximately 5 weeks in total (Day 36 will typically be the last day of study treatment, but this may be extended to a maximum of 43 days to allow the planned RAI to be postponed by up to 1 week if absolutely necessary).

Outcome variable(s):

Efficacy

The primary outcome variable for this study is the rate of complete remission at 18 months post-RAI treatment. Patients will be defined to be in complete remission if all of the following criteria can be demonstrated:

1. Serum thyroglobulin (Tg) levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer[a] by neck US, as assessed by investigator site review.

3. No confirmed radiological evidence of thyroid cancer[a], as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

[a]Confirmation of evidence of structural DTC will be either histopathological (from a biopsy/FNA; as criterion 4 above), or RAI-avid disease (refer to Section 6.4.4.2). In this disease setting, structural abnormalities that are not RAI-avid and do not have confirmed histopathology consistent with DTC (ie are not biopsy proven) are considered benign in the absence of biochemical DTC.

A secondary outcome variable will be the rate of clinical remission at 18 months post-RAI treatment, where clinical remission is defined on the basis of Tg, US and WBS assessments alone, without the additional radiological data.

Safety

AEs/SAEs, physical examination results, lab values, ECG, vital signs.

All randomised patients will be followed for safety monitoring for 3 years following their RAI adjuvant treatment, in order to monitor for selumetinib and RAI-associated side effects.

PK

Where sample collection and PK analysis allow, derived PK parameters for selumetinib and N-desmethyl selumetinib will be produced which may include, but not be restricted to, C_{max} and AUC. Exploratory variables will be analysed outside the clinical study report (CSR).

Statistical methods

Approximately 228 patients will be randomised in a 2:1 ratio in this study. The primary analysis will be performed when patients have been followed for 18 months following their RAI treatment. The primary analysis population will comprise all randomised patients (ITT population) and the primary endpoint of complete remission rate at 18 months will be analyzed using a logistic regression model including treatment as the only covariate. Results will be presented in terms of the odds ratio, 95% confidence interval and associated p-value. Logistic regression modelling including treatment and covariates histology status, mutation status and age, will be performed as sensitivity analyses provided there are enough data points for a meaningful analysis.

Assuming the true complete remission rates in the ITT study population are 30% and 50% for the placebo and selumetinib-containing arms, respectively, the study will have at least 80% power to demonstrate a statistically significant difference at the 5% (2-sided) significance level.

All secondary endpoints will be analysed at the time of the primary analysis. Exploratory biomarker analysis may be analysed after the time of the primary analysis and reported separately to the CSR (apart from the somatic genetic data required for analysis of the second primary endpoint).

All randomised patients will continue to be followed until the final study visit (3 years after their RAI treatment). At this time, data on clinical status, incidence of re-treatment and long-term safety will be summarised.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
^{124}I	Iodine-124
^{131}I	Iodine-131 (radioactive iodine; RAI)
AE	Adverse event (see definition in Section 6.5.1)
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatise
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
AUC	Area under the plasma concentration-time curve from zero to infinity
BD	Twice daily (dosing)
bid	*bis in die* – twice a day
BNP	B-type natriuretic peptide
BP	Blood pressure
Bpm	Beats per minute
BRAF	v-raf murine sarcoma viral oncogene homolog B1
cm	centimetres
C_{max}	Maximum plasma concentration
CRF	Case report form (electronic/paper)
CR	Clinical remission
CR	Complete remission
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
DAE	Discontinuation of investigational product due to adverse event
DNA	Deoxyribonucleic acid
DTC	Differentiated thyroid cancer
D-TC-FCO	Differentiated thyroid carcinoma of follicular cell origin

Abbreviation or special term	Explanation
DUS	Disease under study
EBRT	External beam radiation therapy
EC	Ethics committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ERK	Extracellular signal-regulated kinases
ETA	European Thyroid Association
FDG-PET	2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography
FNA	Fine needle aspiration
FSH	Follicle stimulating hormone
FTC	Follicular thyroid cancer
G1	Gap 1 phase of the cell cycle
GCP	Good clinical practice
g/dL	grams per decilitre
GMP	Good manufacturing practice
hr	hour
I	Iodine
IATA	International Air Transport Association
IB	Investigator brochure
ICH	International Conference on Harmonisation
ICH M3	The European Medicines Agency's International Conference on Harmonisation Topic M3 – "Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals"
IM	Intramuscular
INR	International normalised ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational product
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravascular
IVRS	Interactive voice response system

Abbreviation or special term	Explanation
IWRS	Interactive web response system
kg	kilograms
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LH	Luteinizing hormone
LIMS	Laboratory information management system
LLOQ	Lower limit of quantification
LSLV	Last patient last visit
LT4	Synthetic levothyroxine
LV	Left ventricular
LVEF	Left ventricular ejection fraction
M0, M1, Mx	Distant metastasis status (TNM cancer staging system)
MAPK	Mitogen-activated protein kinase
mCi	millicuries
MedDRA	Medical dictionary for regulatory activities
MEK	MAPK/ERK kinase
MI	Myocardial infarction
µg/L	micrograms per litre
µm	micrometers
mIU/L	milli-International units per litre
mg	milligrams
mg/day	milligrams per day
mL	millilitres
mL/min	millilitres per minute
mm	millimetres
mm^3	cubic millimetres
ms	milliseconds
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
N0, N1, Nx etc	Lymph node disease stage (TNM cancer staging system)
N/A	Not applicable
ng/mL	nanograms per milliliter

Abbreviation or special term	Explanation
NIS	Sodium iodide symporter
NOEL	No observed effect level
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase, receptor, type 1
NYHA	New York Heart Association
OAE	Other significant adverse event (see definition in Section 6.5)
PDTC	Poorly differentiated thyroid carcinomas
PET	Positron emission tomography
PFS	Progression-free survival
PGx	Pharmacogenetic research
PI	Principal investigator
PK	Pharmacokinetics
PRO	Patient reported outcomes
PTC	Papillary thyroid cancer
RAI	Radioactive iodine (^{131}I)
RET	Ret proto-oncogene
Rb	Retinoblastoma protein
RECIST	Response Evaluation Criteria In Solid Tumours
rhTSH	Recombinant human thyroid stimulating hormone
SAE	Serious adverse event (see definition in Section 6.5.2).
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBE-CD	Sulphobutylether β-cyclodextrin
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standard uptake value
T0, T1, Tx etc	Primary tumour disease stage (TNM cancer staging system)
T4	Free thyroxine
Tg	Thyroglobulin
TgAb	Thyroglobulin antibody
TNM	Tumour, nodes, metastasis cancer staging system
TPGS	D-α tocopheryl polyethylene glycol 1000 succinate

Abbreviation or special term	Explanation
TPO	Thyroid peroxidase
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	Ultrasound
WBDC	Web based data capture
WBS	Whole body scintigraphy (also whole body scan)
WHO	World Health Organisation
Wk	Week

1. INTRODUCTION

1.1 Background

1.1.1 Thyroid Cancer

There are approximately 56,500 new cases of thyroid cancer diagnosed in the USA per year, and approximately 34,000 new cases diagnosed in Europe per year. Thyroid cancers are classified according to their histopathological characteristics into 4 main variants: papillary thyroid cancer (PTC, the most common), follicular thyroid cancer, medullary thyroid cancer and anaplastic (undifferentiated) thyroid cancer. The papillary and follicular types together can be classified as differentiated thyroid cancer (DTC), and make up approximately 95% of thyroid cancers. All DTC (including PTC) begins in the follicular cells of the thyroid gland and is termed "of follicular cell origin." Other, rarer variants of thyroid cancer of follicular cell origin include Hürthle cell carcinoma and poorly differentiated thyroid cancer (PDTC). DTC is generally indolent and has a natural history which is measured in decades if treated appropriately (up to 95% 10 year survival). However there are very limited options for patients who ultimately fail radioactive iodine therapy and develop distant refractory metastases, and most of these patients will succumb to their disease (Durante et al 2006).

1.1.2 Radioactive iodine treatment

In addition to primary thyroid surgery, radioactive iodine (RAI, ^{131}I) is the mainstay of therapy for patients with thyroid cancer of follicular origin. It is a targeted therapeutic approach that exploits the expression of the sodium iodide symporter (NIS) to deliver radiation selectively to thyroid cells, which is used as adjuvant therapy after thyroidectomy, and to treat recurrent and metastatic disease.

Most patients with thyroid cancer of follicular origin have differentiated carcinomas which retain at least to some extent the biological properties of normal thyroid cells, including expression of NIS. Presence of this transporter is required for iodine uptake (Riesco-Eizaguirre et al 2006).

Following diagnosis, surgical resection of the thyroid gland with or without removal of the local lymph nodes is performed. Following surgical resection, a set of clinical-pathologic data (such as age at diagnosis, specific histological type, size of the primary tumour, extent of lymph node metastases, presence of distant metastases, gross extrathyroidal extension and completeness of resection) can be used to estimate the risk of recurrence and the risk of disease specific mortality. After surgery, radioactive iodine can be used for the following purposes:

For diagnostic scanning to improve initial staging and extent of disease assessment.

For ablation of the normal thyroid remnant (usually less than 2-3% of normal tissue remains after total thyroidectomy). This treatment facilitates follow-up by achieving an undetectable level of serum thyroglobulin and a subsequent negative diagnostic whole body RAI scan.

As adjuvant therapy, in an attempt to destroy microscopic residual disease in patients at intermediate to high risk of recurrence.

As primary therapy in patients with unresectable RAI-avid loco-regional disease or distant metastases.

Uptake of RAI by tumour tissue is a prerequisite for administration of RAI treatment and for its efficacy. Once patients develop distant metastatic disease, RAI uptake is observed in only two thirds of cases and less frequently in patients with aggressive disease (Durante et al 2006, Mazzaferri and Kloos 2001, Nemec et al 1979, Samaan et al 1985). Patients with no uptake in metastatic foci are considered refractory to RAI, which is then no longer indicated.

1.1.3 Risk stratified remission rates following RAI treatment

Several different risk stratification systems have been published for DTC. The Union Internationale Contre le Cancer/American Joint Committee on Cancer (AJCC) staging system is the most commonly used, but it was developed to predict the risk of death rather than recurrence. To overcome this limitation, the American Thyroid Association (ATA) published guidelines to grade the risk of recurrence into 3 categories (low, intermediate, and high) based on tumour-related parameters (pathological tumour-node-metastasis and histological variant) integrated with other clinical features, including the result of the first post-therapy RAI whole-body scan and serum Tg measurement. Although the ATA risk stratification system has been shown to better predict short-term clinically relevant endpoints of persistent and recurrent disease than the AJCC system, it does not adequately predict longer-term outcomes because the risk of persistent or recurrent disease changes following initial therapy. In addition, the ATA intermediate risk category includes a wide variety of potential risk factors that can have a significant influence on both short term and long-term outcomes (any tumour size, N1a/N1b node status, vascular invasion, extrathyroidal extension, aggressive histology).

Recent evidence suggests that the likelihood of achieving remission varies depending on the size of the primary tumour, extent of invasion, or lymph node status as defined by number and size of affected nodes (refer to Table 1, Tuttle, unpublished sub-analysis of data from Tuttle et al 2010 and Vaisman et al 2012).

Table 1 Remission rates in 2 independent data sets of risk-categorised patients with differentiated thyroid cancer - based on tumour size and lymph node status

TNM status	Description	Remission rate[a] MSKCC[b] n=588 patients	Remission rate[a] Brazil[c] n=506 patients
T1	Tumour diameter 2 cm or smaller	40%	59%
T2	Tumour diameter 2 - 4 cm	47%	52%
T3	Tumour diameter > 4 cm or with minimal extrathyroidal extension	25%	37%
T4	Tumour of any size extending to invade subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia or encasing carotid artery or mediastinal vessels	13%	17%
N0	No metastatic nodes identified	62%	54%
N1a	Metastatic nodes in central neck (pretracheal, paratracheal, or prelaryngeal)	31%	30%
N1b	Metastatic nodes in lateral neck or superior mediastinum	16%	12%

[a] Remission rate within a 2 year follow up period
[b] unpublished sub-analysis of data from Tuttle et al 2010
[c] unpublished sub-analysis of data from Vaisman et al 2012

As can be seen patients with either T3 disease or N1a disease have remission rates that approximate 30%, while patients with T4 disease or N1b disease have remission rates that approximate 15%. From a clinical perspective, these findings are not surprising since T3 disease is very commonly associated with N1a disease, and T4 disease is often associated with N1b disease. Therefore, the similarity in remission rates in T3 and N1a disease, and in T4 and N1b disease, is consistent with observations in clinical practice.

It is important to note that in addition to the location of the lymph node metastases (N1a vs. N1b), the extent of lymph node metastases (size and number of involved nodes) is also a critical factor in assessing the risk of recurrence and risk of failing initial therapy (Randolph et al, 2012, Ricarte-Filho et al 2012). The complete remission rates from the MSKCC and Brazilian cohorts are based on patients with clinically significant, structurally evident N1a and/or N1b disease that required therapeutic neck dissections for clinically apparent metastatic disease (prophylactic neck dissections to remove sub-clinical disease were not performed in either the MSKCC or Brazilian cohorts). For example, in a MSKCC series of 246 papillary thyroid cancer patients who presented with lymph node metastases at the time of diagnosis, a median of 6 metastatic lymph nodes were identified with a median maximal diameter of 1.3 cm (Ricarte-Filho et al 2012). Furthermore, multiple studies have demonstrated that small volume lymph node metastases which are usually identified as incidental findings in the fibroadipose tissue surrounding the thyroid, or as a result of prophylactic central neck dissections, are associated with a low risk of recurrence (Randolph et al, 2012, Ricarte-Filho et al 2012), and these may not even require RAI adjuvant therapy (and therefore would not be

appropriate subjects for the proposed study). Therefore, to prevent patients with lower risk N1a or N1b small volume metastatic disease from enrolling into this study, a requirement is that subjects must have N1a or N1b disease involving 5 or more lymph nodes (of any size) or at least 1 lymph node ≥ 1 cm in the largest diameter.

Since only approximately 30% of patients presenting with any of the following features are expected to achieve clinical remission following total thyroidectomy and RAI remnant ablation, they are at high risk of failing their primary treatment:

- Primary tumour greater than 4 cm
- Primary tumours of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)
- N1a or N1b disease with at least 1 lymph node ≥ 1 cm
- N1a or N1b disease involving 5 or more lymph nodes (of any size)

Total thyroidectomy and RAI ablation is therefore very effective at inducing remission in low risk patients, however approximately 70% of patients with the above characteristics do not enter remission, and have an incomplete response to initial therapy with biochemical and/or structural evidence of persistent disease.

1.1.4 The benefits of achieving remission

Thyroid cancer deaths are exceedingly rare if remission is achieved, and studies have shown that nearly all deaths ultimately occur in the group of patients who do not achieve remission. For example, two recent studies reported disease-specific deaths in 6% and 8% of the patients who did not achieve remission compared to 0% in patients who achieved remission with median follow-up times of 7 and 10 years respectively (Tuttle RM, unpublished sub-analysis of data from Tuttle et al 2010, Vaisman et al 2012). This mortality rate continues to rise with longer periods of follow up with nearly all deaths from thyroid cancer being seen in the cohort of patients that failed to achieve remission.

The importance of a successful initial therapy is demonstrated by the excellent prognosis that even high-risk patients have if therapy results in negative imaging and negative thyroglobulin levels after stimulation by TSH. The majority of patients who achieve remission do not relapse; recurrence rates are typically 1% to 4% over median follow-up periods of 5 to 10 years for patients who achieve remission (Castagna et al 2011, Tuttle et al 2010, Vaisman et al 2012).

In patients that achieve remission, there are important clinical and psychological benefits. Patients that achieve remission are re-classified as low risk patients and require much less frequent follow-up. Thyroglobulin testing and imaging assessments are reduced in frequency, and less aggressive TSH suppressive therapy is required. This in turn reduces the longer-term risks of osteoporosis and atrial fibrillation that are known complications of supra-

physiological dosing of levothyroxine, and reduces the anxiousness and fatigue that can result from the mildly hyperthyroid state caused by TSH suppression.

If remission is not achieved with initial therapy, many patients will be subjected to additional therapies (eg, more RAI, surgery, external beam irradiation), in an effort to control disease progression and achieve a cure. Therapeutic RAI is associated with a cumulative dose-related risk of early and late-onset complications such as salivary gland damage, dental caries, nasolacrimal duct obstruction, and decreased fertility (Cooper et al 2009). Furthermore, a dose-dependent relationship is also seen between cumulative administered RAI activity and the subsequent occurrence of secondary malignancies (Rubino et al 2003, Sawka et al 2009). All of these risks and symptoms constitute significant quality of life issues for the patient. The inconvenience of repeating a low iodine diet, the associated radiation safety precautions and missed days of work are additional factors the patient must consider. Additional surgery carries associated risks related to anesthesia, nerve damage (resulting in hoarseness, permanent tracheotomy in rare occasions, drooping eye lid, loss of control of shoulder muscles and loss of sensation in the neck), increased scarring in the neck (resulting in discomfort and difficulty swallowing), and damage to the parathyroid glands (resulting in hypocalcemia and a lifetime need for vitamin D and calcium supplementation and frequent blood tests). Thus avoidance of further therapy is beneficial to the patient.

Unfortunately, additional therapy is often less effective, particularly in patients with persistent structural disease (Vaisman et al, 2011). Further RAI can be given to patients that have persistent biochemical evidence of disease, and although repeat RAI is often less effective than the initial RAI treatment (especially for patients with persistent structural disease), it can be effective at driving some patients with persistent biochemical disease into remission. Thus, strategies designed to improve the tumouricidal effect of the initial RAI dose should result in higher remission and cure rates.

An intervention that enhances the effectiveness of initial therapeutic RAI in higher risk patients (the target population for this study), should result in higher remission rates and remove the need for further therapy, and would thus be of clear benefit to patients.

1.1.5 Selumetinib

Selumetinib is a potent, selective, noncompetitive inhibitor of MEK, licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma. Selumetinib was discovered by Array Biopharma and had the designation ARRY 142886. Other laboratory code names used during the development of this molecule are AR00142886 and AR-142886-X (where X refers to a sequential lot number). Array BioPharma was responsible for the first-into-human study; the remainder of the clinical development programme for oncology indications is the responsibility of AstraZeneca. AZD6244 has now been assigned the international non-proprietary name selumetinib.

1.1.5.1 MEK and NIS expression

Papillary thyroid cancer (PTC), which is the most common form of the disease, is characterised by a set of genetic alterations, all of which result in the activation of

RAF/MEK/ERK signalling. Of these genetic lesions the most common is the typical V600E mutant of *BRAF* also found in other cancers, most notably melanoma. The other genetic lesions occur in receptor tyrosine kinases (RET and NTRK1), and in *RAS* (*N* and *HRAS*). In total these mutations in effectors of ERK signalling account for approximately 70% of papillary thyroid cancer (Kimura et al 2003, Soares et al 2003). *BRAF* itself is seen in at least 38% of PTC, and is also found in poorly differentiated and anaplastic thyroid carcinomas with a prevalence of 12% and 50%, respectively (Nikiforova et al 2003, Ricarte-Filho et al 2009). These genetic mutations are mutually exclusive and suggest the importance of RAF/MEK/ERK signalling in papillary thyroid cancer.

With regard to the impact on efficacy of RAI therapy, one of the primary effects of activation of the RAF/MEK/ERK signalling pathway is a significant and sustained down regulation of the sodium iodide symporter (NIS) which is responsible for the uptake of iodine into thyroid cells and is required for the uptake of therapeutic ^{131}I into thyroid cancer cells. Studies have demonstrated that the expression of NIS (and other genes typical of differentiated thyroid cells) is suppressed by activation of RAF/MEK/ERK signalling in mouse models of the disease (Franco A et al. 2011). In mice engineered to express V600E *BRAF* in thyroid cells, expression of NIS and other thyroid differentiation markers is reduced (Knauf et al 2005). These mice develop papillary thyroid cancers with dedifferentiated features. Further data using a mouse model of thyroid-specific inducible expression of V600E *BRAF*, show that V600E *BRAF* activation suppresses expression of NIS, thyroid peroxidase (TPO) and thyroglobulin (Tg), and blocks ^{124}I uptake, all of which are re-established once expression of oncogenic *BRAF* is turned off. Treatment of mice expressing the induced V600E *BRAF* with a MEK inhibitor also re-established NIS expression and ^{124}I uptake in the poorly differentiated thyroid carcinomas (PDTC) (Chakravarty D et al 2011). Constitutive activation of MAPK signalling also inhibits the expression of thyroid peroxidase and thyroglobulin in BRAF-induced murine thyroid cancers. Genetic or pharmacological blockade of the pathway restores their expression, and consequently the ability to incorporate iodine into tyrosine (iodine organification), which is associated with greater retention time of ^{131}I in cancer cells (Chakravarty D et al 2011). Other MAPK activating alterations common to thyroid cancer can also cause de-differentiation. Over-expression of either the G12V *HRAS* mutant or *RET/PTC* in thyroid cancer cells suppresses NIS, thyroglobulin and thyroid peroxidase expression, which is restored with MEK inhibitor treatment (Knauf et al 2003, De Vita et al, 2005). These experiments provide a pre-clinical proof of concept that inhibition of ERK signalling by MEK inhibitors can reverse the suppression of NIS, TG and TPO expression and re-establish iodine incorporation into PTC.

NIS expression in clinical thyroid cancer samples

Analysis of clinical tumour samples for NIS expression indicates a relative loss of NIS expression (and the expression of other thyroid specific genes) relative to normal thyroid tissue (Durante et al 2007; Espadinha et al 2009). Furthermore, NIS expression is lower in *BRAF* mutant tumours than in those without *BRAF* mutation (Durante et al 2007; Morai et al 2011; Romei et al 2008). In a well differentiated rat thyroid cell line model, expression of RET/PTC, mutant HRAS, or constitutively active MEK1, blocked TSH-induced expression of Tg and NIS; an effect that was reversed by MEK inhibition. These data are consistent with

the hypothesis that activation of MEK, regardless of the upstream activating mutation is a key factor in the loss of thyroid differentiation specific gene expression including NIS (Knauf et al 2003).

In summary, this data predicts that both an unselected and genetically selected population may benefit from treatment with a MEK inhibitor and RAI. This study will thus assess two populations for the primary endpoint of complete remission rate at 18 months; the genetic 'all comer' population, and also a population of patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that other patients may also benefit.

1.1.5.2 Clinical data in thyroid cancer

The preclinical data generated to date suggests the clinical hypothesis that MAPK pathway inhibition in patients with RAI-refractory tumours will result in reacquisition of RAI uptake and renewed susceptibility to therapeutic ^{131}I. To test this hypothesis, an investigator-sponsored selumetinib pilot study has been performed at MSKCC for patients with RAI-refractory recurrent or metastatic differentiated thyroid carcinoma of follicular cell origin entitled, "Reacquisition Of RAI Uptake Of RAI-Refractory Metastatic Thyroid Cancers By Pre-treatment With The Selective MEK Inhibitor Selumetinib: A Pilot Study" (Ho et al 2012). In this study, the RAI avidity of thyroid tumours was quantified by lesional dosimetry with ^{124}I PET imaging in patients, before and after 4 weeks of treatment with selumetinib. For patients whose tumours reacquired the ability to take up RAI, ^{131}I treatment was administered, and tumour response was assessed both radiographically and with measurement of the serum tumour marker thyroglobulin (Tg).

20 patients were treated with selumetinib in this pilot study. Of the 20 patients, 9 patients had tumours with the V600E *BRAF* mutation, 5 patients had tumours with *NRAS* mutations at codon 61, 3 patients had tumours with *RET/PTC* rearrangements, and the remaining 3 patients were wild-type for these alterations. Twelve of the 20 patients in the study demonstrated increased tumoural ^{124}I uptake, and 8 of these 12 patients achieved sufficient iodine reuptake to warrant treatment with ^{131}I. Interestingly, 5 of these patients were found to have *NRAS* mutations, one a *BRAF* mutation, one a *RET/PTC* rearrangement and one patient was wild-type. Further genotyping and cytogenetic analysis is ongoing to discover other potential oncogenic drivers that may have promoted susceptibility to this therapeutic strategy. The increased iodine incorporation as quantified on the ^{124}I scans translated to clinical efficacy with RAI therapy. Reduction in tumour size by RECIST criteria was achieved in all RAI-treated patients, with 5 confirmed partial responses and 3 patients with stable disease. Substantial decreases in serum thyroglobulin following RAI therapy were achieved in all 8 RAI-treated patients. The mean percent reduction in serum thyroglobulin achieved "post-RAI" (2 months after RAI treatment) compared to "pre-RAI" (within 3 weeks before RAI treatment) was 89%.

Data from the pilot study also suggests that pre-treatment with selumetinib selectively increased RAI uptake in tumoural lesions compared to non-thyroidal tissue (salivary gland).

This pilot study demonstrates that MAPK pathway inhibition can modulate RAI uptake in the most difficult clinical scenario: patients with resistance to RAI therapy. Most patients in the pilot clinical study described above had many metastatic lesions, some of which were refractory to RAI at baseline, and some of which were partially RAI avid at baseline. Importantly, selumetinib not only restored RAI uptake in previously refractory lesions, but also increased RAI uptake in most partially-avid lesions (typically by more than 100% compared to the baseline value; 3 to 7 fold increases in maximum SUVs in such lesions were consistently observed). This provides a strong rationale to develop this strategy in the adjuvant setting for RAI naïve patients, with the goal of further enhancing what is more likely to be RAI-susceptible disease for patients at high risk of primary treatment failure.

In addition to the pilot study described above, a phase II study of 100 mg bid selumetinib (previous mix-and-drink formulation) in 39 patients with RAI-refractory differentiated metastatic thyroid cancer has also been completed (Hayes et al 2012). This study involved continuous monotherapy dosing of selumetinib and no RAI treatment. The results demonstrated few clinical responses (one partial response in 32 evaluable patients), but demonstrated a 66% stable disease rate; median PFS in this poor-prognosis cohort was 33 weeks in patients with mutations in *BRAF* V600E, and 32 weeks in all-comers. Although this study was conducted with the mix and drink formulation (from which selumetinib exposure may be lower), the efficacy of selumetinib as monotherapy in this population was disappointing.

Taken together, these data suggest a strong rationale for investigating selumetinib with RAI in patients with DTC. Given the known prevalence of MEK pathway activation in patients with DTC, and both the pre-clinical and clinical data seen when selumetinib is added to RAI, increasing iodine uptake, specifically with respect to selumetinib's ability to upregulate NIS expression, adding selumetinib to standard of care RAI treatment has the potential to provide important clinical benefit. This benefit may extend to all patients regardless of their genotype, or it may be greater in those patients with tumours driven by mutations in the MEK pathway. This study will allow these hypotheses to be tested.

1.1.5.3 Safety profile of selumetinib

Array BioPharma was responsible for the first study of selumetinib into patients. The remainder of the oncology clinical development programme is the responsibility of AstraZeneca. Selumetinib is currently in phase II development, and has been used as both monotherapy and in combination with other anti-cancer agents, in a variety of adult solid tumour settings (eg, pancreatic cancer, colorectal cancer, melanoma and NSCLC), and paediatric cancer patients.

The formulation taken into the phase I clinical programme by Array Biopharma was an extemporaneous preparation of an oral suspension of selumetinib as the free-base in an aqueous solution of sulphobutylether β-cyclodextrin (SBE-CD, Captisol®), referred to as the free-base suspension formulation (mix and drink). The AstraZeneca phase II monotherapy

clinical programme also utilised this formulation. Subsequent formulation development resulted in a capsule formulation of selumetinib as the hydrogen sulphate salt (AZD6244 Hyd-Sulfate), which will be used in this study. The maximum tolerated dose (MTD) for the suspension formulation was determined to be 100 mg twice daily, whereas for the capsule, the MTD was determined to be 75 mg twice daily. The emerging safety and tolerability profile of the capsule formulation is broadly consistent with that of the suspension formulation, although a higher frequency of fatigue and nausea has been reported with the capsule formulation compared to the suspension formulation in the phase II monotherapy studies.

As of April 2012, over 1200 patients have received selumetinib as monotherapy or in combination with other anti-cancer agents in clinical studies (AstraZeneca and non AstraZeneca-sponsored studies, including investigator-sponsored studies).

Two phase I studies (D1532C00005, D1532C00020) were performed with the Hyd-Sulfate formulation. Comparison of the frequencies from Study D1532C00005 and the AZ-sponsored phase II monotherapy studies described below, shows that there are higher percentages of patients reporting the most frequent AEs such as fatigue, dermatitis acneiform, diarrhoea, nausea and peripheral oedema with the Hyd-Sulfate formulation. This may be due to the higher plasma exposures achieved with the capsule formulation, but may also be in part as a consequence of the more heavily pre-treated patient population in study D1532C00005 having lower tolerances to developing toxicity.

- The frequencies of common AEs observed in Study D1532C00020 were generally more similar to that of Study D1532C00003 (free-base suspension formulation in a phase II population), which may mean that some of the differences in frequencies observed just reflect variations in the study population as the selumetinib safety profile is established.

Two hundred and sixty nine (269) patients received selumetinib free base suspension 100 mg twice daily in 4 completed phase II monotherapy studies (D1532C00003, D1532C00008, D1532C00011, and D1532C00012).

- Rashes (including the preferred terms dermatitis acneiform, rash, rash maculopapular, rash macular, rash papular, acne, and folliculitis) were reported in approximately 70% of patients receiving treatment with selumetinib, and dermatitis acneiform was the most common AE term overall (54%). Other commonly reported AEs were diarrhoea (49%), nausea (33%) and vomiting (24%). Adverse events of peripheral oedema, periorbital oedema, and facial oedema were reported in 31%, 9%, and 4% of patients, respectively. The AEs of fatigue or asthenia were reported in approximately 30% of patients in this phase II population. Dyspnoea exertional or dyspnoea was reported in 13% of patients and, in individual studies, dyspnoea exertional was reported at a higher incidence in the selumetinib groups than in the comparator chemotherapy groups.

- Serious AEs were reported in 24% of patients receiving selumetinib monotherapy. The most frequently reported serious AEs were vomiting (1.5%), diarrhoea,

erysipelas, and pulmonary embolism (in 1.1% patients each). Serious AEs of infections (bacterial sepsis, sepsis, infection, and bacterial arthritis) were reported in 2.2% of patients. The most frequently related reported treatment-related SAE was vomiting (3 patients).

- In Study D1532C00003, small increases in blood pressure were observed after 1 week on selumetinib, with mean increases of 7.4 mmHg (systolic, SBP) and 5.3 mmHg (diastolic, DBP) at Week 8, compared with mean increases of 1.1 mmHg (SBP) and 0.5 mmHg (DBP) in the temozolomide comparator arm. The AE of hypertension was reported in 18 patients (6.7%) receiving selumetinib in phase II monotherapy studies; 6 of these patients had hypertension at entry to the study, and a further 5 patients had documented risk factors for hypertension.

- Reversible asymptomatic reduction in left ventricular ejection fraction (LVEF) to below 55% has been reported in a small proportion of patients with advanced cancers in the monotherapy and randomised placebo controlled studies in combination with standard chemotherapies, with both formulations of selumetinib. In both placebo controlled studies no patient treated with selumetinib had severe LVEF impairment (< 35%) or symptomatic heart failure. Evidence of reversibility on continuing treatment with selumetinib has been demonstrated in some patients. LVEF scheduled assessments were only included in one phase II study (D1532C00003) and in the selumetinib group to evaluate a possible cardiac aetiology of the peripheral oedema reported in earlier studies. The median change in LVEF at Week 4 was 1.2 percentage points, and the individual change from baseline ranged from –20 to +19 percentage points. Adverse events of ejection fraction decreased, left ventricular dysfunction, or ventricular dysfunction were reported in a total of 5 patients (3.3%) receiving selumetinib (including 1 patient who had switched from temozolomide treatment after disease progression) versus 1 patient (1%) in the comparator group.

- Review of clinical laboratory parameters in phase II monotherapy studies identified a trend toward increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels after starting treatment with selumetinib. An increase in serum phosphate was observed in some patients after initiation of selumetinib, compared with patients randomised to comparator treatments.There was a trend toward a small mean decrease in albumin relative to the comparator. No other reports of selumetinib-related changes in laboratory parameters were considered to be of clinical relevance at this time. There was no evidence of myelosuppression or renal impairment.

- Adverse events related to visual function have been reported across the programme with selumetinib. Most often there were no specific clinical findings reported from patients that underwent ophthalmological evaluation after reporting the AE of visual disturbance. AEs consistent with central serous retinopathy have been reported in a

small number of patients receiving treatment with selumetinib, generally in combination with other anti-cancer agents.

- There have been reports of pneumonitis-type events in a small number of patients receiving treatment with selumetinib. An association with selumetinib has not been established. An algorithm for investigation of dyspneoa is provided in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

- Weakness of neck extensor muscles in conjunction with creatine phosphokinase (CPK) increases (reversible on treatment interruption) have been reported in 3 out of 54 patients with uveal melanoma receiving selumetinib 75 mg twice daily in one non-AstraZeneca sponsored study. Increases in CPK levels have been recorded in a small number of patients receiving treatment with selumetinib. CPK elevations are present in some patients with muscle symptoms, although asymptomatic elevations have also been reported. A relationship between selumetinib and elevated CPK levels or myopathy has not been established.

In the DTC pilot study described in Section 1.1.5.2 (Ho et al 2012), where 20 metastatic thyroid cancer patients were treated with a 4 week course of selumetinib 75 mg twice daily, all events attributed to selumetinib were Grade 1 or 2, and included fatigue (80%), maculo-papular rash (70%), acneiform rash (25%), elevation in AST (70%; all Grade 1), elevation in ALT (45%; all Grade 1), diarrhea (45%), nausea (40%), limb edema (30%), oral mucositis (35%), constipation (20%), hypoalbuminemia (15%), decreased white blood cell count (15%), face edema (10%), scalp pain (10%), decreased platelet count (1 patient; Grade 1), eye disorder (1 patient; Grade 1 consisting of visual halos and slight blurriness that resolved after therapy stopped), hypertension (1 patient; Grade 1), periorbital edema (1 patient; Grade 1), and vomiting (1 patient, Grade 1). One patient who was treated with RAI was subsequently diagnosed with myelodysplastic syndrome 51 weeks after RAI administration which subsequently evolved into acute leukaemia (this was determined to be unrelated to selumetinib and likely related to cumulative RAI toxicity as well as previous external beam radiation therapy). All adverse events were readily managed with supportive mediations and were reversible upon discontinuation of selumetinib. None of the 20 patients required dose delays or reductions due to selumetinib toxicity.

In the only other study to specifically investigate selumetinib in differentiated thyroid cancer patients (the phase II study of 100 mg bid selumetinib, previous mix-and-drink formulation) in 39 patients with RAI-refractory differentiated metastatic thyroid cancer (Hayes et al 2012). In these patients with RAI-refractory disease, common drug-related AEs included rash (77%), fatigue (49%), diarrhea (49%), and peripheral oedema (36%). Grade 3 and 4 AEs were consistent with those across the selumetinib program and also included rash (18%), fatigue (8%), diarrhea (5%) and peripheral oedema (5%). Twelve patients required dose reductions for reported AEs across the length of the study (the duration of treatment was greater than 16 weeks for 69% of patients). Six patients (15%) discontinued treatment due to adverse events.

A study of selumetinib in combination with radiation in patients with non-small cell lung cancer has recently been opened but no safety or efficacy results are yet available from this study.

Selumetinib is not mutagenic or clastogenic in vitro but produced increases in micronucleated immature erythrocytes in mouse bone marrow micronucleus studies. Investigatory studies show that this is predominantly via an aneugenic mechanism which is consistent with disruption of normal spindle function as a consequence of the known pharmacological action of a MEK inhibitor. With selumetinib Hyd-Sulfate, a NOEL of 24 mg/kg/day (for 2 days) was established for induction of micronuclei, with plasma exposures significantly above those observed in cancer patients at the maximum tolerated dose of 75 mg twice daily. This suggests that selumetinib will have little potential to cause aneugenicity in dividing cell populations in patients at the proposed clinical dose. Thus, any additional aueugenic risk from a 5 week course (maximum 43 days) of twice daily 75 mg selumetinib dosing in this potentially curative patient setting, is considered to be negligible in comparison with the known and more substantial risk from radiation exposure following a therapeutic dose of ^{131}I (100 mCi) that patients will receive as part of standard of care.

In summary, selumetinib has been shown to have an acceptable profile of side effects, in an extensive safety database for a compound at this stage of development.

Further details regarding the safety profile of selumetinib can be found in the Investigator Brochure.

1.2 Research hypothesis

Pre-treatment with selumetinib enhances the uptake of radioactive iodine in differentiated thyroid cancer, resulting in a greater incidence of complete remission after adjuvant RAI therapy in patients at high risk of primary treatment failure.

1.3 Rationale for conducting this study

Unfortunately a significant proportion of thyroid cancer patients are not cured by their initial surgery and RAI therapy. This is often due to the inability of their cancer cells to adequately incorporate RAI (due to reduced expression of NIS). In such cases, repeated administration of RAI may be given (for RAI avid disease) with the aim of inducing remission and curing their disease. This outcome however is not guaranteed, and patients who subsequently develop refractory metastatic disease have a much poorer prognosis and may eventually succumb to their disease; at least one third of patients who develop metastatic disease have no or very low uptake and are thus not amenable to further RAI treatment. There is thus an urgent need for a medicine that can enhance the effectiveness of initial RAI treatment and increase the probability of achieving remission, thereby preventing more patients from developing distant metastatic disease.

1.4 Benefit/risk and ethical assessment

It is clear from the Investigator-sponsored study (Ho et al 2012), that a short course of selumetinib prior to RAI therapy, is effective in enhancing RAI uptake, reducing tumour marker (Tg) levels, and reducing tumour size in heavily pre-treated patients with documented RAI-refractory disease. Most patients in the pilot clinical study had numerous metastatic lesions, some of which were refractory to RAI at baseline and some of which were partially RAI avid at baseline. Importantly, selumetinib pre-treatment not only restored RAI uptake in previously refractory lesions, but also increased RAI uptake in the majority of partially avid lesions (typically by more than 100% compared to the baseline value; 3- to 7-fold increases in maximum SUVs in such lesions were consistently observed). This pilot data not only supports the preclinical hypothesis that inhibiting the MAPK pathway can convert non-RAI avid lesions to RAI avid tumours, but also demonstrates that iodine uptake in previously iodine sensitive lesions can be significantly increased with selumetinib. This observation broadens the potential clinical applicability of this approach beyond just RAI-refractory thyroid cancer, to the use of selumetinib and RAI as part of upfront adjuvant treatment of RAI-naïve and susceptible DTC.

The potential benefit to patients in this study is therefore high, with an increased chance of complete remission. The toxicity risk from a short course (approximately 5 weeks) of selumetinib treatment has been carefully considered for this potentially curative population; the side effect profile of selumetinib in the short timeframe (maximum 6 weeks of exposure) is considered to be predictable, manageable and reversible (mainly rash and fatigue). The long term risk of secondary malignancies associated with RAI is considered low from a single 100 mCi dose, as these are rare and more typically develop following cumulative RAI treatments and exposure. Patients under the age of 18 years will be excluded to minimise any risk of increased radioactivity exposure in a younger population. The side effect profile of both selumetinib and RAI will be monitored over the entire 3 year study duration for each patient.

2. STUDY OBJECTIVES

2.1 Primary objective

To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in the intention to treat (ITT) study population. Complete remission is defined in Section 6.4.1.

2.2 Secondary objectives

1. To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

2. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the ITT study population. Clinical remission is defined in Section 6.4.6.

3. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

4. To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

5. To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

2.3 Exploratory objectives

1. To explore subsequent thyroid cancer therapy given to patients who receive selumetinib with RAI, or placebo with RAI.

2. To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters.

3. To collect tumour, plasma and serum samples for potential future research on biomarkers relevant to DTC and response and resistance to study treatments.

4. To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib or RAI and/or susceptibility to cancer.

The exploratory analysis will be reported separately from the CSR.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a double-blind, randomised, placebo-controlled study to assess the efficacy and safety of a short course (approximately 5 weeks) of selumetinib (75 mg, orally twice daily) in combination with adjuvant RAI therapy compared to placebo and adjuvant RAI therapy, in patients with differentiated thyroid cancer at high risk of primary treatment failure.

Approximately 228 patients will be randomised 2:1 selumetinib to placebo.

This will be a multi-centre, international study; it is anticipated that approximately 50 centres will recruit patients in South and/or North America and Europe.

3.1.1 Treatment Plan

Following randomisation, patients will take their assigned study treatment (selumetinib or placebo) for a period of approximately 5 weeks, twice daily. Study treatment will begin approximately 4 weeks prior to the planned day of RAI therapy. Refer to Table 2 for an example study treatment plan. The following treatment criteria must be adhered to:

1. Day 1 of study treatment must occur:
   - no earlier than 6 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy), and
   - no later than 16 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).
2. It is essential that patients remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator until the patient has been on study treatment for a minimum of 7 consecutive days beforehand.
3. Study treatment with selumetinib or placebo will typically last for 36 days, but must be for no longer than 43 days (this allows the planned RAI to be postponed by up to 1 week if absolutely necessary).
4. Patients will be required to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI treatment. Refer to Section 5.1.1 and the example diet in Appendix F for further details.
5. For each of the 2 days immediately prior to their planned RAI therapy, patients will receive a recombinant human TSH injection (rhTSH, Thyrogen), in order to stimulate iodine uptake (refer to Section 5.5.4 for details).
6. Following the 2 days of rhTSH injections, patients will receive their planned RAI therapy the immediate next day (refer to Section 5.5.4 for further RAI dosing information).
7. Twice daily dosing of selumetinib/placebo will continue for 5 days following RAI therapy (Day 36 will typically be the last day of study treatment, but this can extend to Day 43 if necessary).

Table 2 Example study treatment plan

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Day 1 X	Day 2 X	Day3 X	Day 4 X	Day 5 X	Day 6 X	Day 7 X
Day 8 X	Day 9 X	Day 10 X	Day 11 X	Day 12 X	Day 13 X	Day 14 X
Day 15 X	Day 16 X	Day 17 X	Day 18 X	Day 19 X	Day 20 X	Day 21 X
Day 22 X	Day 23 X	Day 24 X Low I diet	Day 25 X Low I diet	Day 26 X Low I diet	Day 27 X Low I diet	Day 28 X Low I diet
Day 29 X Low I diet **Thyrogen**	Day 30 X Low I diet **Thyrogen**	Day 31 X Low I diet **RAI**	Day 32 X Low I diet	Day 33 X	Day 34 X	Day 35 X
Day 36 X **last day of study treatment**		Day 38 (Day 36-41) WBS scan (3-10 days after RAI dose)				

X: Study treatment administration (selumetinib or placebo, twice daily)
RAI: radioactive iodine therapy (^{131}I) refer to Section 5.5.4.2 for details
This suggested treatment plan is an example only. The treatments may be planned for different days as long as all criteria in Section 3.1.1 are met.

3.1.2 Follow-up plan

Following completion of RAI therapy and planned discontinuation of study treatment (randomised selumetinib or placebo); patients will be followed up as follows:

1. 3-10 days after RAI therapy, patients will undergo a post-therapy whole body RAI (^{131}I) nuclear medicine scan to determine where the RAI has localized in the body (refer to Section 6.4.4.2 for further detail).

2. Patients will be monitored for TSH and thyroxine (T4) levels as per local standard of care (refer to Section 6.4.3.3 for further detail). Note that T4 levels will not be collected in the study database.

3. At 9 months (±3 months) following RAI treatment, patients will be assessed for:

   (a) TSH-suppressed Tg and Tg antibody levels (TgAb). Refer to Section 5.9.1.1 for further details.

(b) Neck ultrasound (US). Refer to Section 5.9.1.2 for further details.

It is important that these assessments are not performed earlier than 6 months after RAI treatment.

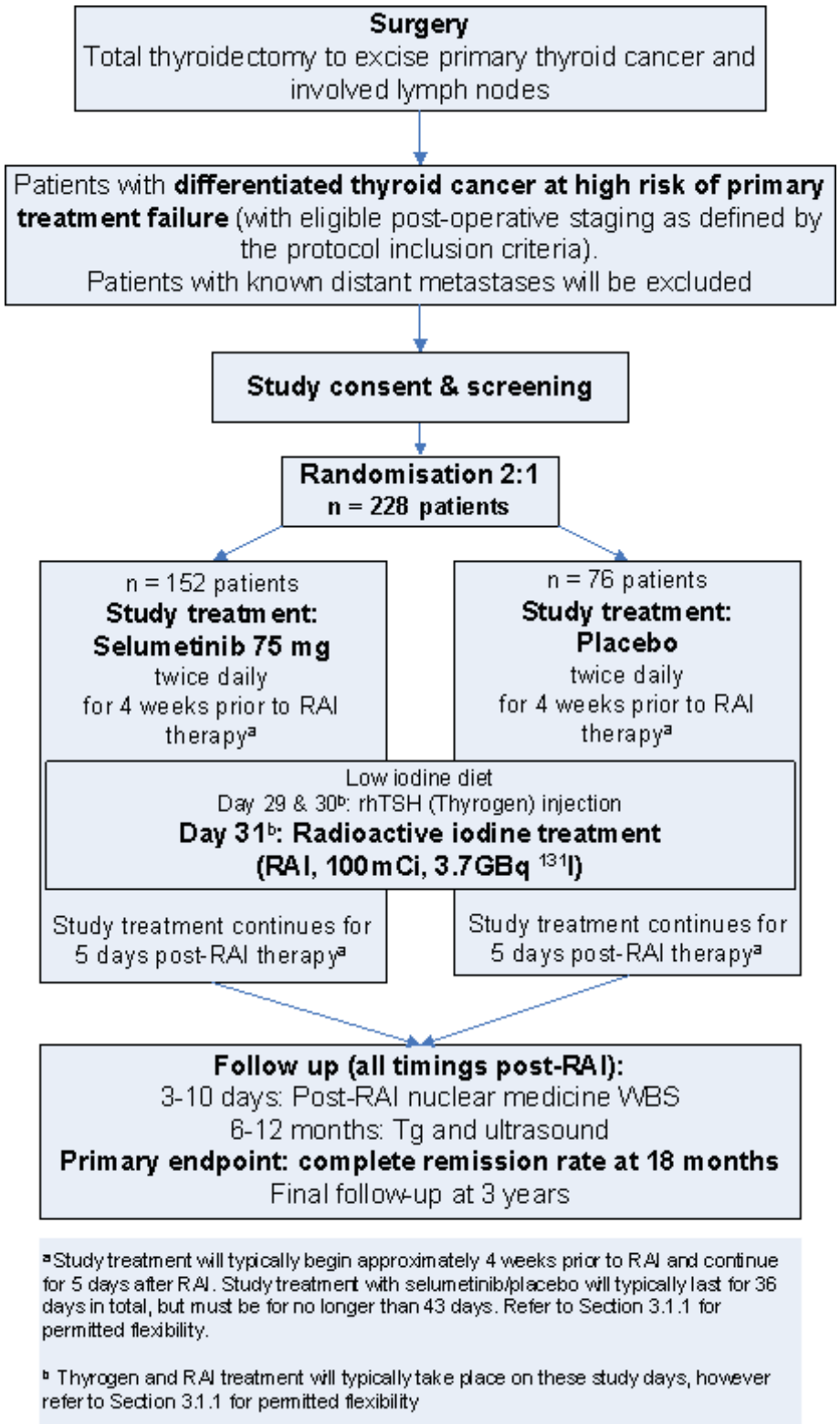
4. Patients will be assessed for their complete remission status at the primary endpoint 18 months following their RAI treatment. A staged approach to the primary endpoint assessments will be used in this study in order to determine remission status (presence or absence of thyroid cancer), such that each patient may not require all assessments. Refer to Section 6.4, Table 4 and Figure 3 for further details. The primary endpoint assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within an 8 week period.

   Further thyroid cancer therapy (eg, additional surgery, RAI re-treatment, external beam radiotherapy or systemic therapy) should only be given during the initial 18 month follow-up period according to the re-treatment criteria in Section 5.9. Any patient that is re-treated in the 18 month period following their RAI therapy will not require any primary endpoint assessments performing (they will be determined not to be in complete remission for the purpose of the study and will enter standard of care follow up, remaining in the study until the 3 year follow up).

5. Following the primary endpoint assessments (or re-treatment), all randomised patients will be further followed-up at 3 years following their RAI treatment. It is the responsibility of the study investigator to ensure they conduct follow-up as described in this protocol if patients transfer to non-study hospitals, or if patients are discharged for routine follow up at other institutions (eg, family doctor or local non-specialist hospital).

Assessments planned at each visit are detailed in Table 3, Table 4 and Section 6.

Figure 1 Study flow chart



[a] Study treatment will typically begin approximately 4 weeks prior to RAI and continue for 5 days after RAI. Study treatment with selumetinib/placebo will typically last for 36 days in total, but must be for no longer than 43 days. Refer to Section 3.1.1 for permitted flexibility.

[b] Thyrogen and RAI treatment will typically take place on these study days, however refer to Section 3.1.1 for permitted flexibility

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Informed consent	X												
Physical examination	X		X	X (Day 29 or 30)			X						6.5.6
Additional screening procedures	X												6.2
Provision of archival tumour[b]		X											6.10.1.1
Plasma/serum sample for exploratory analysis[b]		X (pre-dose)											6.10.2
Pregnancy test	X				X					X[a]			6.5.9.1
Optional genetic consent & sample (whole blood)		X (pre-dose)											6.9
Adverse events[c]	X →	→	→	→	→	→	→	→	→	→	→	→	6.5.3
Concomitant medications	X →	→	→	→	→	→	→	→	→	→	→	→	5.6
Telephone follow up for safety[d]								X			X		6.5.3

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Vital signs (including height at screening), weight	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.8
Clinical chemistry	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.5
Haematology	X	X (pre-dose)	X	X (Day 29 or 30)			X			X		X	6.5.5
Urinalysis	X		X				X						6.5.5
ECG[e]	X	X		X[e] (Day 29 or 30)			X						6.5.7.2
ECHO/MUGA[f]	X						X						6.5.7.1
Ophthalmologic examination[f]	X						X						6.5.9.2
Selumetinib/placebo dosing[g] twice daily		→	→	→	→	→							5.5.2

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On - treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
PK blood samples[h]		X		X[h] (Day 29 or 30)									6.7
Low iodine diet[i]				X	X					X[a]			5.1.1
Thyrogen injection				Xx2 (Day 29 and 30)						Xx2[a]			5.5.4.1
^{131}I (RAI) treatment single 100 mCi dose					X								5.5.4.2
^{131}I 5 diagnostic dose for WBS single 5 mCi dose										X[a]			5.5.4.2
^{131}I nuclear medicine WBS scan						X[j]				X[a]			6.4.4.2
Re-treatment assessment[k]									X	X		X	5.9
Blood sample for TSH									X	X			6.4.3.3
Blood sample for suppressed Tg									X[n]	X			6.4.3.1

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post visit 5	9 months post visit 5	18 months post visit 5	27 months post visit 5	3 years post visit 5	
Visit Window	N/A	N/A	±1wk	N/A	N/A	N/A	± 2 days	± 2 weeks	± 3 months	Refer to Table 4	± 2 months	± 1 month	
Blood sample for TgAb	X								X	X			6.4.3.4
Blood sample for rhTSH-stimulated Tg										X[a]			6.4.3.2
Neck ultrasound	X[l]								X	X			6.4.4.1
Neck MRI	X[l]									X[a]			6.4.4.3
Chest CT without contrast	X[l]									X[a]			6.4.4.4
Final follow-up assessment of clinical status												X	6.4.8
Biopsy/FNA for disease confirmation									X[m]	X[m]			6.4.4.5
Tumour biopsy on progression (optional)	Optional sample on disease progression (for example, if the patient is re-treated for persistent or recurrent thyroid cancer, or has further surgery). Note that both a plasma and serum sample for exploratory analysis should also be taken on disease progression.												6.10.3 6.10.2

Study Plan Table 3 Footnotes

[a] Refer to Table 4 and Section 6.4.2.

[b] Provision of these samples is mandatory in this study. Samples should also be obtained on progression (refer to Section 6.10.2).

[c] All AEs/SAEs should be collected from the day of consent until 30 days following the last dose of study treatment. From then on, all SAEs (regardless of causality), and all AEs related to either RAI, or the combination of RAI and study treatment, should be collected until the last study visit 3 years following the patient's RAI dose. The same AE collection scheme applies for any re-treated patient.

[d] The Investigator (or delegate) is required to contact the patient by telephone to follow up for any safety information (according to the collection scheme detailed in Section 6.5). For re-treated patients, safety follow-up should continue according to the protocol-scheduled visits, but may be collected by telephone if necessary at each visit (refer to Section 5.9).

[e] Single ECG assessments 1-2 hours following the first dose on Day 1 and Day 29 or Day 30 of study treatment. A single ECG assessment is also required whenever an ECHO/MUGA is performed, on any cardiorespiratory AE, and for premature discontinuation.

[f] These assessments must also be performed on symptomatology according to the relevant protocol section.

[g] Study treatment must be initiated no earlier than 6 weeks after the patient's thyroid cancer surgery, and no later than 16 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).

[h] Each patient will be asked to contribute 8 PK blood samples, one from each of the four pre defined time windows on both Day 1 and Day 29 or Day 30. The Day 29 or Day 30 PK blood samples may be taken earlier, from Day 22 onwards of study treatment if preferred, but it is essential that all PK blood samples are collected before the RAI dose is administered. (a) Pre-dose (within 15 minutes of dosing), (b) between 15 minutes and 1 hour post-dose, (c) between 1.5 and 2.5 hours post-dose, and (d) between 3 and 8 hours post-dose.

[i] All patients must adhere to a low iodine diet (an example diet is provided in Appendix F).

[j] The post-RAI WBS may be performed any time from 3-10 days following the patient's RAI dose (thus it does not have to be on the same day as the last dose of study treatment).

[k] The re-treatment assessment will establish whether the patient has received any further treatment for thyroid cancer. Refer to Section 5.9 for the study criteria for re-treatment in the initial 18 months following the patient's RAI dose.

[l] The post-operative imaging assessments must be performed no sooner than 4 weeks post-surgery, and after all other screening assessments have been performed (ie, they should not be performed for any patient that is otherwise ineligible).

[m] Only if required (refer to Section 6.4.4.5)

[n] A repeat sample for suppressed Tg may be required 2-4 weeks later, refer to Section 5.9.1.1.

For imaging data that is required to be sent to the central imaging CRO at any point in the study refer to Section 6.4.4.5.

Table 4 Study Plan for the 18 month Primary Endpoint Assessments

A staged approach to the primary endpoint assessments will be used in this study in order to determine remission status (absence of thyroid cancer), such that each patient may not require all assessments. Full details are outlined in Section 6.4.2.

	Stage 1	**Stage 2**	**Stage 3**	Protocol Section
Time window	Stage 1 assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within an 8 week period.			6.4.2
Thyroid cancer re-treatment assessment[a]	X[a]			5.9
Suppressed Tg	X			6.4.3.1
TSH	X			6.4.3.3
TgAb[b]	X[b]	X[b]		6.4.3.4
Neck US[f]	X			6.4.4.1
Biopsy or FNA[d]	X[d]			6.4.4.5
Haematology	X			6.5.5
Low iodine diet[e]		X[e]		5.1.1
Thyrogen injection[c]		X x 2[c]		5.5.4.1
Stimulated Tg[c]		X[c]		6.4.3.2
Pregnancy test		X		6.5.9.1
Diagnostic 5mCi ^{131}I dose[c]		X[c]		5.5.4.2
WBS (nuclear medicine scan)[c, f]		X[c]		6.4.4.2
Neck MRI with contrast[f]			X	6.4.4.3
Chest CT without contrast[f]			X	6.4.4.4
Selumetinib/RAI-related AE/SAEs	→	→	→	6.5.3

Footnotes for Table 4: Study Plan for the 18 month Primary Endpoint Assessments

[a] Patients that have been re-treated for thyroid cancer between their initial RAI dose and the primary endpoint assessments 18 months later (refer to Section 5.9 for re-treatment criteria), will not have any primary endpoint assessments performed, they will remain in the study and enter standard of care follow up according to local practice. They should still be followed up for safety information at 18 m, 27 m and 3 years following their initial RAI dose.

[b] For decision making purposes at any time in the study, standardised central analysis results must be used. If the stage 1 blood sample is positive for TgAb, but the stage 2 blood sample is negative for TgAb, then a third blood sample 10 days later (± 3 days) is required to confirm absence of TgAb.

[c] Patients will receive 2 Thyrogen injections on consecutive days (day 1 and 2), followed by a diagnostic dose (5mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5.

[d] Only if required to prove absence of disease for suspicious lesions (refer to Section 6.4.4.5).

[e] Patients will be required to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI treatment. Refer to Section 5.1.1 and the example diet in Appendix F for further details.

[f] For imaging data that is required to be sent to the central imaging CRO refer to Section 6.4.4.5.

3.2 Rationale for study design, doses and control group

This study is designed to determine the efficacy of a 5-week course of selumetinib or placebo, and adjuvant RAI therapy, by assessing the rate of complete remission at 18 months post-RAI therapy.

The dose and duration of selumetinib treatment in this study (75 mg twice daily for 5 weeks) is selected to be consistent with the pilot study, which has previously demonstrated enhanced RAI uptake following selumetinib treatment, reduction in Tg levels, and reduced tumour size following RAI therapy, in patients with RAI-refractory metastatic thyroid cancer (Ho et al 2012). In addition to the effects of selumetinib on the sodium iodine transporter (refer to Section 1.1.5.1), selumetinib may also increase levels of thyroid peroxidase and thyroglobulin in any remaining thyroid cells. These proteins are required to organify and retain iodide in thyroid cells, thus facilitating greater retention of ^{131}I, and a higher dose of radiation to cancer cells. For this reason, patients will remain on selumetinib treatment for 5 days after receiving the therapeutic dose of RAI.

Since RAI is the standard of care for this patient population, the selumetinib/RAI treatment group will be compared to a placebo/RAI control group for all study endpoints.

The population who will participate in this study will be patients with differentiated thyroid cancer at high risk of primary treatment failure that would routinely require RAI adjuvant therapy as standard of care. This risk-stratified population has been selected because it is known that they are at an increased risk of failing to achieve remission following standard initial therapy, and therefore require more effective treatment strategies (refer to Section 1.1.3). This study is intended to be an adjuvant therapy trial for patients without known structural persistent disease; patients with known distant metastases at screening will be excluded in order to minimise heterogeneity of the efficacy recorded.

A secondary efficacy endpoint will be assessed in patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that these patients are not likely to be the only population to benefit. Incorporation of a genetically predefined study population enables this hypothesis to be examined (mutation analysis of samples to identify the genetically predefined study population will be performed post-randomisation, and prior to data base lock for the primary endpoint data analysis).

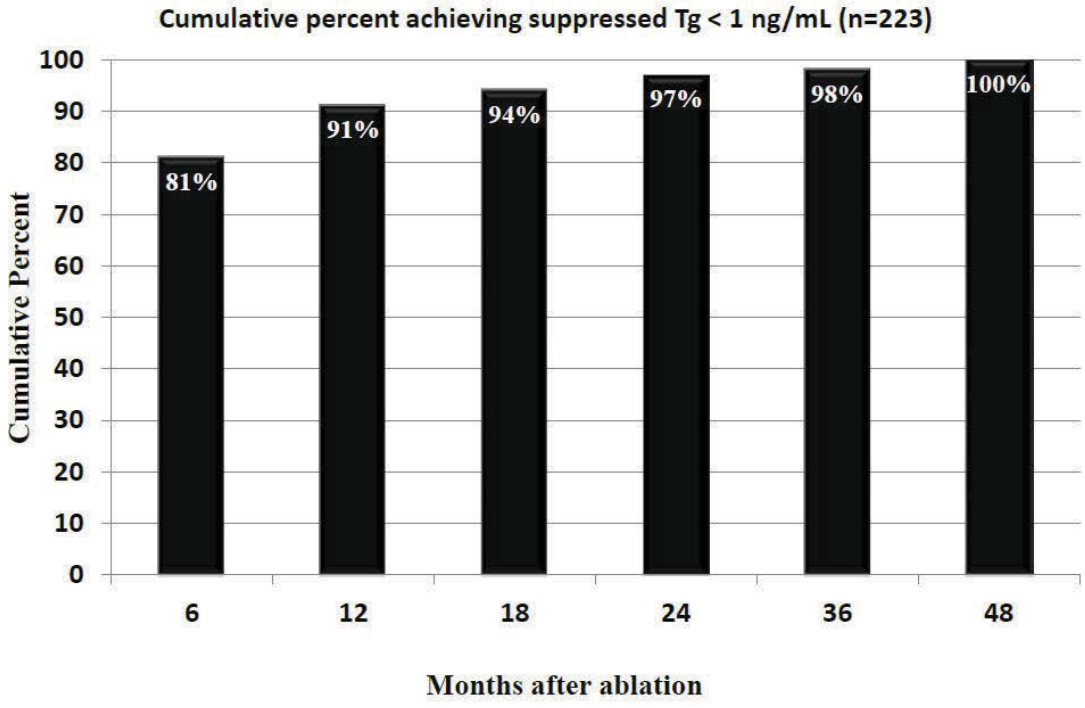
Enhancing RAI uptake into thyroid cancer cells has the potential to increase the incidence of complete remission following RAI treatment. It has been shown that the incidence of complete remission following initial RAI treatment correlates with long-term outcome, and if complete remission has not been achieved, further treatment is frequently administered (Castagna et al 2011, Tuttle et al 2010).

A study has retrospectively evaluated the time to nadir Tg in 299 patients who did not receive additional therapy after total thyroidectomy and RAI (Padovani et al 2012). This patient

population includes both patients with no evidence of disease (remission) and patients with low level disease who are being observed (median follow up time is 7 years). Figure 2 illustrates that 94% of the 223 patients with no evidence of disease achieved a suppressed Tg level of < 1 ng/mL (the biochemical component of remission) by 18 months after initial RAI therapy. Therefore, it is expected that most patients who are likely to achieve remission in both arms will have done so by this time (for the purpose of this study both biochemical and structural absence of disease will be assessed). Longer follow-up would not be expected to change the conclusions regarding an efficacy difference between the two study arms. In patients with similar characteristics to those planned in this study, a similar pattern and extent of Tg decline is also seen (Tuttle RM, unpublished sub-analysis of data from Padovani et al 2012). Previous studies have used time-points ranging from 8 to 24 months to assess remission rates after primary treatment of surgery and RAI (Castagna et al 2011, Tuttle et al 2010, Vaisman et al 2012).

Taking all the data into consideration, the incidence of complete remission at 18 months following initial RAI therapy has been selected as the primary endpoint for the proposed study. Each randomised patient will be followed beyond their 18 month primary endpoint assessment, until 3 years after their RAI treatment, in order to further assess both the clinical status of patients, and the safety profile of selumetinib and RAI beyond the primary analysis (refer to Section 6.4.8).

Figure 2 **Time course to achieving a suppressed Tg<1 ng/mL in patients receiving total thyroidectomy and RAI therapy**



4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, (eg, patient screening log), of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures. The main study consent will include mandatory consent to provide a sample of archival tumour material.

2. Males and females aged 18 years or above.

3. Patients with histologically or cytologically confirmed follicular cell derived differentiated thyroid cancer including papillary thyroid cancer and all variants, follicular thyroid cancer and all variants, and poorly differentiated thyroid cancer.

4. Note: Patients with a diagnosis of Hürthle cell carcinoma should be excluded. These are defined as having an invasive tumour composed of >75% of oncocytic (Hürthle) cells lacking the nuclear features of papillary carcinoma, tumor necrosis and marked mitotic activity. Patients with oncocytic (Hürthle cell variants) of papillary thyroid carcinoma defined as a tumour composed of a majority of oncocytic (Hürthle) cells having the nuclear features of papillary carcinoma are eligible to participate.

5. Patients presenting with any one of the following staging categories post-surgery:

   (a) Primary tumour greater than 4 cm

   (b) Primary tumour of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)

   (c) N1a or N1b disease with at least 1 lymph node ≥ 1 cm

   (d) N1a or N1b disease involving 5 or more lymph nodes (of any size)

   Note: Patients with known metastatic disease at screening will be ineligible for this study as per the exclusion criteria.

6. Patients must have had a one or two-stage total thyroidectomy with therapeutic neck dissection of any clinically apparent metastatic lymph nodes (levels I to VII of the lateral and central neck). All known tumour must have been resected.

Note, the optimal surgical procedure is based on the findings from preoperative ultrasound, to identify the extent of lymph node metastases and thereby facilitate compartment-oriented neck dissection for complete surgical removal of all gross disease. Prophylactic neck dissection is not required or encouraged, but may be performed at the discretion of the treating surgeon. As the surgical procedure(s) will have been performed before study consent, any patient for whom a total thyroidectomy cannot be verified must be excluded from the study (note that patients having undergone a robotic or endoscopic thyroidectomy, or any other novel or remote access surgical technique must also be excluded). For patients who have had a two-stage thyroidectomy, the second surgical procedure must have taken place no later than 12 weeks after the first procedure, otherwise the patient is not eligible.

7. Patients must have all of the following post-operative assessments performed no sooner than 4 weeks post-surgery (post their last surgery if it was a 2-stage thyroidectomy) and the results from each must verify the absence of macroscopic disease:

   (a) Neck US exam

   (b) Neck MRI with contrast

   (c) Chest CT without contrast

   Refer to Section 6.3 for further details. These assessments must be performed within the 28 day screening period (but ideally after all other screening assessments have been performed, ie, they should not be performed for any patient that is otherwise ineligible).

8. Patients must be suitable for radioactive iodine therapy.

9. Patients must be suitable for TSH suppression with a goal of ≤0.5 mIU/L TSH for the duration of the study (this may exclude some patients with cardiac conditions or osteoporosis).

10. Patients must be willing and able to start study treatment within 16 weeks of their thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy). Note that study treatment must not be initiated within 6 weeks of the patient's last surgery.

11. WHO or ECOG Performance Status 0 or 1.

12. Females must:

   (a) be using adequate contraceptive measures (refer to Section 5.1.2),

(b) not be breast feeding (breast feeding must be discontinued in order to participate in this study),

(c) have a negative pregnancy test prior to the start of dosing if they are of child-bearing potential,

(d) or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

(i) Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.

(ii) Women under 50 years old will be considered postmenopausal if they have been amenorrheic for at least 12 months following cessation of exogenous hormonal treatments, and with LH and FSH levels in the post-menopausal range for the institution.

(iii) Documentation of irreversible surgical sterilisation by hysterectomy and/orbilateral oophorectomy and/or bilateral salpingectomy but not tubal ligation.

13. Male patients with sexual partners who are pregnant or who could become pregnant (ie, women of child-bearing potential) must agree to use acceptable methods of contraception until 12 weeks after completing study therapy, or longer if required for standard RAI administration restrictions and in accordance with local labels, to avoid pregnancy and/or potential adverse effects.

14. Adequate organ function as defined by:

(a) ANC $\geq 1.5 \times 10^9$/L (1500 per mm^3)

(b) Platelets $\geq 100 \times 10^9$/L (100,000 per mm^3)

(c) Hemoglobin ≥ 9 g/dL

(d) ALT/SGOT and AST/SGPT < 2.5 X upper limit of normal (ULN).

(e) Bilirubin ≤ 1.5 X ULN (with the exception that patients with elevated unconjugated bilirubin due to a pre-existing diagnosis of Gilbert's syndrome are eligible for the study)

(f) Serum creatinine clearance > 50mL/min by either Cockcroft-Gault formula (see Appendix E) or 24hr urine collection analysis.

15. Patients must be able to swallow selumetinib/placebo capsules for the duration of the study treatment period. This may exclude some patients with swallowing

dysfunction due to the specific technique required for their thyroid surgery. Functional assessment of swallowing ability may be made by the treating Investigator.

4.1.1 Genetics research study (optional blood sample)

1. For inclusion in the optional genetics research study patients must provide optional genetics research informed consent.

2. If a patient declines to participate in the genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

4.1.2 Biomarkers research study on tumour progression biopsy

For inclusion in the optional progression tumour sample study, patients must provide optional consent for this sample to be obtained.

If a patient declines to provide consent to obtain optional tumour sample on progression, there will be no penalty or loss of benefit to the patient, and the patient will not be excluded from any other aspect of the main study.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Known distant metastatic disease at study entry. Investigators are not required to specifically screen patients for distant metastasis beyond their normal Standard of Care practices and the protocol-specific post-operative imaging assessments, but any patient with known distant metastatic disease at screening must be excluded.

2. Diagnosis of anaplastic thyroid cancer, medullary thyroid cancer, or Hürthle cell carcinoma (refer to inclusion criterion 4 for further details on Hürthle cell eligibility).

3. Presence of anti-Tg antibodies at screening (as determined by standardised central methodology, refer to Section 6.4.3.4).

4. Previous treatment with ^{131}I (RAI) or external beam radiation therapy (EBRT) at any time in the past.

5. Any unresolved toxicity ≥ CTCAE Grade 2 from previous anti-cancer therapy including the patient's recent thyroid cancer surgery.

6. Having received an investigational drug during the last 4 weeks prior to first dose of study treatment.

7. Receiving herbal supplements or medications known to be strong inhibitors or inducers of the CYP1A2, CYP2C19 and CYP3A4 enzymes unless such products can be safely discontinued at least 14 days before the first dose of study medication.

8. Recombinant human TSH (rhTSH, Thyrogen):

   (a) Patients with known hypersensitivity to rhTSH will be excluded.

   (b) Patients not willing to use rhTSH prior to their RAI treatment will also be excluded (ie, patients or clinicians choosing withdrawal of thyroid hormone treatment prior to their RAI treatment will be ineligible for this study).

9. Patients requiring medication with high content in iodide (amiodarone), or patients receiving IV iodine containing contrast as part of radiographic procedure within the last 3 months prior to the planned RAI treatment (unless a urine measurement demonstrates that urinary iodide level has returned to normal range earlier than 3 months following administration of a contrast agent).

10. Patients with clinically significant cardiovascular disease as defined by the following:

    (a) Uncontrolled hypertension (BP ≥150/95 despite optimal therapy)

    (b) LVEF < 55% measured by echocardiography (or MUGA)

    (c) Symptomatic heart failure (NYHA grade II-IV), prior or current cardiomyopathy, or severe valvular heart disease

    (d) Uncontrolled angina (Canadian Cardiovascular Society grade II-IV despite medical therapy)

    (e) Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest

    (f) Acute coronary syndrome within 6 months prior to starting treatment

    (g) Mean QTc interval >470 ms

11. Patients with the following ophthalmological findings/conditions:

    (a) Intraocular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intraocular pressure)

    (b) Current or past history of central serous retinopathy or retinal vein occlusion

12. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to agents used in the study.

13. Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

14. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

15. Pregnant women will be ineligible (breast feeding should be discontinued if the mother is treated with study therapy).

16. Male or female patients of reproductive potential who are not employing an effective method of contraception (refer to Section 5.1.2).

17. Refractory nausea and vomiting, chronic gastrointestinal diseases, or significant bowel resection that in the Investigator's opinion would preclude adequate absorption of study therapy.

18. History of another primary malignancy within 5 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ and the disease under study.

19. Clinical judgement by the investigator that the patient should not participate in the study.

20. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

21. Previous treatment with any MEK or BRAF inhibitor.

22. Previous enrolment or treatment in the present study.

4.2.1 Genetics research study (optional blood sample)

1. Exclusion criteria for participation in the optional genetics research component of the study:

(a) Previous allogeneic bone marrow transplant

(b) Whole blood transfusion within 120 days of the date of genetic sample collection (except for leukocyte depleted blood transfusion, which is allowed)

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

5.1.1 Low-iodine diet

Published data and opinion regarding the necessity for a low iodine diet prior to RAI therapy or a diagnostic whole body scan is variable. For the purpose of this study a low iodine diet will be mandated in order to standardise patient care and study data as best as possible. Compliance to the low iodine diet will not be recorded or assessed, and all randomised patients will receive RAI treatment as planned. Refer to Table 2 and the Study Plan (Table 3) for further details. An example low iodine diet is provided as Appendix F to this protocol.

A low iodine diet is necessary at two occasions in the study:

Prior to RAI adjuvant treatment

All patients must be willing to adhere to the low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI therapy.

Prior to the primary endpoint Stage 2 assessments

All patients must be willing to adhere to the low iodine diet for a period of 1 week before the diagnostic ^{131}I dose used prior to the primary endpoint WBS assessment (^{131}I nuclear medicine scan), until the diagnostic WBS assessment is completed. This is only relevant for patients who pass Stage 1 primary endpoint assessments (refer to Section 6.4.2).

5.1.2 Other study restrictions

The following restrictions also apply while the patient is receiving selumetinib or placebo:

1. Female patients of child-bearing potential will be required to use reliable methods of contraception until 4 weeks after the last dose of selumetinib/placebo or longer if required for standard RAI administration restrictions and in accordance with local labels. Male patients will be required to use reliable methods of contraception until 12 weeks after the last dose of the last study treatment, or longer if required for standard RAI administration restrictions and in accordance with local labels. Reliable methods of contraception should be used consistently and correctly. Acceptable methods include implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception), some IUDs and vasectomised partner. Sexual abstinence is also an acceptable method of contraception according to ICHM3.

2. Fasting restrictions for the study are described in Section 5.5.2.

3. Patients should avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.

4. Patients should avoid large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study treatment period.

5. Selumetinib capsules contain D-α- Tocopheryl polyethylene glycol 1000 succinate (TPGS, a water-soluble form of vitamin E) as an excipient. Patients should not therefore take vitamin E supplements or multivitamin supplements which provide a total daily dose in excess of 100% of the recommended daily allowance for vitamin E. The maximum dose of vitamin E patients may receive from selumetinib is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided. High doses of vitamin E have been reported to potentiate the anticoagulant activity of coumadins such as warfarin. Patients who are taking coumadin anticoagulants should increase the frequency of assessment of anticoagulation, such as INR measurements, upon initiation of dosing with study treatment.

6. Permitted and excluded antiemetic medications in this study are described in Section 5.6.

7. Permitted and excluded medications for management of skin toxicities (eg, rash) are described in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib." All patients will be given prophylactic provision of emollient cream to take home and to start using when starting study treatment.

8. Unless patients require re-treatment, they should not be enrolled in other studies evaluating novel therapies for thyroid cancer for the entire study duration.

5.2 Patient enrolment, randomisation and initiation of investigational product

The Principal Investigator or delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 4.1 and 4.2

3. Call IVRS/IWRS to assign the eligible patient a unique enrolment number (beginning with 'E#'), and randomisation code (subject number). Randomisation codes will start at 001 and go up.

Randomisation codes will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for randomisation.

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused.

If a patient withdraws from the study after they have been enrolled or have received study treatment then they cannot re-enter the study.

5.2.1 Procedures for randomisation

Patients who satisfy all the entry criteria will be centrally assigned by the IVRS/IWRS, according to the randomisation scheme generated by the Biostatistics Group, AstraZeneca, to selumetinib or placebo in a ratio of 2:1.

Every effort should be made to minimise the time between randomisation and starting treatment. Patients must not be randomised unless all eligibility criteria have been met.

IVRS/IWRS will be used for allocation of enrolment number, allocation of randomisation number, study medication assignment, discontinuation from study treatment, emergency code breaks and study drug shipment confirmation.

5.3 Procedures for handling patients incorrectly enrolled, randomised or initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are incorrectly enrolled but are not yet randomised or initiated on treatment should be withdrawn from the study.

Where patients that do not meet the inclusion and/or exclusion criteria, are enrolled in error, or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the AstraZeneca Physician immediately.

The AstraZeneca Physician must ensure all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The active and placebo capsules will appear identical and presented in the same packaging to ensure blinding of the medication. Medication will be labelled using a unique material pack code which is linked to the randomisation scheme. IVRS/IWRS will allocate randomisation numbers sequentially when sites call IVRS/IWRS to randomise an eligible patient. IVRS/IWRS will allocate the medication pack code to be dispensed to the patient.

All patients must remain blinded until after the 18 month primary endpoint data analysis has been conducted for the study; most patients will thus remain blinded for longer periods of time than their initial 18 month follow up period. Any patient that is re-treated prior to the 18 month primary endpoint time-point (refer to guidelines in Section 5.9), must not be unblinded until after the primary analysis of 18 month primary endpoint data from all patients in the study.

The personnel analyzing the PK samples will be unblinded to treatment allocation in order to organise the appropriate sample analysis. The treatment allocation information will be kept in a secure location until the end of the study.

Once the 18 month primary endpoint data analysis has been conducted for the study, patients may be unblinded for the remaining study follow up.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Procedures for emergency unblinding will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Selumetinib	25 mg Hyd-Sulfate capsule	AstraZeneca
Placebo to match selumetinib	Capsule	AstraZeneca

5.5.2 Doses and treatment regimens

Patients will be randomised on a 2:1 basis, via IVRS/IWRS, to receive either selumetinib 75 mg twice daily, or matching placebo.

Patients will be instructed to take 3 capsules orally on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing), twice a day approximately 12 hours apart according to the Study Plan. Capsules should be taken with water only. On clinic days when PK samples are scheduled to be taken, dosing should be delayed until arrival at the clinic and until the pre-dose PK sample has been taken.

Selumetinib/placebo will be supplied in bottles of 60 capsules of 25 mg strength. At Randomization visit, selumetinib/placebo for the entire treatment period will be dispensed (5

bottles). Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Day 1 of study treatment must occur within 16 weeks of the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).

5.5.3 Management of study treatment related toxicity

The immediate management of any adverse event should be according to standard clinical practice for that event. Subsequent management of treatment related adverse events should be guided by the Investigators' assessment of causality.

5.5.3.1 Selumetinib dose interruption or reduction

It is essential that patients remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator until the patient has been on study treatment for a minimum of 7 consecutive days (as long as the total duration of study treatment does not exceed 43 days, this allows the planned RAI to be postponed by up to 1 week if absolutely necessary).

For all adverse events reported in this study that are considered at least partly causal to administration of selumetinib, the following dose modification guidance should be applied.

Study treatment with selumetinib/placebo should be temporarily interrupted if one of the following AEs are observed (and considered causal to study treatment), **despite optimal supportive care** (ie, supportive treatment may be given prior to withholding study treatment):

- Any intolerable adverse event regardless of Grade
- Any adverse events ≥ CTCAE Grade 3

On improvement of the adverse event to Grade 1 (Grade 2 for rash) or baseline, study treatment may be restarted at the original dose or may be reduced at the discretion of the investigator. One dose reduction of study treatment to 50 mg twice daily is permitted before permanent discontinuation.

- If a further episode of the same AE subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the AE.
- If a different AE subsequently requires dose interruption, selumetinib may be restarted at the same dose or at the next dose level down on improvement of the AE.
- Selumetinib should not be re-escalated to an earlier dose level on improvement of an AE.

- The schedule of assessments described in Table 3 should continue relative to Day 1 in the event of selumetinib dose interruption or reduction.

Therefore, the dose reduction/adjustment algorithm in the study allows for 2 steps only:

75 mg twice daily (initial dose)
↓
50 mg twice daily
↓
permanent discontinuation

All dose delays, reductions and adjustments will be recorded in the appropriate electronic Case Report Form (eCRF).

The guidance above should also be followed for dose interruptions or reductions for adverse events of rashes or diarrhoea. Guidance for interruption or reduction of treatment with selumetinib may be considered for particular events, as indicated in the algorithms provided as a separate study aid in the "Guidance for Management of Specific Adverse Events in Studies of Selumetinib" (refer to Section 5.5.3.2).

5.5.3.2 Management and investigation of specific selumetinib related AEs

Recommendations for the management or investigation of the following specific AEs is provided in Appendix G: Guidance for Management of Adverse Events in Studies of Selumetinib.

- Rash: early initiation of treatment for rash is strongly recommended to minimise the duration and severity of the adverse event. All patients should be given prophylactic provision of emollient cream to take home and to start using when starting study treatment as indicated in the algorithm for management and investigation of rash included in Appendix G.

- Visual disturbances: symptoms, including blurred vision, have been reported during treatment with selumetinib. Events consistent with central serous retinopathy have been reported in a small number of patients receiving treatment with selumetinib, generally in combination with other novel targeted anti-cancer agents. AEs of central serous retinopathy and retinal vein occlusion have been reported in studies of other MEK inhibitors (Lemech & Arkenau 2012). Investigation to determine the underlying cause of visual disturbance is recommended.

- Diarrhoea: early initiation of treatment for diarrhoea is strongly recommended to minimise the duration and severity of the adverse event. Treatment provision will be according to Investigator discretion according to local practice and regulations.

- Dyspnoea: new or worsening dyspnoea has been reported during treatment with selumetinib; investigation to determine the underlying cause is recommended.

5.5.4 Additional study drugs

5.5.4.1 Thyrogen (rhTSH, thyrotropin alfa for injection)

Thyrogen use prior to the RAI ablative dose

Effective use of RAI therapy requires stimulation by TSH in order to maximise RAI uptake by thyroid cells. Recombinant human TSH (rhTSH or Thyrogen) will be used to stimulate iodide uptake according to the manufacturer's recommendation (0.9 mg intra-muscular injection for 2 days immediately prior to the RAI treatment according to the Study Plan Table 3). rhTSH is approved for use in routine clinical care as a diagnostic tool to stimulated serum thyroglobulin and RAI uptake for diagnostic scanning and as an adjunct to RAI ablation in many countries. This allows patients to avoid the hypothyroidism state, since they can maintain their routine thyroid hormone supplementation. Patients or clinicians choosing withdrawal of thyroid hormone treatment for this purpose will be ineligible for this study. All randomised study patients will receive Thyrogen twice prior to their RAI treatment dose.

Thyrogen use for the primary endpoint assessments (18 months post-RAI)

For those patients that progress to Stage 2 of the primary endpoint assessments (refer to Section 6.4.2), Thyrogen will be used to stimulate iodide uptake immediately prior to administering the diagnostic ^{131}I dose for the primary endpoint WBS assessment. Patients will receive a 0.9 mg intra-muscular Thyrogen injection for two consecutive days. Refer to Section 6.4.2.2 for further details.

5.5.4.2 Radioactive iodine (RAI)

All RAI for the study will be locally provided at each site.

Therapeutic RAI dose (^{131}I)

A single oral RAI dose of 100 mCi (3.7 GBq) ^{131}I (+/- 10% at the time of administration) will be administered to all patients according to the Study Plan Table 3, according to standard practice at each site.

Diagnostic WBS dose (^{131}I)

For those patients that progress to Stage 2 of the primary endpoint assessments (refer to Section 6.4.2), a single oral RAI dose of 5 mCi (185 MBq) ^{131}I (+/- 10% at the time of administration) will be administered for the primary endpoint WBS (nuclear medicine scan) 18 months following the ablative treatment dose of RAI. Refer to the Study Plan Table 3, and Section 6.4.4.2 for further details.

5.5.4.3 Thyroid hormone supplementation (TSH suppression)

Routine thyroid hormone supplementation (levothyroxine, LT4) is required during the study as per standard clinical practice. The purpose of this is both to correct resulting hypothyroidism using a dosage appropriate to achieve normal blood levels of thyroid hormone, and to inhibit TSH-dependant growth of residual thyroid cancer cells. Thyroid

hormone supplementation will be adjusted in individual patients with the aim of achieving suppressed TSH levels of <0.5 mIU/L for the duration of the study.

5.5.5 Study drug labelling

Each bottle of selumetinib and matching placebo capsules will be labelled by Pharmaceutical Development Supply Chain, AstraZeneca or its designee.

All labels will comply with good manufacturing practice (GMP) regulations, and will state that the drug is for clinical use only or that it is the investigational drug and is to be used by qualified investigators only and should be kept out of reach of children. The labels will have blank spaces for the site personnel to complete the following at the time of drug dispensing: enrolment code, visit number and dispensing date.

Label text will be translated into local language.

Each bottle of selumetinib/placebo capsules will have a tear-off portion that will be removed at the time of dispensing and attached to the Drug Label Accountability Log.

5.5.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

5.6 Concomitant medications

The use of antiemetic medication for the prevention of nausea caused by administration of radioactive iodine is permitted in this study according to local clinical practice (with the exception of aprepitant which is an excluded medication in this study, due to the potential for modification of selumetinib exposure via CYP3A4). The administration of any antiemetic medication must be recorded in the appropriate sections of the Case Report Form.

All patients will be given prophylactic provision of emollient cream to take home and to start using when starting study treatment as indicated in the algorithm for management and investigation of rash included in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

The following treatments/drugs are restricted in this study:

- No other anti-cancer agents, or investigational drugs should be administered whilst patients are receiving study medication or are in follow-up in this study (unless the patient withdraws from the study, or meets the re-treatment criteria in Section 5.9).
- Patients who are taking coumarin anticoagulants should increase the frequency of assessment of anticoagulation, such as INR measurements, during the study treatment period with selumetinib/placebo.

- The maximum dose of vitamin E patients may receive from selumetinib is approximately 210 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided in patients receiving the capsule formulation.

- Throughout the study, patients should avoid changes to, or the addition of all other concomitant medications, in particular any that may affect the metabolism of selumetinib (eg, CYP1A2 or 3A4 inhibitors/inducers), unless considered clinically indicated.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

All concomitant medications will be recorded on the CRF until 30 days after the last dose of study treatment, and after this time a study-specific record must be kept of any further treatment for thyroid cancer (including surgery), or treatment for RAI-related AEs/SAEs until the last study visit for all patients (refer to Section 5.9).

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Where appropriate facilities and procedures for drug destruction exist, and prior approval from the site monitor has been received, site personnel will account for all unused drugs and for appropriate destruction.

Where such facilities do not exist study site personnel/study monitor will return all unused drugs to AstraZeneca or its designee according to country rules.

The AstraZeneca monitors will ensure that all drug-handling procedures at sites are appropriate, and that all certificates of delivery and return are completed and signed by the site, AstraZeneca, or its delegate, as appropriate. In addition, the monitor will check that the certificate of destruction has been signed by the site, if study drug destruction is performed at the site.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Risk to patients as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- A female patient becoming pregnant

5.8.1 Procedures for premature discontinuation of a patient from investigational product

A patient that decides to prematurely discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.5.3 and 6.5.4), and all study drugs should be returned by the patient. In this situation, a treatment discontinuation visit will be conducted as soon as possible after the patient received the last dose of study drug (selumetinb/placebo). A single 12-lead ECG is also required at premature discontinuation of treatment.

If a patient is withdrawn from the study (ie, withdraws consent for follow-up procedures), see Section 5.10.

Collection of all AEs/SAEs will continue until 30 days after the last dose of study drug (selumetinib/placebo) for prematurely withdrawn patients. As long as the patient does not withdraw consent, follow up in this study will continue as planned.

Any patient with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (±7days) after discontinuation.

5.9 Criteria for further thyroid cancer therapy during the study

5.9.1 Re-treatment prior to the 18 month primary endpoint assessments

It is acknowledged that there is variability in thyroid cancer re-treatment clinical practice. The study-specific criteria below are designed to standardise re-treatment prior to the primary endpoint assessments for the purpose of this study as best as possible. Thus, further thyroid cancer therapy (eg, additional surgery or RAI treatment) prior to the primary analysis of complete remission at 18 months post-RAI, must not be administered unless any of the following criteria are met.

Patients meeting the following re-treatment criteria do not have to be re-treated, they can instead be followed expectantly without re-treatment at the discretion of the treating Investigator.

5.9.1.1 Biochemical disease re-treatment criteria

The first scheduled post-RAI follow up for serum Tg will be assessed 9 months after the RAI dose (± 3 months). Tg assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (**but not before 6 months**).

All biochemical sample analysis for study re-treatment criteria must be performed by standardised central laboratory methodology (for further details refer to the Laboratory Manual).

Patients must not be re-treated for thyroid cancer unless any of the following biochemical criteria are met:

1. If a serum Tg level ≥ 5 ng/mL on central analysis is measured **during TSH suppression**, then a repeat Tg sample must be assessed by central analysis 2-4 weeks later. The patient must not be re-treated unless both centrally analysed samples demonstrate the suppressed Tg level to be 5 ng/mL or higher.

2. If a serum Tg level ≥ 10 ng/mL is measured **following TSH stimulation**, the patient may be re-treated (a repeat sample for confirmation is not necessary). Note, a stimulated Tg assessment is not part of the study-specific follow up plan for patients prior to the 18 month primary endpoint assessments (thus it is not recommended or required, and is not included in the Study Plan). However, if a stimulated Tg assessment is performed due to local practice, this re-treatment criterion applies.

3. If an increase (delta change) in serum Tg level of 3 ng/mL or more is determined between two Tg assessments taken 2-4 weeks apart (due to a repeat sample), the patient may be re-treated.

Thus, in the absence of structurally identifiable disease, patients in this study should have continued observation without additional thyroid cancer treatment (eg, additional RAI, surgery) until the study primary endpoint (18 months after RAI treatment), if the serum Tg level remains below 5 ng/mL during TSH suppression, below 10 ng/mL following TSH stimulation (if assessed), and is either stable/declining, or rising less than 3 ng/mL between samples 2-4 weeks apart.

Note: If a patient has Tg levels below the above re-treatment criteria, but TgAb are detected (ie, the patient is TgAb positive; refer to Section 6.4.3.4), the patient should not be re-treated unless new structural disease is detected according to Section 5.9.1.2 (ie, it is recommended that patients are not re-treated on the basis of new antibodies alone, in the absence of structural disease).

Unscheduled samples and local analysis

It is acknowledged that Investigators may wish to also perform their own local biochemical analysis according to local standard of care. In general, unscheduled samples that are taken

either outside of the visit window specified, or in addition to the scheduled study samples, should not be sent for standardised central analysis. Only if such unscheduled local analysis leads the Investigator to wish to administer further therapy for thyroid cancer, should a sample ideally be sent for central analysis and the above criteria applied before the patient is re-treated.

5.9.1.2 Structural disease re-treatment criteria

The first post-RAI ultrasound follow up will be assessed 9 months after the RAI dose (± 3 months). Ultrasound assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (but not before 6 months).

Patients must not be re-treated for thyroid cancer unless any of the following structural criteria are met:

1. In the absence of any biochemical evidence of thyroid cancer, structural DTC should be confirmed prior to re-treatment, by positive histology/cytology from a biopsy/FNA of ultrasonographically suspicious lesions or lymph nodes ≥ 5 mm in the smallest diameter (refer to Section 6.4.4.5).

2. Identification of new distant metastases (these do not need to be confirmed by biopsy). Assessment of potential distant metastases is not required, but may be performed if clinically indicated at the discretion of the treating Investigator.

5.9.1.3 Patient management on study (up to the primary analysis at 18 months post-RAI)

At the required follow up visits, the following questions should be answered for each subject:

1. Does the patient have a suppressed Tg ≥ 5 ng/mL, a TSH stimulated Tg ≥ 10 ng/mL or a rising Tg level (increase of 3 ng/mL or more) according to the guidelines in Section 5.9.1.1?

2. Does the patient have new loco-regional structural thyroid cancer according to the guidelines in Section 5.9.1.2?

3. Does the patient have new distant metastatic lesions according to the guidelines in Section 5.9.1.2?

If the answer is yes to any of the questions, the patient is unlikely to enter remission and may be re-treated for thyroid cancer (but does not have to be).

Full details of any thyroid cancer re-treatment must be recorded on the appropriate eCRF.

Any re-treated patients will remain in the study and should enter standard of care follow up according to local practice until 3 years after their initial RAI therapy (refer to Section 6.4.8). Patients who are re-treated prior to the primary endpoint at 18 months post-RAI do not require primary endpoint disease assessments performing, however these patients should continue to

follow all protocol-scheduled visits for safety (AE/SAE follow-up) as described in the Study Plan Table 3 and in Section 6.5. Patients do not need to attend these follow up visits in person (telephone contact is permitted), however when local follow-up visits coincide with protocol-specified visits, these should ideally be in person where possible.

If the answer is no to all questions, the patient should continue the study follow-up as per protocol without additional thyroid cancer re-treatment.

5.9.2 Re-treatment after the 18 month primary endpoint assessments

Following completion of all assessments for complete remission at the primary endpoint 18 months post-RAI, patients may receive re-treatment for thyroid cancer as per clinically indicated according to local standard of care. Any re-treated patients will remain in the study and should enter standard of care follow up according to local practice until 3 years after their initial RAI therapy (refer to Section 6.4.8).

Full details of any thyroid cancer re-treatment must be recorded on the appropriate eCRF.

5.10 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and follow-up assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.5.3 and 6.5.4); any remaining study drug should be returned by the patient.

5.11 Replacement of patients

There will be no replacement of randomised patients in this study for any reason.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

6.2 Data collection at enrolment

The following data will be collected & procedures performed for each patient:

1. Informed consent (to include consent for archival tumour sample provision)

2. Demography (date of birth, sex, race)

3. Histological/cytological confirmation of thyroid cancer, including post-operative disease staging

4. Medical and surgical history

5. Concomitant medications and previous anti-cancer therapy

6. Assessment of WHO or ECOG performance status (refer to Section 6.2.1)

7. Collection of AEs will start after signing the consent form

8. Physical examination

9. Vital signs (resting blood pressure (BP), pulse rate), weight and height

10. Single ECG

11. Blood samples for clinical chemistry and haematology

12. Blood sample for determination of interfering Tg antibodies (central standardised analysis)

13. Local derived *BRAF* and/or *NRAS* mutation status (where available)

14. Urinalysis (at sites where the local laboratory is able to determine the required parameters, see Section 6.5.5)

15. Pregnancy test for female pre-menopausal patients

16. Full ophthalmologic examination, including slit-lamp fundoscopy and intraocular pressure examination

17. ECHO or MUGA

18. The following imaging assessments must be performed within the 28 day screening period but only after all other screening procedures have confirmed eligibility status (refer to Section 6.3):

    (a) Neck ultrasound (US)

    (b) Neck MRI with contrast

    (c) Chest CT scan without contrast

19. Overall assessment of patient eligibility for the study

20. Upon confirmation of patients' eligibility, patients will be invited to attend the randomisation visit. Patients must not be randomised unless all eligibility criteria have been met.

21. Call interactive voice response system (IVRS)/interactive web response system (IWRS) to randomise the patient

6.2.1 Performance status definitions

Performance status will be assessed at screening according to either the WHO or ECOG criteria as follows:

0 = Fully active, able to carry out all pre-disease performance/activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

6.3 Post-operative imaging assessments for eligibility

The post-operative imaging assessments of US, neck MRI and chest CT are performed during screening to determine study eligibility. These assessments must determine the absence of macroscopic persistent disease post-surgery for a patient to be eligible prior to randomisation. The post-operative imaging assessments must be scheduled once all other screening assessments and eligibility criteria have been verified.

The screening chest CT procedure must be performed **without iodine containing contrast agent**.

Eligibility will be determined by the local investigational site.

Acquisition guidelines for the post-operative imaging assessments will be provided separately to this protocol.

In addition to information recorded on the eCRF for US, the post-operative images for chest CT and neck MRI must be collected and sent to the central imaging CRO.

6.4 Efficacy

6.4.1 Complete remission

The primary endpoint for this study is **complete remission rate at 18 months** (following RAI treatment).

Definition of complete remission:

Patients will be defined to be in complete remission if all of the following criteria can be demonstrated:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer[a] on neck US, as assessed by investigator site review.

3. No confirmed radiological evidence of thyroid cancer[a], as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

There are two main components to complete remission: biochemical remission and structural remission. Biochemical remission is measured by Tg and structural remission is assessed by the imaging assessments US, MRI, CT and WBS in conjunction with biopsy/FNA.

A staged approach will be taken for performing assessments contributing to the primary endpoint, to avoid unnecessary assessments for individual patients who received further therapy prior to the primary assessment, and for those patients not in biochemical remission (as determined by serum Tg levels in the absence of interfering Tg antibodies).

[a]Confirmation of evidence of structural DTC will be either histopathological (from a biopsy/FNA; as criterion 4 above), or RAI-avid disease (refer to Section 6.4.4.2). In this disease setting, structural abnormalities that are not RAI-avid and do not have confirmed histopathology consistent with DTC (ie are not biopsy proven) are considered benign in the absence of biochemical DTC.

6.4.2 Staged approach to primary endpoint assessments

Full details of the staged approach to the primary endpoint assessments are outlined below.

There will be 3 stages of assessments. Patients that have been re-treated for thyroid cancer will not have any primary endpoint assessments performed. All patients who have not been re-treated for thyroid cancer will have stage 1 assessments performed. The decision on whether to proceed to stage 2 and 3 assessments for patients that have not been re-treated will be based on centrally analysed biochemical data (Tg and TgAb data).

Sites will receive results from standardised central laboratory analysis of the biochemical data and make a decision to proceed based on these results. Patients identified as not in

biochemical remission will not be required to have all imaging assessments described in Section 6.4.1 performed.

For patients that have imaging assessments performed, the appropriate data will be sent to the imaging CRO for blinded independent central review to identify presence or absence of structural disease. Note: results from the central imaging review will not be reported to clinical sites.

Briefly:

In stage 1, suppressed Tg will be determined together with neck US assessment for all patients who did not require re-treatment for thyroid cancer during the first 18 months of follow up (refer to Section 6.4.2.1).

In stage 2, rhTSH stimulated Tg and diagnostic WBS will be performed (refer to Section6.4.2.2).

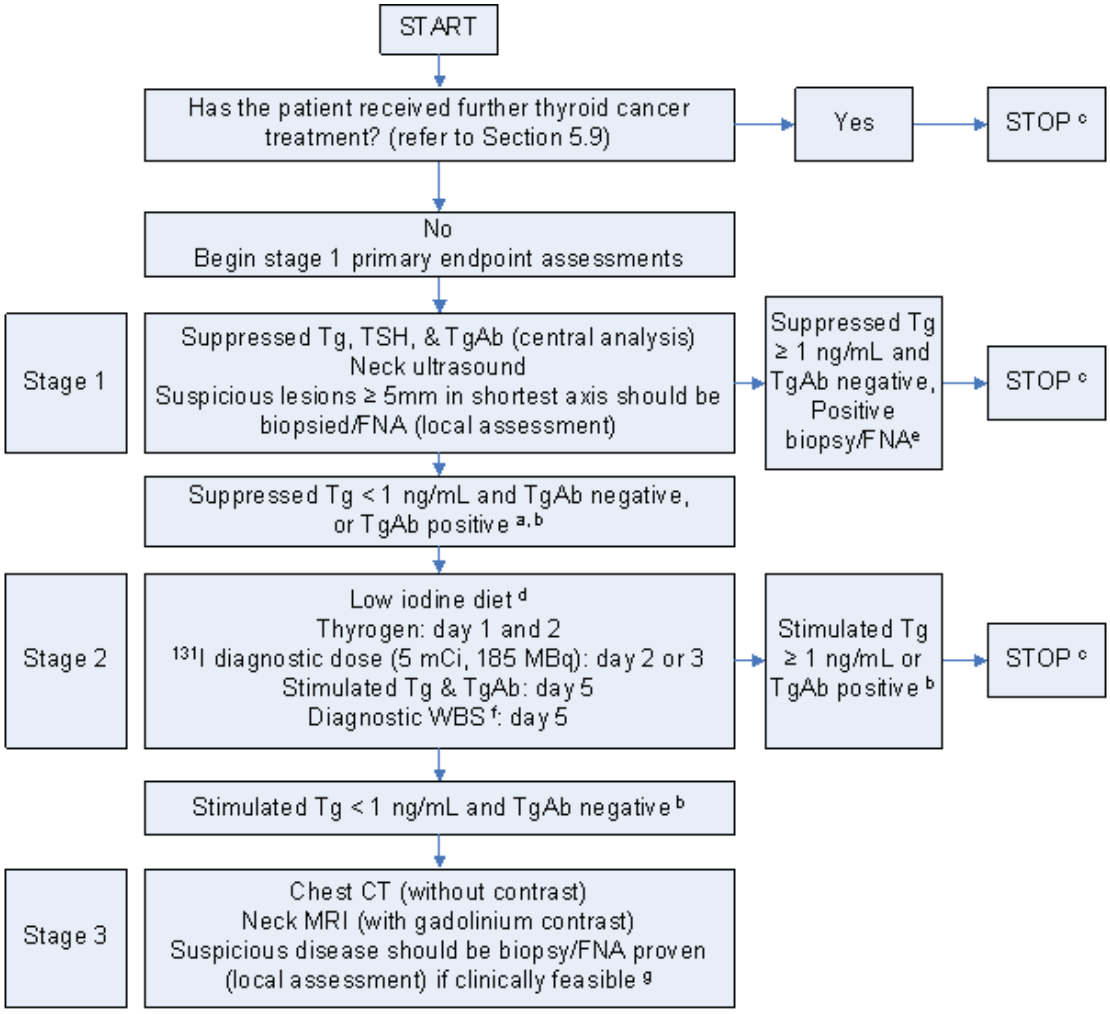
In stage 3, additional radiological imaging (chest CT and neck MRI) will be performed (refer to Section 6.4.2.3).

Stage 1 assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments (all 3 stages if required) must be completed within an 8 week period (refer also to Table 4).

Refer to the flowchart Figure 3 for a visual representation of the staged approach for primary endpoint assessments.

Refer to Section 6.4.5 for the process of determining complete remission from the primary endpoint assessment data.

Figure 3 Flow chart for staged primary endpoint assessments



[a] Patients should progress to stage 2 assessments based on biochemical data only (regardless of US results). Any TgAb positive patients should progress to stage 2 regardless of their suppressed Tg result.
[b] If both stage 1 and stage 2 blood samples are positive for TgAb, then the stimulated Tg result will be deemed to be uninterpretable, and for the purpose of this study the patient will be classified as not in complete remission. No further primary endpoint assessments are required. The patient will remain in the study for follow up until 3 years following their initial RAI treatment. If the stage 1 and stage 2 samples are discordant for TgAb status, then a third blood sample 10 days later (± 3 days) is required to confirm TgAb status.
[c] For the purpose of this study, patient will be classified as not in complete remission. The patient should remain in the study for follow up until the final study visit 3 years following their initial RAI treatment, and enter standard of care treatment/follow up according to local clinical practice.
[d] Low iodine diet is required from 1 week before the diagnostic dose of ^{131}I is administered, until completion of the WBS assessment. Refer to Appendix F.
[e] If a patient has a biopsy/FNA result available that confirms the presence of structural DTC then no further assessments are required. If a biopsy/FNA was taken, but the result is not yet available, then the patient should not delay moving to stage 2 assessments (even if the biopsy/FNA is subsequently confirmed to be positive for structural DTC).
[f] For study endpoint purposes the WBS will evaluated by blinded independent central review. Even if local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).
[g] For the size criteria for biopsy/FNA from MRI/CT assessments, refer to Sections 6.4.4.3 and 6.4.4.4 respectively.

6.4.2.1 Primary endpoint assessments Stage 1

Patients that have been re-treated for thyroid cancer between their initial RAI dose and the primary endpoint assessments 18 months later (refer to Section 5.9 for re-treatment criteria), will not have any primary endpoint assessments performed. For the purpose of the primary endpoint, such re-treated patients will be determined not to be in complete remission.

In stage 1, all patients that have not previously been re-treated for thyroid cancer will have:

- Suppressed Tg level determined by standardised central laboratory analysis.
- TSH and TgAb (using the same blood draw for suppressed Tg) determined by standardised central laboratory analysis. Refer to Section 6.4.3.
- Neck US assessment for structural disease to be assessed by investigator site review. Refer to Section 6.4.4.1.

Suspicious lesions identified by US ≥ 5 mm in the shortest diameter should be biopsied or aspirated by fine needle. All biopsy/FNA samples will be assessed locally at each site. Lesions identified by US < 5 mm in the shortest diameter do not require a biopsy.

All neck US and biopsy/FNA samples will be assessed locally at each site. The relevant US information with any biopsy findings will be provided to the imaging CRO as part of the blinded independent central review.

When to proceed to stage 2 assessments

All patients in the following situations should proceed to stage 2 assessments:

1. Patients with suppressed Tg < 1 ng/mL. These patients should proceed to stage 2 regardless of the TgAb or US results.
2. Patients who are TgAb positive in stage 1 (regardless of the suppressed Tg level, and US results).
3. Patients who fulfil either of the 2 above criteria, and have a biopsy/FNA result pending (ie, Investigators should not wait for the biopsy/FNA result before performing stage 2 assessments).

When not to proceed to stage 2 assessments

All patients in the following situations will be classified not in complete remission and should not proceed to stage 2 assessments:

1. Patients who have suppressed Tg level ≥ 1 ng/mL in the absence of TgAb (unequivocal biochemical disease).

2. Patients with a positive biopsy/FNA that confirms the presence of structural DTC. Note that if the biopsy/FNA results are not yet available, the patient should not delay proceeding to stage 2 assessments.

Patients who demonstrate presence of disease and do not proceed to stage 2 assessments will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, **and will continue to be followed in this study** until 3 years following their initial RAI dose (refer to Section 6.4.6).

6.4.2.2 Primary endpoint assessments Stage 2

In stage 2, patients will have:

- rhTSH stimulated Tg level determined by standardised central laboratory analysis.
- TgAb (from the same blood draw for rhTSH stimulated Tg) determined by standardised central laboratory analysis. TSH will not be analysed from this sample. A repeat (third) sample for TgAb analysis may be required 10 days ± 3 days later if the stage 1 and 2 TgAb status is discordant (refer to Table 5).
- Diagnostic nuclear medicine ^{131}I scan (WBS) to be evaluated by blinded independent central review.

These assessments will require the patient to follow a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose, until the diagnostic WBS assessment is completed (refer to Section 5.1.1 and Appendix F). Patients will also receive two Thyrogen injections (refer to Section 5.5.4.1) on consecutive days (day 1 and 2), followed by a diagnostic dose (5 mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5.

When to proceed to stage 3 assessments

Patients should proceed to stage 3 assessments in the absence of biochemical disease. Patients with stimulated Tg < 1 ng/mL and TgAb negative (for the definition of TgAb negativity refer to Section 6.4.3.4) should proceed to stage 3 **regardless of the WBS results**.

- Note that if the stage 1 and 2 blood samples are discordant for TgAb, a repeat (third) blood sample for central analysis is required 10 days (±3 days) later. Only if the third sample is negative for TgAb will the stimulated Tg level from stage 2 be considered to be interpretable and valid for decision making. Refer also to Table 5.
- Note also that for study purposes the WBS will evaluated by blinded independent central review, and even if local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).

When not to proceed to stage 3 assessments

All patients in the following situations will be classified not in complete remission and should not proceed to stage 3 assessments:

1. Patients who have stimulated Tg level ≥ 1 ng/mL in the absence of TgAb (unequivocal biochemical disease by standardised central laboratory analysis).

2. Patients confirmed to be TgAb positive (regardless of all other data):

   (a) When both the stage 1 and 2 blood samples are TgAb positive (refer to Section 6.4.3.4).

   (b) When the repeat (third) blood sample confirms positive TgAb following a discordant TgAb status from stage 1 and 2.

In these situations the stimulated Tg value will be deemed to be uninterpretable, and the patient will be deemed not to be in complete remission because absence of biochemical disease cannot be proven.

These patients will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, and will continue to be followed in this study until 3 years following their initial RAI dose (refer to Section 6.4.6).

Note that for study purposes the WBS will evaluated by blinded independent central review. If local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).

Table 5 Criteria for biochemical decision making (based on standardised central analysis results)

Scenario	Stage 1		Stage 2		Repeat 3rd TgAb sample[b]	Biochemical remission?
	Suppressed Tg	TgAb[a]	Stimulated Tg	TgAb[a]		
1	≥ 1ng/mL	Negative	Not required	Not required	Not required	No. Stop.[c]
2	< 1 ng/mL	Negative	< 1 ng/mL	negative	Not required	Yes. Proceed to stage 3
3	< 1 ng/mL	Negative	≥ 1 ng/mL	negative	Not required	No. Stop.[c]
4	Any	Positive	< 1 ng/mL	negative	negative	Yes. Proceed to stage 3
5	Any	Positive	< 1 ng/mL	negative	positive	No. Stop.[c]
6	< 1 ng/mL	Negative	< 1 ng/mL	positive[d]	negative	Yes. Proceed to stage 3
7	< 1 ng/mL	Negative	< 1 ng/mL	positive	positive	No. Stop.[c]
8	Any	Positive	Any	positive	Not required	No. Stop.[c]

[a] Standardised central methodology will be used to define TgAb negative/positive status, refer to Section 6.4.3.4.
[b] When the TgAb results from stage 1 and 2 are discordant, a repeat (third) blood sample for TgAb is required 10 days (± 3 days) after the stage 2 blood sample.
[c] For the purpose of the study, the patient will be deemed not to be in complete remission and no further stage 3 assessments are required. These patients will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, and will continue to be followed in this study until 3 years following their initial RAI dose (refer to Section 6.4.6).
[d] Although this stimulated Tg blood sample is positive for TgAb, the patient will be declared to be in biochemical remission if the other two TgAb samples are both negative by standardised central analysis. It is not feasible to repeat a second stimulated Tg assessment.

6.4.2.3 Primary endpoint assessments Stage 3

In stage 3, patients with biochemically-negative disease will have:

- Neck MRI with gadolinium contrast to be evaluated by blinded independent central review.
- Chest CT without contrast to be evaluated by blinded independent central review.
- If clinically indicated, a biopsy/FNA should be performed as follows:
  - For any suspicious lymph nodes on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter.
  - For any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter should be biopsied/FNA.

6.4.3 Blood sample assessments for efficacy

All protocol-scheduled samples for serum Tg (suppressed and stimulated), TSH and TgAb assessment, will be sent for central laboratory analysis using standardised methodology. All decision making for study purposes will be based on the standardised central analysis results; values obtained from different assay methods may be different and cannot be used interchangeably.

Full details of the sample collection, shipment and analytical methodology is provided in the Laboratory Manual.

Unscheduled samples and local analysis:

Investigators may also perform local biochemical analysis for these parameters as per standard site practice if desired, however this data will not be used for study-related decision making. If local analysis is performed, Investigators must ensure that the maximum permissible blood volumes for individual patients at their institutions are not exceeded.

In the case that an investigator performs additional assessment of Tg (and TSH, TgAb) outside of the protocol scheduled visits, such samples should not be sent for central laboratory analysis. Only if such unscheduled local analysis leads the Investigator to wish to administer further therapy for thyroid cancer, should an additional sample ideally be sent for central analysis and the protocol-specified re-treatment criteria applied (Section 5.9.1.1) before the patient is re-treated.

6.4.3.1 Suppressed Tg

Prior to the 18 month primary endpoint assessments:

A blood sample for TSH-suppressed serum Tg is required at 9 months after the RAI dose (± 3 months) in order to assess whether thyroid cancer re-treatment is clinically indicated;

refer to the thyroid cancer re-treatment guidelines in Section 5.9.1.1. Tg assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (but not before 6 months). A second blood sample 2-4 weeks later may also be required to verify the biochemical re-treatment criteria (refer to Section 5.9).

Stage 1 primary endpoint assessments:

For all patients that have not been re-treated for thyroid cancer prior to the primary endpoint assessments 18 months following their RAI dose, a blood sample to centrally analyse the TSH-suppressed serum Tg level will be taken.

Anytime that a Tg blood sample is taken, the same sample will also be centrally analysed for TSH and TgAb (refer to Sections 6.4.3.3 and 6.4.3.4 respectively).

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

6.4.3.2 Stimulated Tg

Prior to the 18 month primary endpoint assessments:

Prior to the 18 month primary endpoint assessments, stimulated Tg levels are not recommended and not included as part of the patient follow up for this study.

Stage 2 primary endpoint assessments:

Serum Tg measured during TSH suppression is not sufficiently sensitive to confirm that a patient is free of thyroid cancer. For this reason, rhTSH (Thyrogen) stimulated serum Tg level will also be assessed at the primary endpoint, only for patients proceeding to stage 2 of the primary endpoint assessments.

For patients that require stimulated Tg assessment, 0.9 mg of rhTSH will be administered IM for 2 consecutive days (refer to Section 5.5.4.1), with the blood sample taken for stimulated Tg central analysis on day 5.

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

Each time that a blood sample is taken for central stimulated Tg analysis, the same sample will also be centrally analysed for TgAb (refer to Sections 6.4.3.4 respectively).

6.4.3.3 TSH

Thyroid hormone supplementation will be adjusted in individual patients with the aim of achieving suppressed TSH levels of 0.5 mIU/L or less for the duration of the study. Each time that a suppressed Tg sample is taken, TSH should also be assessed (by central standardised methodology).

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

6.4.3.4 Tg antibody (TgAb)

Each time that a blood sample is taken for central Tg analysis, the same sample will also be centrally analysed using standardised methodology for TgAb. Full details of the sample collection, shipment and analytical methodology to be used will be provided in the Laboratory Manual.

TgAb cut-off for decision making

For decision making purposes at any time in the study, standardised central analysis results must be used. The cut-off value for positive/negative TgAb status according to the standardised central methodology will be provided to sites prior to the start of recruitment.

At screening:

Patients with TgAbs present at screening will be ineligible for the study (refer to the exclusion criterion in Section 4.2, screening samples must be sent for standardised central analysis).

Prior to the 18 month primary endpoint assessments:

If TgAbs are detected in the follow-up Tg blood sample (at 9 months ±3 months), the patient should not be re-treated unless new structural disease is detected according to Section 5.9.1.2 (ie, it is strongly recommended that patients are not re-treated on the basis of new antibodies alone, in the absence of structural disease). Refer to Section 5.9.

Primary endpoint assessments (Stage 1 and 2)

The TgAb status of the stage 1 blood sample will not be taken into consideration alone. The following rules will apply (refer also to Table 5):

1. If both stage 1 and stage 2 blood samples are negative for TgAb, then the Tg results will be valid for decision making.

2. If both stage 1 and stage 2 blood samples are positive for TgAb, then the stimulated Tg result will be deemed to be uninterpretable, and for the purpose of this study the patient will be classified as not in complete remission. No further primary endpoint assessments are required.

3. If the stage 1 and 2 blood samples are discordant for TgAb status, then a repeat (third) blood sample is required 10 days later (± 3 days). Only if the repeat sample is confirmed negative for TgAb, will the stimulated Tg level in stage 2 be considered to be interpretable and valid for decision making.

6.4.4 Imaging assessments for efficacy

6.4.4.1 Neck ultrasound (US)

Neck US assessments will take place at the times indicated in the Study Plan Table 3. Refer also to Section 6.4.2 and Table 4 for further details of US assessment at the primary endpoint.

Any suspicious lymph nodes or lesions in the neck ≥ 5 mm in the smallest diameter identified by US during the study should be biopsied/FNA.

Note: for a lesion to be suspicious it must be new or enlarged compared to the previously obtained imaging data, and be consistent with the biological characteristics of DTC.

Biopsy/FNA samples, where performed, will be assessed at each site. Needle washout may be analysed locally for Tg according to local standard practice. The totality of the information obtained from a biopsy/FNA (including washout Tg data where analysed), will be assessed locally to determine presence or absence of thyroid cancer in the sample.

US definition of structural DTC

Any soft tissue or lymph node lesions that are new or enlarged compared to previous ultrasound assessment (either post operatively and/or at 9 months) that are consistent with the biological characteristics of DTC and fulfil the following criteria will be considered as structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is subsequently shown to be RAI avid/positive on central review of WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on US that is non-RAI avid on the subsequent WBS, will be considered benign even in the absence of a biopsy.

The assessment of neck US and biopsy/FNA sample will be made by investigator site review.

The local ultrasound information will be recorded in the eCRF (with FNA/biopsy results if performed) and provided to the central imaging CRO if necessary as supporting clinical data (refer to Section 6.4.4.6).

Guidelines for standardised acquisition, defining suspicious lesions and reporting of US assessments required for this study will be provided to each study site.

6.4.4.2 Whole body diagnostic ^{131}I nuclear medicine scan (WBS)

Pre-RAI treatment

There is no pre-ablation WBS in this study. This is a fixed RAI dose study (100mCi, 3.7GBq) with Thyrogen stimulation. Study-specific post-operative imaging will be used to ensure that enrolled patients do not have overt macronodular disease remaining in the neck or distant metastatic disease in the lungs.

Post-RAI treatment

All randomised patients will have a WBS performed 3-10 days following their RAI treatment dose to assess where the administered ^{131}I has localised.

It is acknowledged that this assessment may identify a small number of patients with distant metastatic disease that was not previously identified (patients with known metastatic disease at study entry will be excluded). Such patients will continue in the study and should not be withdrawn; they will continue to be followed according to the protocol and will be included in both the Intention To Treat (ITT) efficacy and safety analysis sets for the study.

Primary endpoint (stage 2)

If required according to Section 6.4.2, the diagnostic WBS to assess the primary endpoint will be performed following a diagnostic dose of 5 mCi ^{131}I (refer to Section 5.5.4.2). Patients will receive 2 Thyrogen injections on consecutive days (day 1 and 2), followed by a diagnostic dose (5 mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5. Patients will be required to adhere to a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose, until the diagnostic WBS assessment is completed.

Standardised acquisition and submission guidelines for every WBS procedure will be provided separately to this protocol.

WBS definition of structural DTC

The WBS evaluation will be made by blinded, independent central review.

If the central review determines no visible ^{131}I uptake then the WBS for that patient will be considered normal/negative (no disease). Areas considered to be anatomically normal (for example uptake in the salivary glands, stomach, gastrointestinal, urinary tract and bladder) will not be considered disease.

If the central review determines there is a low level of visible uptake in the thyroid bed:

- Uptake must be < 0.1% to be considered normal/negative (no disease).
- If uptake in the thyroid bed region is ≥ 0.1%, the patient will be deemed not to be in remission due to the presence of iodine-avid DTC.

The % uptake in the thyroid bed (using the region-of-interest method drawn over the thyroid bed) will be measured and calculated by the local Investigator site and entered into the eCRF, to be made available to the central reviewer.

If an abnormality identified by US is subsequently shown to be RAI avid on WBS, the WBS data takes precedent over a negative biopsy/FNA.

6.4.4.3 Neck MRI

Post-operative (screening)

This baseline assessment is performed to determine study eligibility according to Section 4.1). The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Primary endpoint (stage 3)

Neck MRI to define the primary endpoint will be performed in stage 3 of the assessments in patients deemed to be biochemically-negative for thyroid cancer. Refer to Section 6.4.2.3 and Figure 3.

The neck MRI must be performed using T1 weighted image sequences with and without gadolinium contrast agent, and T2 weighted image sequences.

If clinically indicated, any suspicious lymph nodes on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter, should be biopsied/aspirated by fine needle.

MRI definition of structural DTC

New lesions (nodal or non-nodal) or significantly enlarged lymph node lesions compared to previous post operative (screening) MRI which are consistent with the biological characteristics of DTC and fulfil either of the following criteria will be considered to represent structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is shown to be RAI avid/positive on WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on MRI that is non-RAI avid on the WBS, will be considered benign even in the absence of a biopsy.

This assessment will be made by blinded, independent central review.

6.4.4.4 Chest CT

In this study all chest CT procedures should be performed without iodine containing contrast agent.

Post-operative (screening)

This baseline assessment is performed to determine study eligibility according to Section 4.1). The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Primary endpoint (stage 3)

Chest CT to define the primary endpoint will be performed in stage 3 of the assessments in patients deemed to be biochemically-negative for thyroid cancer. Refer to Section 6.4.2.3 and Figure 3.

If clinically indicated, any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter should be biopsied/FNA.

CT definition of structural DTC

New lesions (nodal or non-nodal) or significantly enlarged lymph node lesions compared to previous post operative (screening) CT which are consistent with the biological characteristics of DTC and fulfil either of the following criteria will be considered to represent structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is shown to be RAI avid/positive on WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on CT that is non-RAI avid on the WBS, will be considered benign even in the absence of a biopsy.

This assessment will be made by blinded, independent central review

6.4.4.5 Biopsy or fine needle aspirate (FNA)

A biopsy or FNA should be performed in the following situations:

- **US:** For any suspicious lymph nodes or lesions in the neck ≥ 5 mm in the smallest diameter identified by US during the study.
- **MRI:** If clinically indicated, for lymph nodes suspicious on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter.

- **CT**: If clinically indicated, for any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter.

Note: for a lesion to be suspicious it must be new or enlarged compared to the previously obtained imaging data, and be consistent with the biological characteristics of DTC.

All biopsy/FNA samples taken during the study will be assessed at each site according to local standard practice. Needle washout may be analysed locally for Tg according to local standard practice (this is not a mandatory requirement). The totality of the information obtained from a biopsy/FNA (including washout Tg data where analysed), will be assessed locally to determine presence or absence of thyroid cancer in the sample. This information will be provided to the central imaging CRO.

Refer to Section 6.10.3 for details regarding tumour sample acquisition on disease progression.

6.4.4.6 Information to be sent to the central imaging CRO

The following information will be sent to the central imaging CRO (further details are provided in the imaging charter/guidelines for this study).

1. Post-operative screening assessments (refer to Section 6.3): images for chest CT and neck MRI. This data must be sent for all patients as soon as possible after each patient is randomised.

2. Post-RAI WBS images taken 3-10 days after each patient's RAI dose. This data must be sent for all patients as soon as possible after each patient has their post-RAI WBS assessment.

3. Primary endpoints assessments stage 1: site ultrasound and biopsy information. The required data must be entered into the clinical database for each patient as soon as possible after completion of the assessment (NOTE: this information is not sent to the central imaging CRO, but instead must be entered into the database directly using eCRF).

4. Primary endpoint assessments stage 2: diagnostic WBS images. This data must be sent for all patients as soon as possible after completion of the assessment.

5. Primary endpoint assessments stage 3: chest CT and neck MRI images and biopsy information (if performed). This data must be sent for all patients as soon as possible after completion of the assessments. Biopsy data must be entered into the clinical database for each patient as soon as possible after completion of the assessment.

6.4.5 Derivation of primary endpoint of complete remission

The complete remission status of each patient will be determined programmatically by AstraZeneca, by incorporating data on re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, and structural disease assessment from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in complete remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer, all available imaging data will be sent to the imaging CRO. Determination of presence or absence of structural thyroid cancer will be made by the imaging CRO only for biochemically negative patients. A list of biochemically negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

The imaging CRO will assess the WBS, MRI and CT and also review the site assessment of neck US to provide an overall assessment: presence or absence of structural thyroid cancer, or not evaluable based on all of the available information. For the derivation of the complete remission endpoint, patients that are not evaluable for structural disease assessment will be considered as not achieving complete remission, regardless of the result of other assessments.

AstraZeneca will programmatically combine information on further therapy, biochemical data, and the determination of structural disease from the central imaging CRO, to determine the complete remission status of each patient as shown in Table 6.

The dates on which assessments were performed will be incorporated into the derivation of the primary endpoint to ensure patients are assessed within a time window around the scheduled 18 month post-RAI treatment. The first assessment must be started at 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within a 8 week period. If a patient has assessments/scans that fall outside of these time windows, the patient will be considered not to be in complete remission, regardless of the assessment of disease status.

Table 6 Programmatic derivation of complete remission status

Scenario	Further thyroid cancer therapy[a] (re-treatment)	Biochemical data[b]		Structural disease assessment[c]	Complete remission
		Stimulated Tg[b]	TgAb[b]		
1	Yes	N/A	N/A	N/A	No
2	No	< 1 ng/mL	Negative[d]	Absence of disease	Yes
3	No	≥ 1ng/mL	Any	Any	No
4	No	Any	Positive[d]	Any	No
5	No	Any	Any	Presence of disease	No
6	No	NE	Any	Any	No
7	No	Any	NE	Any	No
8	No	Any	Any	NE	No

[a] As assessed by investigator at site.
[b] As assessed by standardised central laboratory analysis.
[c] As assessed by blinded, independent central review.
[d] If the stage 1 and 2 blood samples are discordant for TgAb status, then a third blood sample 10 days later (± 3 days) is required. Only if the third sample is negative for TgAb will the overall TgAb result be considered negative for the primary endpoint assessments. Refer also to Table 5.
N/A primary endpoint assessments are not required for patients that have received further treatment for thyroid cancer in the previous 18 months.
NE Not evaluable (for example due to missing samples or assessments).

6.4.6 Clinical remission

The secondary efficacy endpoint for this study is **clinical remission rate at 18 months** (following RAI treatment). This is designed to more typically reflect clinical practice. As such, the definition of clinical remission will exclude the additional radiological assessments performed for the purpose of complete remission in this study.

Definition of clinical remission:

Patients will be defined to be in clinical remission if all of the following criteria can be demonstrated:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer on neck US, as assessed by investigator site review.

3. No evidence of thyroid cancer on diagnostic WBS, as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed to clarify equivocal US findings, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

6.4.7 Derivation of clinical remission status

The clinical remission status of each patient will be determined programmatically by AstraZeneca, by incorporating data on re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, structural disease assessment based on US by investigator site review and structural disease assessment based on WBS from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in clinical remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer:

A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the investigator based on US.

A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the central imaging CRO based on WBS for only biochemically negative patients. Information on US will not be reviewed as part of this assessment. A list of biochemically

negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

AstraZeneca will programmatically combine information on further therapy, biochemical data, determination of structural disease from the investigator site assessment of US and determination of structural disease from the central imaging CRO of WBS, to determine the clinical remission status of each patient.

Full details of the programmatic derivation of clinical remission will be provided in the SAP.

6.4.8 Final study follow up at 3 years

The final study follow-up will take place 3 years post-RAI for each patient, and will include:

1. The clinical status of each patient, for example: remission, persistent disease, recurrent disease, survival status.

2. The incidence of further therapy (re-treatment) for thyroid cancer, for example, additional RAI or surgery.

3. Final assessment of selumetinib or RAI-related AEs and SAEs.

Note, following the primary endpoint assessments until the final study visit at 3 years following each patient's initial RAI treatment, each patient will enter standard of care treatment or follow up according to local practice. No study-specific assessments will be performed, and locally performed assessments and data will not typically be collected as routine in the clinical study database (except for safety data, refer to Section 6.5.3). The patient's clinical status at the final study follow up will be collected (along with any relevant supporting local assessment data). For example, remission status will be defined by the Investigator on the eCRF based on the relevant local standard of care assessments (eg, locally assessed Tg and no evidence of thyroid cancer on locally assessed US).

6.5 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.5.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.5.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.5.3 Recording of adverse events

All adverse events will be graded according to NCI CTCAE Version 4.

Time period for collection of adverse events

All AEs/SAEs will be collected from informed consent until 30 days following the last dose of study treatment (selumetinib or placebo).

After this time:

- all SAEs regardless of causality will be collected until the final study follow-up (3 years post-RAI for each patient, refer to Section 6.4.8)
- only AEs considered causal to RAI or the combination of RAI and study treatment will be collected until the final study follow-up (3 years post-RAI for each patient, refer to Section 6.4.8).

Follow-up of unresolved adverse events

Any AE or laboratory change occurring during the study treatment period should be followed up by the investigator for as long as medically indicated (resolution or stabilisation), and follow up information recorded in the eCRF.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade information
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no) and/or RAI (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study treatment
- Treatments patient received for AE
- Outcome
- Whether event constitutes an SAE.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (if applicable)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.5.2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The Investigator will assess causal relationship between Investigational Product and RAI and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication, study procedures and additional study drug (eg, RAI). Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient, or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation, will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs etc should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

After the 30 day follow up visit, AEs associated with RAI or the combination of study treatment and RAI, should continue to be collected by AE reporting, these would include abnormalities, for example, white blood cell count or Hb reductions.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law,' for further instructions. All patients with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (± 7 days) later for follow-up.

6.5.3.1 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.5.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.5.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (Table 3). For samples taken after Day 1 during the study treatment period, the sample may be taken any time of day (ie, it does not matter whether it is pre-dose or post-dose). Day 1 samples should be taken pre-dose.

The following laboratory variables will be measured:

Table 7 Laboratory safety assessments

Clinical chemistry	Haematology	Urinalysis [a]
s-Albumin	Erythrocyte count	u-Albumin
s-ALT	Haemoglobin	u-Creatinine
s-AST	Platelet count	
s-ALP	Leucocyte cell count	
s-Total Calcium	Leucocyte differential count (absolute count):	
s-Creatinine	Neutrophils	
s-Gamma glutamyl transferase (γGT)	Eosinophils	
s-Glucose	Basophils	
s-Magnesium	Lymphocytes	
s-Phosphate	Monocytes	
s-Potassium		
s-Sodium		
s-Total protein		
s-Total bilirubin		
s-Urea nitrogen		
s-Creatine kinase		

[a] A single-spot urine specimen will be collected on the day of scheduled visit, at sites where the local laboratory is able to determine the concentration of urine albumin and urine creatinine from a single-spot urine specimen. Investigational sites unable to report these parameters will perform routine urinalysis according to the local standard of care.

s serum
u urine

All laboratory safety assessments will be analysed by the local laboratory.

Clinical chemistry, haematology and urinalysis testing will be repeated as clinically indicated as part of the routine management of the patient on the occurrence of AEs.

For blood volume see Table 9.

6.5.6 Physical examination

A complete physical examination will be performed at the times indicated in the Study Plan Table 3.

6.5.7 Cardiac monitoring

Note: troponin assessment in this study is only required for cardiac AE follow up as clinically indicated.

6.5.7.1 ECHO or MUGA

An ECHO or MUGA assessment (according to site preference) will be conducted at the timepoints indicated in the Study Plan (Table 3). A further assessment should be performed as part of the assessment package for any cardiorespiratory adverse event with no obvious diagnosis. Medical management of the event should follow local clinical practice. Selumetinib interruption should be considered until resolution of the event or until return to baseline.

LVEF can be measured in many different ways but echography is the preferred choice when possible. The same modality should be used as baseline for any ECHO/MUGA follow up. Recommendations include having complete high quality standardized 2-D with Doppler echocardiographic examinations performed by an experienced sonographer (preferably with the same operator performing all studies for a given patient), according to a specified protocol including evaluation of both systolic and diastolic left ventricular function. Ejection fraction determinations should be assessed quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.

6.5.7.2 Resting 12-lead ECG

ECGs will be analysed locally at each site. Patients should be supine and at rest 10 minutes prior to recording the ECG.

Parameters including heart rate, duration of QRS complex, PR and QT intervals will be collected. R-R interval and QTcF will be calculated by AstraZeneca from the data provided.

The investigator should review the paper copy of the ECGs on each study day and may refer to a local cardiologist if appropriate.

Any symptoms from the patient should be registered as a comment and if AE criteria are met, recorded as an AE.

At screening all patients will have a single 12-lead ECG performed. The screening ECG can be conducted up to 28 days prior to randomisation.

During the treatment phase of the study, patients will have single 12-lead ECGs assessments at the following timepoints:

- 1-2 hours after the first dose of study treatment on Day 1

- 1-2 hours after the morning dose of study treatment on Day 29 or 30
- At the 30-day follow up visit following completion of study treatment
- Single ECGs must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event
- A single 12-lead ECG is also required at premature discontinuation of treatment

6.5.8 Vital signs

Resting blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size. Vital sign assessments, including weight, will be performed at the times indicated in the Study Plan Table 3. Pulse and blood pressure must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event. Height will be assessed at Visit 1 only.

Any changes in vital signs should be recorded as an AE if applicable.

6.5.9 Other safety assessments

6.5.9.1 Pregnancy test

A serum or urine pregnancy test (according to local practice) will be performed at the times indicated in the Study Plan Table 3. Following the RAI treatment, monitoring for pregnancy will be performed according to standard clinical practice at each centre.

6.5.9.2 Ophthalmologic examination

An ophthalmologic examination (best corrected visual acuity, intraocular pressure, slit lamp fundoscopy) should be performed at the timepoints indicated in the Study Plan (Table 3), and if a patient experiences a visual symptoms (including blurring of vision) with additional tests if clinically indicated e.g. consider OCT scans.

Patients who have a retinal abnormality prior to discontinuation of selumetinib/placebo should have a follow up eye examination performed within 30 days after discontinuation of selumetinib/placebo in order to document reversibility.

An algorithm for management and investigation of visual symptoms is provided in Appendix G: “Guidance for Management of Adverse Events in Studies of Selumetinib.”

6.6 Patient reported outcomes (PRO) – not applicable

Patient reported outcomes will not be collected in this study.

6.7 Pharmacokinetics

6.7.1 PK samples required

Blood samples (2 mL) for determination of plasma concentrations of selumetinib and N-desmethyl selumetinib will be collected from every patient according to the time points below. Other metabolites (eg, selumetinib amide) may also be determined in the PK analysis. Each patient will be asked to contribute 8 blood samples, one from each of the pre defined time windows below on both Day 1 and Day 29 or Day 30. The Day 29 or Day 30 PK blood samples may be taken earlier, from Day 22 onwards of study treatment if preferred, but it is essential that all PK blood samples are collected on a visit day **prior** to the RAI dose being administered.

- Pre-dose (within 15 minutes of dosing)
- Between 15 minutes and 1 hour post-dose
- Between 1.5 and 2.5 hours post-dose
- Between 3 and 8 hours post-dose

Depending on emerging data/information, the timings and number of the PK samples may be altered, but the maximum total blood volumes given in Table 9 will not be exceeded. The actual sample date and time of all PK samples must be recorded in the eCRF.

Samples will be collected, labelled, stored and shipped as detailed in Laboratory Manual.

6.7.2 Determination of drug concentration

Samples for determination of selumetinib and N-desmethyl selumetinib concentrations in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Other metabolites (eg, selumetinib amide) may also be determined in the PK analysis. Full details of the bioanalytical method used will be described in a separate bioanalytical report.

For each placebo patient, samples will only be analysed on a ‘for cause’ basis, for example, if no quantifiable concentrations were observed in a patient’s samples when the drug was expected to be present.

All samples still within the known stability of the analytes of interest (ie, selumetinib, N-desmethyl selumetinib and its metabolites) at the time of receipt by the bioanalytical laboratory will be analysed.

6.8 Pharmacodynamics – not applicable

Pharmacodynamic samples will not be taken during this study.

6.9 Pharmacogenetics

6.9.1 Genetic blood sample at study entry

An optional blood sample for genetic research will be obtained from eligible patients at Visit 1 or 2 ideally. If for any reason the sample is not drawn at Visit 1 or 2, it may be taken at any visit **before the RAI dose is administered** (radioactive samples for this purpose will not be accepted). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. Only one sample should be collected per patient for this purpose. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volumes see Section 7.1.

6.10 Biomarker analysis

6.10.1 *BRAF* and *NRAS* patient population

Archival tumour sample from each patient will be analysed for *BRAF* and *NRAS* mutational status centrally using standardised methodology. Analysis may include, but is not limited to, *BRAF* V600E and *NRAS* Q61R, Q61K, Q61L.Full analytical methodology details will be provided in the CSR.

The genetic analysis of archival tumour samples to identify the *BRAF* and *NRAS* patient population will be performed retrospectively in the study (after randomisation but prior to the primary endpoint data analysis).

BRAF/NRAS positive = mutations in *BRAF/NRAS* have been detected

BRAF/NRAS not detected = no mutation in *BRAF/NRAS* has been detected

BRAF/NRAS unknown = mutation status in *BRAF/NRAS* cannot be confirmed

6.10.1.1 Archival tumour sample

All patients will be required to provide consent for AstraZeneca to collect and analyse samples of their previously obtained tumour material (ie, from their recent surgery) for analysis of biomarkers relevant to DTC. Archival tumour sample provision is mandatory in this study, and each Investigator should make every effort to collect a sample from all randomised patients. It is accepted that it may not be possible to obtain all samples prior to commencement of study treatment (which should continue as planned). However, it should be established during the screening period that sufficient sample exists and is available. Samples are expected to be made available as soon as possible. Note, no replacements will be made for patients where an archival tumour sample is not provided.

These samples will be analysed for the biomarkers necessary for the definition of the second primary objective patient population (*BRAF* and *NRAS* mutational status), and may also be

used for exploratory analyses on residual material. Such analyses may include (but are not restricted to):

- Mutational status of *BRAF* and *NRAS* genes, *RET* rearrangements, and other known MAPK and PI3K effector oncogenes.
- Baseline expression of pathway and thyroid differentiation specific genes such as *NIS*, *Tg*, *TPO*, and *PAX8*.
- Comprehensive genetic analysis to ensure coverage of the major mutational events in DTC.

The exploratory analyses from tumour material may include but are not limited to mRNA expression profiling, microRNA expression profiling, gene copy number analysis and protein expression by immunohistochemistry for any markers relevant to DTC, either known at the time of analysis, or identified in the future.

For the tumour samples detailed below, each site will be asked to provide one of the following for each randomised patient:

– Formalin-fixed, paraffin-embedded tumour tissue block,

or

– 20 pre-cut sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 μm thick.

Sites should ship the tumour sample as soon as it is available. If mutational status cannot be adequately determined from the initial tumour biopsy sample, and histopathological review shows it to be a poor quality sample, a second sample should be submitted for re-testing.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

If requested, unused tumour samples will be repatriated. For further details see the Laboratory Manual.

6.10.2 Collection of plasma and serum for exploratory biomarker research

All randomised patients will be required to provide a blood sample at or before randomisation, and disease progression (for example, when the patient is re-treated for persistent or recurrent thyroid cancer) for exploratory biomarker research.

All patients will be required to provide:

– 1x 10ml blood sample for preparation of serum at randomisation (any time before the first dose of study treatment for eligible patients) and disease progression.

– 1x 10ml blood sample for preparation of plasma at randomisation (any time before the first dose of study treatment for eligible patients) and disease progression.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Residual material may be used for exploratory biomarker research.

6.10.3 Collection of disease progression tumour sample

Patients will be asked to provide a tumour sample removed during the study when the patient's cancer is deemed to have progressed (for example, when the patient is re-treated for persistent or recurrent thyroid cancer, or has had further surgery). This is an optional sample.

This will enable a comparison to be made of (for example) tumour genetics and relevant signal transduction pathways between the randomisation and the disease progression tumour sample and also the evolution of the tumour biology in response to treatment with selumetinib can be explored. Such changes may reflect an evolution in phenotype of the tumour, which ultimately may guide future treatment decisions post progression on selumetinib.

Samples can be of any type (such as FNA, or tumour sample taken from a surgical procedure performed as part of the patient’s disease management plan), and will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Table 8 Biomarker summary table

Biomarker sample	Time point	Protocol Section
Archival tumour for *NRAS* and *BRAF* analysis[a]	Randomisation	6.10.1.1
Plasma sample for exploratory biomarker analysis	Randomisation and disease progression	6.10.2
Serum sample for exploratory biomarker analysis	Randomisation and disease progression	6.10.2
Disease progression tumour biopsy (optional)	Disease progression	6.10.3
Blood sample for genetic analysis (optional)	Randomisation	6.9.1

[a] Residual tissue sample material will be stored for potential retrospective biomarker analysis, which will be performed in an AstraZeneca laboratory or AstraZeneca approved laboratory.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood (maximum) that will be drawn from each patient in this study is as follows:

Table 9 Volume of blood to be drawn from each patient

Assessment		Maximum sample volume [a] (mL)	Typical number of samples (over 18+ months)	Total volume (mL)
Safety	Clinical chemistry (local analysis)	5	5	25
	Haematology (local analysis)	3	7	21
Efficacy	Tg, TSH, TgAb (central analysis)	10	4[b]	40
PK		2	8	16
Genetics at randomisation (optional)		10	1	10
Exploratory biomarkers at randomisation, serum		10	1	10
Exploratory biomarkers at randomisation, plasma		10	1	10
Exploratory biomarkers on progression, serum		10	1	10
Exploratory biomarkers on progression, plasma		10	1	10
Total				152 [b]

[a] All volumes presented are maximums. The actual volume requirements will be detailed in the Laboratory Manual.

[b] For efficacy samples up to 2 repeat samples may be required, this would result in 10-20 mL additional blood and bring the maximum total to 172 mL.

7.2 Handling, storage and destruction of biological samples

Biological samples for future research may be retained at or on behalf of AstraZeneca for a maximum of 25 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report or Scientific Publication.

7.2.1 Pharmacokinetic samples

Samples will be anonymised by pooling or will be disposed of after the Bioanalytical report finalisation or six months after issuance of the draft Bioanalytical report (whichever is earlier), unless requested for future analyses. Pooled, anonymised samples may be used for analytical method development and/or validation. Anonymised samples will be retained for no more than 5 years after the CSR is finalised. Samples may also be disposed of earlier, pending further notification.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical report.

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 25 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document.'

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of any optional donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central and bioanalytical laboratories holding the samples are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

In the USA the Principal Investigator is also responsible for providing the Ethics Committee with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of

AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study.' All patients in this study will be followed for 3 years following their RAI treatment.

The study is expected to start in 2013 and to end in 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with selumetinib.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the principal investigator has signed the eCRF electronically as per eCRF instructions, the subject's data will be locked.

Medical coding will be performed using the AstraZeneca Autocoder application. The Data Management Centre Coding Team will perform coding using agreed coding conventions. AEs and medical and surgical history will be coded using the standard dictionary – Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medication will be coded using the AstraZeneca Drug Dictionary.

SAEs will be entered into a global patient safety database for regulatory reporting purposes and be reconciled with the AEs in the clinical database.

Data associated with biological samples will be transferred to the data manager as an electronic file and merged with study data as appropriate.

Data from external providers (eg, central laboratory) will be validated as appropriate to ensure that it is consistent with the clinical data and included in the final database.

Clean file will be declared for the database once all data have been received, entered, validated and all queries resolved. The database will be locked after clean file has been declared. Treatment codes will not be broken until after clean file. Following database lock, all data will be extracted as SAS (Statistical Analysis Software) data sets for the statistical analysis to be performed by AstraZeneca.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate. Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Complete remission rate at 18 months post-RAI treatment

Patients will be considered to be in complete remission if they are alive and all of the criteria in Section 6.4.1 are met at 18 months post-RAI treatment.

Complete remission rate at 18 months post-RAI treatment is defined as the proportion of patients who have achieved complete remission at this time point. The complete remission rate will be calculated using all randomized patients as the denominator.

11.1.2 Clinical remission rate at 18 months post-RAI treatment

Patients will be considered to be in clinical remission if they are alive and all of the criteria in Section 6.4.6 are met at 18 months post-RAI treatment.

Clinical remission rate at 18 months post-RAI treatment is defined as the proportion of patients who have achieved clinical remission at this time point. The clinical remission rate will be calculated using all randomized patients as the denominator.

11.1.3 Thyroid cancer recurrence

The occurrence and date of any thyroid cancer recurrence will be recorded for patients who have previously entered either complete or clinical remission (at any point during the study or follow up periods). The rate of thyroid cancer recurrence will be calculated using only patients who have achieved remission as the denominator.

11.1.4 Survival status

The survival status and survival assessment date of all patients will be recorded. Survival time will be calculated as the time from the date of randomisation to the date of death. Patients who have not died at the time of the final study follow up will be censored at the last date the patient was known to be alive.

11.1.5 Further therapy

The dates and type of any further therapy for thyroid cancer will be recorded during the study and follow up periods.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Adverse events

Adverse events will be listed for each patient and summarised by treatment received according to the System Organ Class (SOC) and preferred term assigned to the event using the MedDRA. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs Version 4. The CTC Grade will be assigned by the Investigator.

AE summaries will include all of the following:

- Any AEs occurring after commencement of study treatment and within 30 days of the last dose of study medication
- AEs related to RAI or the combination of RAI and study treatment occurring between 30 days after the last dose of study medication and the final study visit at 3 years following the initial RAI dose
- All SAEs occurring after commencement of study treatment until the final study visit at 3 years following the initial RAI dose

AEs occurring before commencement of study treatment will not be included in AE summaries but will be included and identified in the patient listings.

11.2.2 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2.3 Vital signs, laboratory data, ECGs, ECHO/MUGA, physical examination and ophthalmologic examination

For change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF (Fredericia) will be calculated programmatically by AstraZeneca using the reported ECG values (RR and QT).

QTcF = QT / RR^ (1/3) where RR is in seconds

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality. For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded

The denominator in vital signs data should include only those patients with recorded data.

11.3 Calculation or derivation of PK variables

The final PK analyses will be the responsibility of Clinical Pharmacology and Pharmacometrics, AstraZeneca.

Using appropriate PK software the available PK data will be used to derive PK parameters such as, but not restricted to, C_{max}, AUC for Selumetinib, N-desmethyl selumetinib and any other metabolites determined.

The selumetinib, N-desmethyl selumetinib and metabolite concentration-time profiles, along with the derived PK variables, will be listed for each patient per dose and dosing day and summarised appropriately, as described in the SAP.

Population PK models may be used to derive the PK parameters and will aim to characterise variability in the population by investigating the influence of covariates such as weight, age, sex, and/or concomitant medications. In addition, if the data are suitable, potential relationships between plasma selumetinib and N-desmethyl selumetinib concentrations will be investigated using a graphical approach and/or appropriate PK/PD modelling techniques. A detailed PK analysis plan will be produced prior to any such investigations and will be reported separately.

11.4 Calculation or derivation of pharmacogenetic variables

Genetic data (except *BRAF* and *NRAS* data) will be reported separately to the CSR for this study.

11.5 Calculation or derivation of biomarker variables

11.5.1 Analysis of *NRAS* and *BRAF*

Tumour samples will be collected as outlined in the study plan and assessed for *BRAF* and *NRAS* mutational status (as detailed in section 6.10.1) to identify patients for this patient population.

11.5.2 Further biomarker research analysis

Methods of analysis for all other biomarker research may include investigation of genetic variability, gene expression profiling, protein expression profiling.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Intention to treat (ITT) analysis set

The ITT analysis set will include all randomised patients. The ITT analysis set will be used for all efficacy analyses and treatment groups will be compared on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment will be included in the ITT analysis set.

12.1.2 *BRAF/NRAS* mutation positive analysis set

For the analysis of the *BRAF* and *NRAS* mutation positive population (secondary objective), only those patients from the ITT population with genetic samples that are positive for *BRAF* or *NRAS* will be included.

12.1.3 Treatment-compliant (TC) analysis set

The treatment-compliant analysis set will be a subset of the ITT population containing patients that adhered to the minimum study treatment requirements specified in Section 3.1.1, i.e. patients who take study treatment twice daily for a **minimum** of 7 consecutive days prior to RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. Patients must also have had their RAI dose.

The TC analysis set will be used as a sensitivity analysis for the primary endpoint.

12.1.4 Safety analysis set

The safety analysis set will consist of all patients who received at least one dose of randomised treatment. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment combination received, ie, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

12.1.5 PK analysis set

PK data will be analysed according to treatment received. This population will comprise all patients who receive study treatment as per protocol and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the AstraZeneca Study Team Physician, Pharmacokineticist and Statistician prior to any analyses being performed.

12.2 Methods of statistical analyses

A comprehensive SAP will be prepared prior to start of recruitment (first subject in).

Since there is only one primary endpoint/comparison of interest (complete remission rate at 18 months for selumetinib vs. placebo in the ITT population) the primary endpoint will be considered statistically significant if the two-sided p-value is less than 0.05.

12.2.1 Complete remission rate at 18 months post-RAI treatment

The primary endpoint of complete remission rate at 18 months will be compared between selumetinib in combination with RAI, and placebo in combination with RAI in the ITT population using a logistic regression model including treatment as the only covariate. Results will be presented in terms of the odds ratio, 95% confidence interval and associated p-value. A sensitivity analysis will be performed using a logistic regression model including treatment and adjusted for the covariates histology status (papillary, follicular, poorly differentiated), mutation status (*BRAF/NRAS* positive, *BRAF/NRAS* not detected) and age, provided there are enough data points for a meaningful analysis.

A secondary analysis of complete remission rate will be performed to compare selumetinib in combination with RAI vs. placebo in combination with RAI in the *BRAF*/*NRAS* mutation positive population using a logistic regression model including treatment as the only covariate. A sensitivity analysis will be performed using a logistic regression model adjusted for the covariates histology status (papillary, follicular, poorly differentiated) and age, provided there are enough data points for a meaningful analysis.

For the sensitivity analyses using each covariate adjusted logistic regression models, the following missing data approach for each covariate will be adopted:

- Missing age; impute the mean of observed ages
- Missing histology status; add an additional ‘unknown’ category to make 4 categories (papillary, follicular, poorly differentiated, and unknown)
- Missing mutation status; add an additional ‘unknown’ category to make 3 categories (*BRAF/NRAS* positive, *BRAF/NRAS* not detected and unknown)

The results of the analyses, in terms of treatment effects, will be presented as odds ratios together with their associated 95% profile likelihood confidence intervals and 2-sided p-values. The p-value will be based on twice the change in log-likelihood resulting from the

addition of a treatment factor to a model that contains the covariates defined above. The complete remission rate and 95% confidence interval will be estimated for each treatment arm.

Sensitivity analyses for the primary endpoint

The primary endpoint analysis, a logistic regression model including treatment as the only covariate for complete remission rate at 18 months, will be repeated:

- using the treatment-compliant population.
- to allow patients that were identified as being in complete remission outside of the specified time windows to be classed as being in complete remission, in order to investigate time bias between arms.
- excluding patients with high TSH. Elevated TSH can be caused by poor compliance and can mean a patient is less likely to achieve remission, therefore this sensitivity analysis excludes patients with high TSH, which is defined as a value >10 mIU/L recorded at any point by standardised central laboratory analysis.

Treatment by covariate interactions

The extent to which the treatment effect is consistent across the subgroups histology status, mutation status (ITT population only), gender, race and age will be assessed in the ITT population and in the *BRAF*/*NRAS* mutation positive population. The presence of a quantitative interaction will be assessed by means of an overall global interaction test. This will be performed by comparing the fit (likelihood ratio test) of a model including all covariate-by-randomised treatment interaction terms, treatment and covariate terms with a model that excludes the interaction terms. If the global interaction test is found to be statistically significant at the 10% significance level, an attempt to determine the cause and type of interaction will be made. Stepwise backward selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

For quantitative interactions identified, the presence of any qualitative interactions will be assessed using the approach of Gail and Simon (Gail & Simon 1985). For categorical covariates the test statistics, based on the appropriate degrees-of-freedom, can be taken directly from the paper. For the continuous covariate, the approach will be adapted as follows:

Identify the cut-point ($-\beta_1/\beta_3$) of the covariate where the odds ratio for the treatment effect is 1, where β_1 is the treatment parameter estimate and β_3 is the treatment-by-covariate parameter

estimate. Re-analyse the data separately for the values of the covariate above and below the cut-point and use the separate chi-square values in the Simon and Gail test.

Subgroup data

Subgroup data (histology status, *BRAF* or *NRAS* mutation status, gender, race and age) will be summarised by a forest plot where the odds ratio is plotted on the log scale. For this, age will be categorised as ≤45 or >45 years. The treatment effect and 95% confidence intervals for each level of the subgroup will be obtained from a single logistic regression model that contains a treatment, factor and treatment-by-factor interaction term.

12.2.2 Clinical remission rate at 18 months post-RAI treatment

The secondary endpoint of clinical remission rate will be analysed as described in Section 12.2.1, except for primary endpoint specific sensitivity analyses and treatment by covariate interaction testing.

12.2.3 Thyroid cancer recurrence

Very few thyroid cancer recurrences are expected on this study, therefore no formal analysis of thyroid cancer recurrence data will be performed; data will be listed and summarised.

12.2.4 Survival status

Very few deaths are expected on this study therefore no formal analysis of survival data will be performed; data will be listed and summarised. Kaplan-Meier plots of survival may produced if appropriate.

12.2.5 Further therapy

No formal analysis of further therapy data will be performed; data will be listed and summarised. Kaplan-Meier plots of time to further therapy may produced if appropriate.

12.2.6 Safety data analysis

Safety data will not be formally analysed. All patients who commenced study treatment will be included in the assessment of safety and will be summarised by treatment received.

12.2.7 PK data analysis

The selumetinib, N-desmethyl selumetinib and metabolite concentration-time profiles, along with the derived PK variables, will be listed for each patient per dose and dosing day and summarised appropriately.

12.2.8 Genetics

Any genetic data analysis (other than *BRAF* and *NRAS*) will be reported outside the CSR for this study.

12.2.9 Biomarker data

BRAF and *NRAS* mutation assessment of tumour biopsy will be used to identify patients for this primary patient population.

The results of any other exploratory biomarker investigations will be reported outside of the CSR.

12.2.10 Interim analyses

There are no interim analyses planned for this study.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The primary objective of the study is to compare the efficacy of selumetinib with RAI versus placebo with RAI, by assessment of the complete remission rate at 18 months post-RAI treatment in the ITT study population. Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumentinib-containing arms, respectively, a total of 228 patients, randomised in a 2:1 ratio (152 and 76 patients in the selumentinib and placebo-containing arms, respectively) provides at least 80% power to show statistical significance, based on a two-sided 5% significance level.

12.4 Data monitoring committee

Due to the short treatment duration in this study there will not be a data monitoring committee for this study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.5.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Physician. If the Study Delivery Team physician is not available, contact the Study Delivery Team Leader.

Name	Role in the study	Address & telephone number
PPD	AstraZeneca Physician responsible for the protocol at central R&D site	PPD
PPD	AstraZeneca Study Delivery Team Leader responsible for the protocol at central R&D site	PPD
24-hour emergency cover at central R&D site.	24-hour emergency cover at central R&D site.	PPD

13.2 Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.5.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.5.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

The outcomes of any conception occurring from the date of the first dose, until 30 days after last dose, must be followed up and documented in the "Pregnancy Outcome Report" form.

Male patients must refrain from fathering a child for 12 weeks following the last dose of study treatment, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated. Restrictions from

fathering children should also take into account local recommendations following therapy with RAI.

Pregnancy of the patients' partner is not considered to be an AE. However, the outcome of all pregnancies (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

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Clinical Study Protocol Appendix B	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
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Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C	
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample

containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix D	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
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Appendix D

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. ACTIONS REQUIRED IN CASES OF AST OR ALT ≥ 3X ULN OR TBL ≥ 2X ULN

The Investigator is responsible for, without delay, determining whether the subject meets potential Hy's law (PHL) criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN **or** TBL ≥ 2x ULN, please follow the instructions below.

- Review each laboratory report and if a subject has an increase in AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit:
  - Notify the AstraZeneca representative
  - Promptly enter the laboratory date into the laboratory CRF.

1.2 Determination and Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the subject **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP

- Inform the AZ representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

1.2.2 Potential Hy's Law Criteria met

If the subject **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- Notify the AZ representative who will then inform the central ST

The Study Physician (SP) contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data.

The Investigator:

- Follows the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigates the etiology of the event and perform diagnostic investigations as discussed with the SP
- Completes the Liver CRF Modules.
- If at any time (in consultation with the SP) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

1.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

For the purpose of this process a Hy's Law case is defined as:

Any subject with an increase in both Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum Alkaline Phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug

If there **is** an agreed alternative explanation for the AST or ALT **and TBL** elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** other explanation that would explain the AST or ALT and TBL elevations:

- Report an SAE (report term Hy's Law') according to AZ standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

– As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

2. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm

Clinical Study Protocol Appendix E

Drug Substance	Selumetinib (AZD6244)
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Appendix E
Cockcroft-Gault Formula

COCKCROFT-GAULT FORMULA

The Cockcroft-Gault formula has been provided for reference, as the protocol allows for the serum creatinine clearance to be calculated using the Cockcroft-Gault formula (see Section 4.1, Inclusion criteria):

For serum creatinine values in µmol /L:

Estimated creatinine clearance rate (eCCr) (for men) = [(140 – age) x weight (kg) x 1.23] / creatinine (µmol/L)

eCCr (for women) = [(140 – age) x weight (kg) x 1.04] / creatinine (µmol/L)

For serum creatinine values in mg/dL:

eCCr (for men) = [140 – age] x weight (kg) / [72 x creatinine (mg/dL)]

eCCr (for women) = 0.85 x ([140 – age] x weight (kg) / [72 x creatinine (mg/dL)])

Reference: Cockcroft D, Gault MD. Nephron 16: 31-41, 1976.

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Clinical Study Protocol Appendix F	
Drug Substance	Selumetinib (AZD6244)
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Appendix F
Low Iodine Diet

LOW IODINE DIET

Published data and opinion regarding the necessity for a low iodine diet prior to RAI therapy or a diagnostic whole body scan is variable. For the purpose of this study a low iodine diet will be mandated in order to standardise patient care and study data as best as possible. Compliance to a low iodine diet will not be recorded or assessed, and all randomised patients will receive RAI treatment as planned.

A low iodine diet is necessary at two occasions in the study:

Prior to RAI adjuvant treatment

All patients must be willing to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI therapy.

Prior to the primary endpoint Stage 2 assessments

All patients must be willing to adhere to a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose used prior to the primary endpoint WBS assessment (^{131}I nuclear medicine scan), until the diagnostic WBS assessment is completed. This is only relevant for patients who progress to Stage 2 primary endpoint assessments (refer to Section 6.4.2 of the main protocol).

What is Iodine?

Iodine is a mineral. It plays an important role in several processes that take place in the body. One is the production of a hormone called thyroxine, which occurs in the thyroid gland.

Where is Iodine Found?

The amount of iodine found in food varies. Much of the iodine we get comes from iodized salt and breads. Adults need 150 micrograms of iodine a day. This appendix describes an example of a low iodine diet typically used in this treatment setting. This is a diet with less than 50 micrograms of iodine per day. A local low iodine diet may be used instead, as long as it is equivalent to this appendix.

Why is a Low Iodine Diet Necessary?

The iodine in your diet can block the uptake of radioactive iodine by the thyroid gland.

What Should You Avoid?

Read all food labels to check for iodine content. Do NOT eat or use:

- Iodized salt.
- Sea salt in any form.
- Onion salt.

- Celery salt.
- Garlic salt.
- Seasoned salt.
- Kelp (seaweed).
- Any food that has:
  - **Iodates**
  - **Iodides**
  - **Algin**
  - **Alginates**
  - **Carrageen**
  - **Agar**
- Commercial breads and bakery products, because they often contain iodate.
- Milk (except for 1 ounce a day), egg yolks, and seafood.
- Vitamins and food supplements if they have iodine. If you have any doubt, do not take them.
- Food, pills, or capsules with food dyes or that are orange, red, or brown in color. Examples include red or pink cereals or candies/sweets.
- Antiseptics, such as tincture of iodine (Betadine®) applied on a cut.
- Cough medicines (especially those with red coloring).
- Supplements such as:
  - **Ensure®**
  - **Boost®**
  - **Commercial shakes**
  - **Nutrament®**.

- Restaurant and processed foods, because they are often high in iodine content.
- Soy products such as edamame, tofu, soy burgers etc.
- All canned foods, because the lining of the can contains iodine.

Do not stop taking any of your medicines unless your doctor tells you.

Ask your doctor about drinking alcohol during a low iodine diet.

This low iodine diet does not meet the suggested daily allowance for all nutrients. You will be on it for a short time only.

Drink Plenty of Fluids

Note: Unless your doctor tells you differently, you must drink at least 8 to 10, 8-ounce cups of fluid a day. This includes the drinks in the diet guidelines and as much water as you want.

LOW IODINE DIET GUIDELINES

Breads and Cereals **Total number of servings per day:** 6-8 (1 serving equals 1 slice of bread or 1/2 cup of cooked pasta)	
Include	**Avoid**
Plain cooked barley, oats, millet, buckwheat, bulgur wheat, quinoa; unsalted unprocessed preservative-free boxed cereals such as puffed rice and shredded wheat; rice, plain macaroni, spaghetti, noodles; unsalted grits, cream of rice or cream of wheat hot cereals; unsalted rice cakes, unsalted plain crackers, English muffins, plain unsalted popcorn, homemade breads prepared without commercial dough.	All commercial breads and rolls, processed boxed cereals, salted crackers, potato chips/crisps, pretzels, bagels, Melba toast, egg noodles, packaged rice and pasta mixes.

Meat and Meat Substitutes **Total number of servings per day:** Two–three (1 serving equals 3 ounces of meat, fish, poultry, or 2 Tablespoons of unsalted peanut or almond butter)	
Include	**Avoid**
Fresh beef, veal, pork, lamb, chicken and turkey; unsalted peanut or almond butter; freshwater fish such as carp, riverbass, lake trout, and river perch; fresh egg white.	Egg yolks and whole eggs, foods made with eggs; all fast foods; all canned fish such as salmon and tuna; seafood, shellfish (clams, crabs, oysters, lobsters), or any food made with fish stock; all processed meats; liver and all organ meats; all canned, dried, salted, or cured meats such as bacon, sausage, ham, frankfurters, chipped beef, luncheon meats (salami, bologna, pastrami); spicy meats such as chili, beef jerky, liverwurst; all canned or processed poultry such as turkey or chicken roll; tofu and soy products, such as soy burgers (e.g., Boca); salted peanut butter.

Milk and Milk Products **Total number of servings per day:** Zero	
Include	**Avoid**
None allowed Exception: Only 1 ounce of milk a day in your coffee or tea.	All milk (except for one ounce daily) and milk products such as condensed or evaporated milk, cheese, yogurt, puddings, ice cream, custard; any cream such as heavy/double or light/single cream, whipped cream, sour cream; any foods made with cream or milk or cheese such as soup, pizza, macaroni and cheese.

Fruits **Total number of servings per day:** Five (1 serving equals 1 small piece of fruit or 3/4 cup of juice)	
Include	**Avoid**
All fresh fruit, exception: limit bananas to 1 serving per day; fresh apple sauce; all natural frozen fruits; fresh fruit juices (including bottles or cartons of fruit juice without artificial coloring or preservatives); white grape juice.	Cranberries, all dried fruits, all canned fruits and canned fruit juices; jarred applesauce; cranberry and grape juice, canned or bottled cherries; rhubarb.

Vegetables **Total number of servings per day:** Four (1 serving equals 1/2 cup of cooked or 1 cup raw vegetable)	
Include All fresh vegetables except spinach, fresh potatoes without skin, all plain frozen vegetables without added salt, fresh or dried lentils and peas.	**Avoid** All canned vegetables and all canned vegetable juices, fresh or dried beans such as red kidney beans, lima beans, navy beans, pinto beans; canned legumes (such as beans, peas, and lentils); canned soups; sauerkraut, celery; commercially prepared potatoes (e.g., instant mashed potatoes); frozen vegetables with added salt; spinach.

Fat **Total number of servings per day:** Suggest four to six servings a day (1 serving equals 1 teaspoon of butter or oil)	
Include Unsalted margarine or sweet butter **(not more than 1 teaspoon of each per day),** oils, vegetable shortening, plain oil and white vinegar dressing.	**Avoid** Salted nuts and seeds, mayonnaise, commercial salad dressings and salad cream, and lard.

Beverages **Total number of servings per day:** No restrictions One serving equals 12 ounces of a carbonated beverage or 1 cup (8 ounces) of any of the other beverages listed	
Include	**Avoid**
Water; bottled carbonated beverages without added coloring (such as Sprite®, 7Up®, sodium-free seltzer); brewed coffee, tea steeped from tea leaves; white tea bags; fresh lemonade or fresh orangeade.	Mineral water containing sodium; all bottled, canned, or powdered: iced tea, lemonade, instant coffee, instant tea, instant iced-tea, fruit punch, and other powdered or commercial drinks, such as Hi-C® and Kool-Aid®; tea steeped from tea bags; soy milk and rice milk (which contain sea salt); ginger ale, Coke®, Pepsi® or any other carbonated beverages with added coloring.

Desserts and sweets **Total number of servings per day:** Two (See below for serving equivalents)	
Include	**Avoid**
Each of the following equals 1 serving: • 1 cup Knox® or equivalent clear gelatin • 2 tablespoons (T) sugar • 2T honey • 2T maple syrup • 2 regular size marshmallows • 1/2 cup natural sorbets with no coloring or added salt	All bakery products such as pies, cakes, pastries, danishes, muffins, doughnuts and cookies; sweet crackers/biscuits; Jell-O® (or equivalent jelly), colored gelatins; chocolate and chocolate desserts; candy.

Miscellaneous **Total number of servings per day:** Unlimited	
Include	**Avoid**
Pepper, spices such as cinnamon; herbs such as oregano; white vinegar, and non-iodized salt (contains trace amounts of iodine, use sparingly).	All salted foods such as salted nuts, Chinese food, soy sauce, catsup, Worcestershire sauce, chili sauce, all commercial sauces, tomato sauce, all gravies, olives, pickles, relish, bouillon cubes, soup bases, iodized salt, sea salt, onion salt, garlic salt, celery salt, seasoned salt, kelp (seaweed); molasses; any food containing food coloring, iodates, iodides, iodate dough conditioners or stabilizers, algin, alginate, carrageens, agar, or nori (seaweed); all sushi; red wine vinegar, balsamic vinegar (with caramel coloring); all additives, preservatives, or artificial colorings.

EXAMPLE MENU FOR A LOW IODINE DIET

BREAKFAST

1 Fruit	½ cup orange juice
3 Breads	½ cup oatmeal (no milk) 1-2 plain unsalted cracker/crispbreads
1 Meat	1 egg white omelet
Misc.	2 teaspoons sugar
1 Beverage	1 cup brewed coffee

MID MORNING SNACK

1 Bread	2 rice cakes
1 Fat	1 teaspoon unsalted butter
1 Beverage	1 cup water

LUNCH

1 Meat	3 oz fresh turkey breast
2 Fats	2 tsp oil
2 Breads	2 slices homemade white bread
1 Vegetable	1 cup Romaine lettuce
1 Beverage	1 cup fresh lemonade

MID AFTERNOON SNACK

1 Fruit	1 fresh apple
1 Meat	2 tablespoons unsalted peanut butter

DINNER

1 Meat	3 oz roast beef
2 Breads	1 baked potato (no skin)
2 Vegetables	1 cup fresh broccoli
2 Fats	2 tsp oil (used in cooking)
1 Fruit	1 orange
1 Beverage	1 cup white tea

BEDTIME SNACK

1 Fruit	1 small pear
1 Beverage	1 cup tea made from fresh tea leaves

Clinical Study Protocol Appendix G	
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Appendix G
Guidance for Management of Adverse Events in Studies of Selumetinib

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1. GUIDANCE FOR THE MANAGEMENT OF PATIENTS WITH RASH

Recommendations to start on day 1 of treatment with selumetinib‡ and for the duration of treatment

- Use skin moisturiser (thick, alcohol-free) at bedtime
- Avoid excessive exposure to sunlight
- Use sunglasses/sunscreen (PABA-free, SPF ≥15; UVA and UVB protection) as needed
- Use of topical retinoids or benzoyl peroxide is not recommended

CTC Grade 1 rashes

Mild or moderate strength topical steroid

and/or topical antibiotic

CTC Grade 2 rashes

Moderate strength topical steroid

and oral antibiotic

CTC grade ≥3 rashes
CTC grade 2 rashes considered by the patient to be intolerable

Moderate strength topical steroid

and oral antibiotic
(consider broad spectrum/Gram negative cover if infection suspected)

Consider referral to a dermatologist: manage rash per recommendation

Interrupt selumetinib‡ until rash improves to grade 2 or less

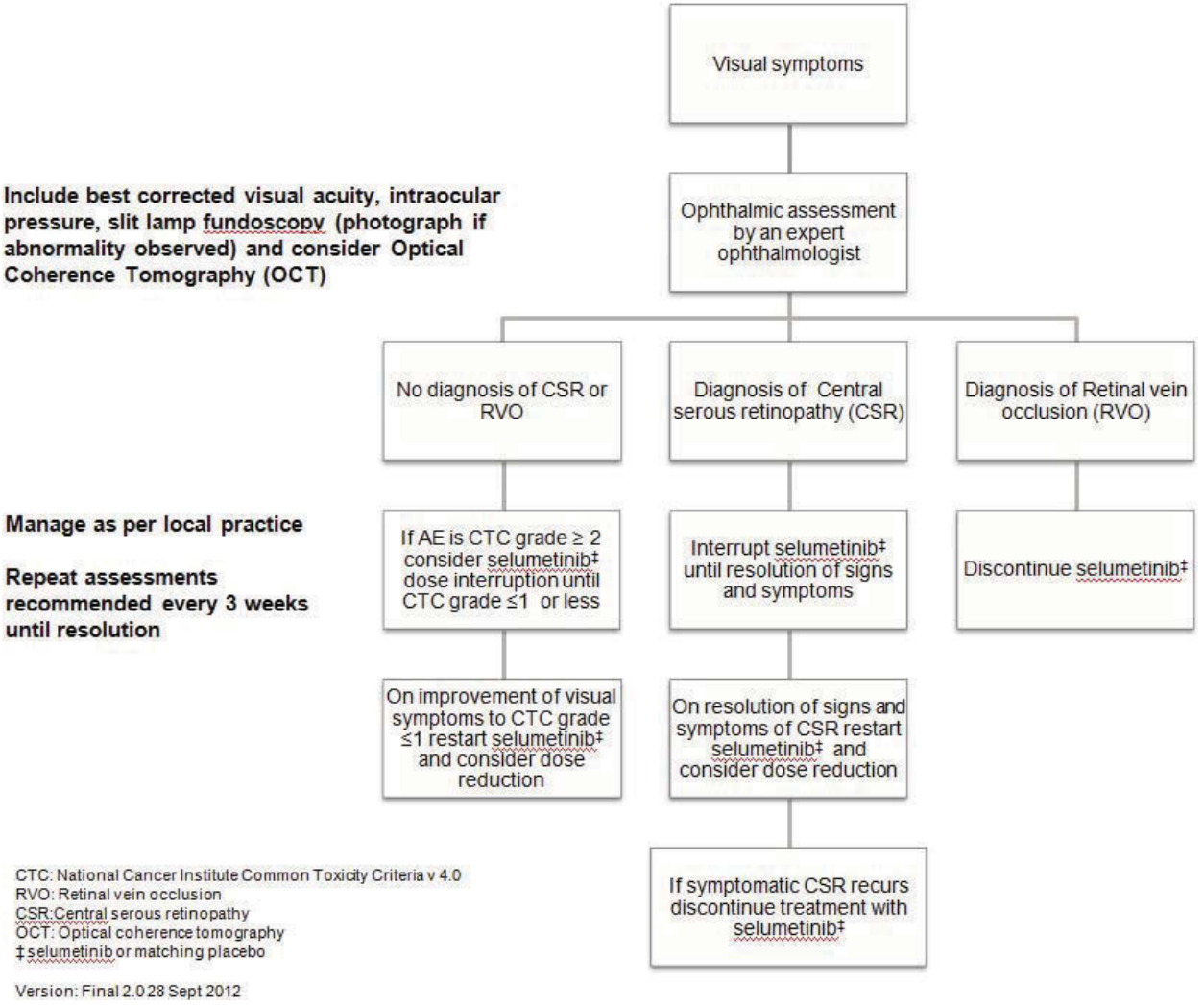
Selumetinib‡ may be restarted at original dose or reduced at the discretion of the investigator

‡ selumetinib or matching placebo
Version: Final 2.0 28Sep2012

Table 1 Example topical steroids and antibiotics (use according to local guidelines)

Topical steroids moderate strength	Triamcinolone acetonide 0.025% Fluticasone proprionate 0.05% Desonide 0.05% Aclometasone 0.05%
Topical antibiotics	Clindamycin 1 - 2% Metronidazole 1% Erythromycin 1% - 2% Silver sulphadiazine 1%
Oral antibiotics	Doxycycline 100 mg bd Minocycline 100 mg bd Oxytetracycline 500 mg bd

2. GUIDANCE FOR MANAGEMENT OF PATIENTS WITH VISUAL SYMPTOMS



3. RECOMMENDATIONS FOR DIARRHOEA MANAGEMENT

Diarrhoea may occur during treatment with selumetinib (AZD6244) and action should be taken as soon as symptoms develop. The recommendations for diarrhoea management are based on guidelines from the American Society of Clinical Oncology (J Clin Oncol 2004; 22:2918-26). These guidelines recommend that treatment-induced diarrhoea should be carefully monitored and treated aggressively to ensure that severe complications are avoided and that treatment is not delayed.

- Patients should be made aware that they may experience diarrhoea and be encouraged to record the number of stools and report possible associated symptoms
- Patients should be given loperamide (in accordance with local regulation and local practice) to take home with them and be advised to start immediately after the first episode of unformed stool.
- Patients should be given dietary advice in case of diarrhoea (eg. BRAT [bananas, rice, apple sauce, toast, plain pasta] diet; readily digestible food; avoidance of lactose-containing products, fried, fatty or spicy food) and increase fluid intake (8 to 10 glasses of clear fluids daily, including water and fluids containing salt and sugar, such as sports drinks and clear broth).
- Patients should seek advice early, from their physician or study nurse, if:

  (a) Persistent Grade 1 or 2 diarrhoea (refer to Section 3.2), or

  (b) Grade 3 or 4 diarrhoea, or

  (c) Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension.

Table 2 CTCAE (version 4) grading for diarrhoea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 1	Increase in number of stools per day (<4)	Mild increase in loose watery colostomy output compared with pre-treatment
Grade 2	Increase in number of stools per day (4-6) or nocturnal episodes	Moderate increase in loose watery colostomy output compared with pre-treatment, not interfering with normal activity
Grade 3	Increase of more than 7 stools per day or incontinence or needing support for dehydration.	Severe increase in loose watery colostomy output compared with pre-treatment and interfering with normal activity

Table 2 CTCAE (version 4) grading for diarrhoea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 4	Life-threatening consequences (eg, hemodynamic collapse)	

3.1 Initial management of uncomplicated Grade 1 or 2 diarrhoea

- Patients should immediately start loperamide after the first episode of diarrhoea (4 mg initially) and continue loperamide (2 mg every 4 hours or after each unformed stool) until they have been free from diarrhoea for at least 12 hrs
- If after 12 hours of loperamide treatment the diarrhoea is not improving or resolved, the patient should be instructed to contact the centre and to increase to high dose loperamide (2 mg every 2 hours, or 4 mg every 4 hours at night) and continue to take loperamide until they have been free from diarrhoea for at least 12 hrs. Additional treatment may be considered according to local practice.

3.2 Management of persistent (>24h) Grade 1 or 2 diarrhoea despite loperamide at high dose

The patient should be seen by the physician or study nurse for full evaluation and the following should be considered:

- Rehydration and electrolytes replacement as appropriate
- Infectious causes and aetiologies such as Clostridium difficile or viral gastroenteritis;
- Antibiotics if appropriate (for example an oral fluroquinolone for 7 days) particularly if the patient is neutropenic ($<1 \times 10^9$/L) or has a fever;
- Discontinuation of loperamide and start of octreotide (Sandostatin);

It may also be appropriate to consider:

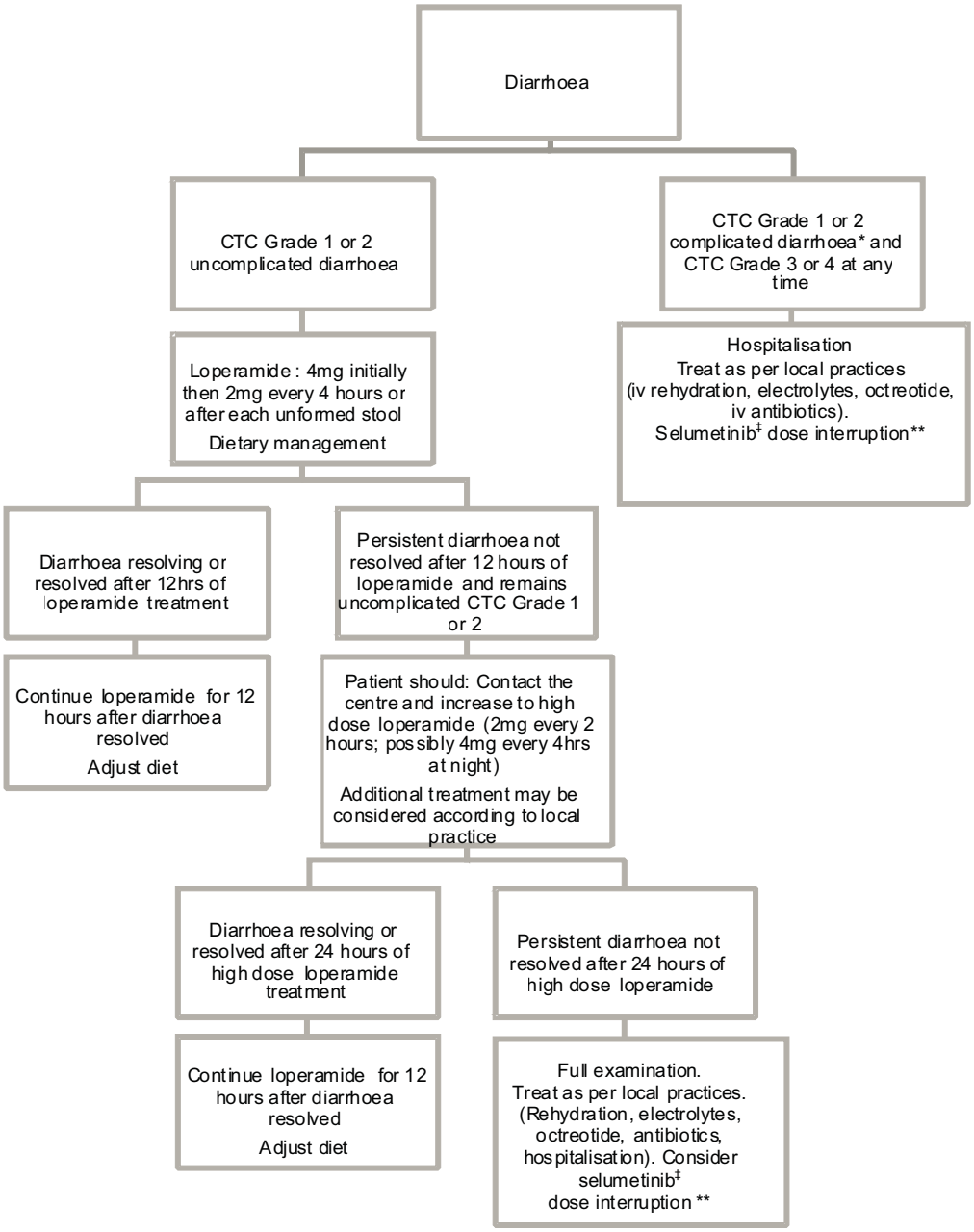
- Addition of other second-line anti-diarrhoeal agents according to local practice
- Selumetinib (or matching placebo) interruption until resolution of the diarrhoea
- Hospitalisation

3.3 Management of any grade uncontrolled or complicated diarrhoea, or Grade 3-4 diarrhoea

- Hospitalisation and full evaluation,

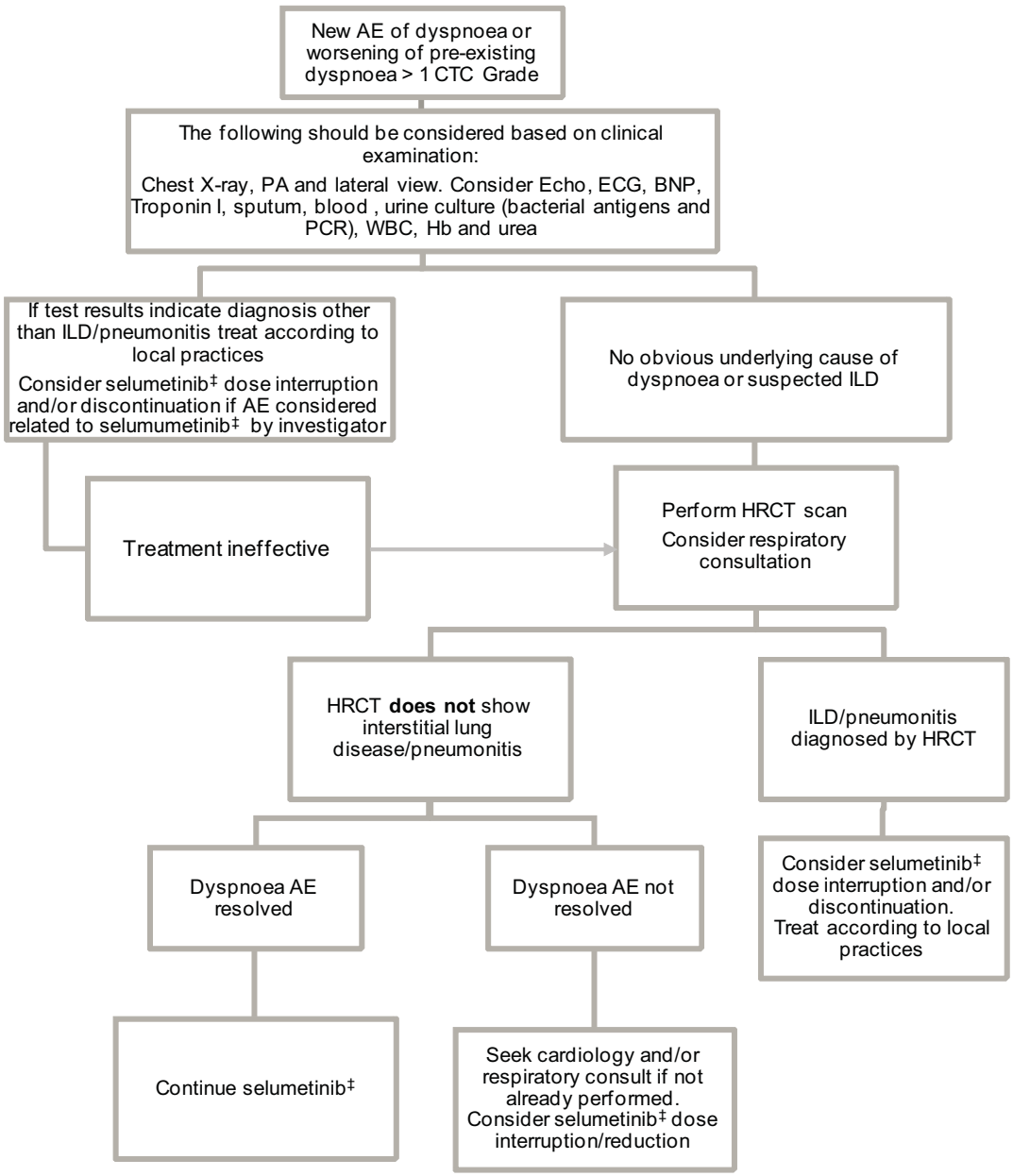
- Intravenous fluids, electrolytes and antibiotics if needed (eg. fluroquinolone)
- Interrupt selumetinib (or matching placebo) until diarrhoea and associated symptoms resolve
- Start octreotide (Sandostatin).
- In studies involving combination of selumetinib (or matching placebo) with other anti-cancer treatment, interruption or delay of the combination agent may be considered according to manufacturer's guidance or local practice.

Figure 1 Guidance for the management of patients with diarrhoea



*Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension
****Consider interruption or delay of combination anticancer agent if applicable**
‡ selumetinib or matching placebo
Document version: Final 2.0 28Sept2012

4. RECOMMENDATIONS FOR INVESTIGATIONS OF PATIENTS WITH A NEW OR WORSENING DYSPNOEA



BNP: Brain Natriuretic Peptide
CTC: National Cancer Institute common toxicology criteria
Echo: Echocardiography
Hb: Haemoglobin
HRCT: High resolution computerised tomography
‡ selumetinib or matching placebo

ILD: Interstitial Lung Disease
PA: posteroanterior
PCR: Polymerase chain reaction
WBC: White blood cells
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AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
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A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative PPD PPD

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
3	01 July 2014		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Randomised, Double Blind Study to Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer

International Co-ordinating Investigator

PPD

Study centre(s) and number of patients planned

Approximately 228 patients with newly diagnosed differentiated thyroid cancer at high risk of primary treatment failure will be recruited from approximately 50 sites in Europe, South and/or North America.

Objectives

Primary objective

To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in the intention to treat (ITT) study population. Complete remission is defined in Section 6.4.1.

Secondary objectives

To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the ITT study population. Clinical remission is defined in Section 6.4.6.

To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

Exploratory objectives

To explore subsequent thyroid cancer therapy given to patients who receive selumetinib with RAI, or placebo with RAI.

To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters.

To collect tumour, plasma and serum samples for potential future research on biomarkers relevant to DTC and response and resistance to study treatments.

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib or RAI and/or susceptibility to cancer.

Study design

This is a double-blind, randomised, placebo-controlled study comparing the efficacy of a short course (approximately 5 weeks) of selumetinib (75 mg, orally twice daily) with adjuvant RAI, to placebo with RAI.

Following recovery from surgery (1 or 2-stage total thyroidectomy), and screening to determine study eligibility, patients will be randomised and will take their assigned study treatment (selumetinib or placebo) twice daily for a period of approximately 5 weeks. Study treatment will begin approximately 4 weeks prior to the planned day of single dose RAI therapy, and will be continuous until 5 days following RAI therapy. Patients will be required to adhere to a standardised low iodine diet prior to their RAI therapy. For each of the 2 days immediately prior to their planned RAI therapy, patients will receive a 0.9 mg intramuscular (IM) recombinant human TSH injection (rhTSH, Thyrogen), in order to stimulate iodide uptake (patients or clinicians choosing to prepare for RAI ablation by withdrawal of thyroid hormone treatment will be ineligible for this study). Following the 2 consecutive days of rhTSH injections, patients will receive their planned RAI therapy as a fixed single 100 mCi (3.7 GBq) dose of ^{131}I the immediate next day. Study treatment will be taken as normal on the day of RAI therapy, and will be discontinued 5 days following the patient's RAI therapy.

Following RAI therapy, each patient will be followed up for a period of 18 months until the primary endpoint assessment of complete remission. The biochemical analysis contributing to the 18 month primary endpoint of complete remission will be performed by standardised central methodology, and the radiological imaging for structural disease at the primary endpoint will be subject to a blinded independent central review. Additional thyroid cancer therapy (eg, surgery or RAI treatment) must only be given during the 18 month primary endpoint follow up period according to the pre-specified study re-treatment criteria (refer to Section 5.9). Patients who do receive re-treatment in the 18 months following their initial RAI

therapy, will not have any 18 month primary endpoint assessments performed; they will remain in the study and enter standard of care follow up according to local practice.

Following the primary endpoint assessments (or re-treatment), all randomised patients will be further followed-up at 3 years after their initial RAI treatment, in order to further assess both the clinical status of patients, and the safety profile of selumetinib and RAI beyond the primary analysis (refer to Section 6.4.8).

Target patient population

Patients with histologically or cytologically confirmed follicular cell derived differentiated thyroid cancer (including papillary thyroid cancer and all variants, follicular thyroid cancer and all variants, and poorly differentiated thyroid cancer), who are determined to be at high risk of primary treatment failure, as defined by any one of the following staging categories post-surgery:

- Primary tumour greater than 4 cm
- Primary tumour of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)
- N1a or N1b disease with at least 1 lymph node ≥ 1 cm
- N1a or N1b disease involving 5 or more lymph nodes (of any size)

Patients with known distant metastatic disease will be excluded from this study.

Investigational product, dosage and mode of administration

Selumetinib Hyd-Sulfate (75 mg) will be administered orally twice daily as capsules (blue). The Hyd Sulfate formulation will be used in this study, and unless otherwise specified is the formulation referenced throughout this document.

Comparator, dosage and mode of administration

Placebo (to match selumetinib) will be administered orally twice daily.

Duration of treatment

The duration of study treatment (selumetinib/placebo) will be approximately 5 weeks in total (Day 36 will typically be the last day of study treatment, but this may be extended to a maximum of 43 days to allow the planned RAI to be postponed by up to 1 week if absolutely necessary).

Outcome variable(s):

Efficacy

The primary outcome variable for this study is the rate of complete remission at 18 months post-RAI treatment. Patients will be defined to be in complete remission if all of the following criteria can be demonstrated:

1. Serum thyroglobulin (Tg) levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer[a] by neck US, as assessed by investigator site review.

3. No confirmed radiological evidence of thyroid cancer[a], as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

[a]Confirmation of evidence of structural DTC will be either histopathological (from a biopsy/FNA; as criterion 4 above), or RAI-avid disease (refer to Section 6.4.4.2). In this disease setting, structural abnormalities that are not RAI-avid and do not have confirmed histopathology consistent with DTC (ie are not biopsy proven) are considered benign in the absence of biochemical DTC.

A secondary outcome variable will be the rate of clinical remission at 18 months post-RAI treatment, where clinical remission is defined on the basis of Tg, US and WBS assessments alone, without the additional radiological data.

Safety

AEs/SAEs, physical examination results, lab values, ECG, vital signs.

All randomised patients will be followed for safety monitoring for 3 years following their RAI adjuvant treatment, in order to monitor for selumetinib and RAI-associated side effects.

PK

Where sample collection and PK analysis allow, derived PK parameters for selumetinib and N-desmethyl selumetinib will be produced which may include, but not be restricted to, C_{max} and AUC. Exploratory variables will be analysed outside the clinical study report (CSR).

Statistical methods

Approximately 228 patients will be randomised in a 2:1 ratio in this study. The primary analysis will be performed when patients have been followed for 18 months following their RAI treatment. The primary analysis population will comprise all randomised patients (ITT population) and the primary endpoint of complete remission rate at 18 months will be analyzed using a logistic regression model including treatment as the only covariate. Results will be presented in terms of the odds ratio, 95% confidence interval and associated p-value. Logistic regression modelling including treatment and covariates histology status, mutation status and age, will be performed as sensitivity analyses provided there are enough data points for a meaningful analysis.

Assuming the true complete remission rates in the ITT study population are 30% and 50% for the placebo and selumetinib-containing arms, respectively, the study will have at least 80% power to demonstrate a statistically significant difference at the 5% (2-sided) significance level.

All secondary endpoints will be analysed at the time of the primary analysis. Exploratory biomarker analysis may be analysed after the time of the primary analysis and reported separately to the CSR (apart from the somatic genetic data required for analysis of the second primary endpoint).

All randomised patients will continue to be followed until the final study visit (3 years after their RAI treatment). At this time, data on clinical status, incidence of re-treatment and long-term safety will be summarised.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
^{124}I	Iodine-124
^{131}I	Iodine-131 (radioactive iodine; RAI)
AE	Adverse event (see definition in Section 6.5.1)
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatise
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATA	American Thyroid Association
ATC	Anaplastic thyroid cancer
AUC	Area under the plasma concentration-time curve from zero to infinity
BD	Twice daily (dosing)
bid	*bis in die* – twice a day
BNP	B-type natriuretic peptide
BP	Blood pressure
Bpm	Beats per minute
BRAF	v-raf murine sarcoma viral oncogene homolog B1
cm	centimetres
C_{max}	Maximum plasma concentration
CRF	Case report form (electronic/paper)
CR	Clinical remission
CR	Complete remission
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
DAE	Discontinuation of investigational product due to adverse event
DNA	Deoxyribonucleic acid
DTC	Differentiated thyroid cancer
D-TC-FCO	Differentiated thyroid carcinoma of follicular cell origin

Abbreviation or special term	Explanation
DUS	Disease under study
EBRT	External beam radiation therapy
EC	Ethics committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ERK	Extracellular signal-regulated kinases
ETA	European Thyroid Association
FDG-PET	2-[F-18]-fluoro-2-deoxy-D-glucose positron emission tomography
FNA	Fine needle aspiration
FSH	Follicle stimulating hormone
FTC	Follicular thyroid cancer
G1	Gap 1 phase of the cell cycle
GCP	Good clinical practice
g/dL	grams per decilitre
GMP	Good manufacturing practice
hr	hour
I	Iodine
IATA	International Air Transport Association
IB	Investigator brochure
ICH	International Conference on Harmonisation
ICH M3	The European Medicines Agency's International Conference on Harmonisation Topic M3 – "Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals"
IM	Intramuscular
INR	International normalised ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational product
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravascular
IVRS	Interactive voice response system

Abbreviation or special term	Explanation
IWRS	Interactive web response system
kg	kilograms
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LH	Luteinizing hormone
LIMS	Laboratory information management system
LLOQ	Lower limit of quantification
LSLV	Last patient last visit
LT4	Synthetic levothyroxine
LV	Left ventricular
LVEF	Left ventricular ejection fraction
M0, M1, Mx	Distant metastasis status (TNM cancer staging system)
MAPK	Mitogen-activated protein kinase
mCi	millicuries
MedDRA	Medical dictionary for regulatory activities
MEK	MAPK/ERK kinase
MI	Myocardial infarction
µg/L	micrograms per litre
µm	micrometers
mIU/L	milli-International units per litre
mg	milligrams
mg/day	milligrams per day
mL	millilitres
mL/min	millilitres per minute
mm	millimetres
mm^3	cubic millimetres
ms	milliseconds
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
N0, N1, Nx etc	Lymph node disease stage (TNM cancer staging system)
N/A	Not applicable
ng/mL	nanograms per milliliter

Abbreviation or special term	Explanation
NIS	Sodium iodide symporter
NOEL	No observed effect level
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase, receptor, type 1
NYHA	New York Heart Association
OAE	Other significant adverse event (see definition in Section 6.5)
PDTC	Poorly differentiated thyroid carcinomas
PET	Positron emission tomography
PFS	Progression-free survival
PGx	Pharmacogenetic research
PI	Principal investigator
PK	Pharmacokinetics
PRO	Patient reported outcomes
PTC	Papillary thyroid cancer
RAI	Radioactive iodine (^{131}I)
RET	Ret proto-oncogene
Rb	Retinoblastoma protein
RECIST	Response Evaluation Criteria In Solid Tumours
rhTSH	Recombinant human thyroid stimulating hormone
SAE	Serious adverse event (see definition in Section 6.5.2).
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBE-CD	Sulphobutylether β-cyclodextrin
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standard uptake value
T0, T1, Tx etc	Primary tumour disease stage (TNM cancer staging system)
T4	Free thyroxine
Tg	Thyroglobulin
TgAb	Thyroglobulin antibody
TNM	Tumour, nodes, metastasis cancer staging system
TPGS	D-α tocopheryl polyethylene glycol 1000 succinate

Abbreviation or special term	Explanation
TPO	Thyroid peroxidase
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	Ultrasound
WBDC	Web based data capture
WBS	Whole body scintigraphy (also whole body scan)
WHO	World Health Organisation
Wk	Week

1. INTRODUCTION

1.1 Background

1.1.1 Thyroid Cancer

There are approximately 56,500 new cases of thyroid cancer diagnosed in the USA per year, and approximately 34,000 new cases diagnosed in Europe per year. Thyroid cancers are classified according to their histopathological characteristics into 4 main variants: papillary thyroid cancer (PTC, the most common), follicular thyroid cancer, medullary thyroid cancer and anaplastic (undifferentiated) thyroid cancer. The papillary and follicular types together can be classified as differentiated thyroid cancer (DTC), and make up approximately 95% of thyroid cancers. All DTC (including PTC) begins in the follicular cells of the thyroid gland and is termed "of follicular cell origin." Other, rarer variants of thyroid cancer of follicular cell origin include Hürthle cell carcinoma and poorly differentiated thyroid cancer (PDTC). DTC is generally indolent and has a natural history which is measured in decades if treated appropriately (up to 95% 10 year survival). However there are very limited options for patients who ultimately fail radioactive iodine therapy and develop distant refractory metastases, and most of these patients will succumb to their disease (Durante et al 2006).

1.1.2 Radioactive iodine treatment

In addition to primary thyroid surgery, radioactive iodine (RAI, ^{131}I) is the mainstay of therapy for patients with thyroid cancer of follicular origin. It is a targeted therapeutic approach that exploits the expression of the sodium iodide symporter (NIS) to deliver radiation selectively to thyroid cells, which is used as adjuvant therapy after thyroidectomy, and to treat recurrent and metastatic disease.

Most patients with thyroid cancer of follicular origin have differentiated carcinomas which retain at least to some extent the biological properties of normal thyroid cells, including expression of NIS. Presence of this transporter is required for iodine uptake (Riesco-Eizaguirre et al 2006).

Following diagnosis, surgical resection of the thyroid gland with or without removal of the local lymph nodes is performed. Following surgical resection, a set of clinical-pathologic data (such as age at diagnosis, specific histological type, size of the primary tumour, extent of lymph node metastases, presence of distant metastases, gross extrathyroidal extension and completeness of resection) can be used to estimate the risk of recurrence and the risk of disease specific mortality. After surgery, radioactive iodine can be used for the following purposes:

For diagnostic scanning to improve initial staging and extent of disease assessment.

For ablation of the normal thyroid remnant (usually less than 2-3% of normal tissue remains after total thyroidectomy). This treatment facilitates follow-up by achieving an undetectable level of serum thyroglobulin and a subsequent negative diagnostic whole body RAI scan.

As adjuvant therapy, in an attempt to destroy microscopic residual disease in patients at intermediate to high risk of recurrence.

As primary therapy in patients with unresectable RAI-avid loco-regional disease or distant metastases.

Uptake of RAI by tumour tissue is a prerequisite for administration of RAI treatment and for its efficacy. Once patients develop distant metastatic disease, RAI uptake is observed in only two thirds of cases and less frequently in patients with aggressive disease (Durante et al 2006, Mazzaferri and Kloos 2001, Nemec et al 1979, Samaan et al 1985). Patients with no uptake in metastatic foci are considered refractory to RAI, which is then no longer indicated.

1.1.3 Risk stratified remission rates following RAI treatment

Several different risk stratification systems have been published for DTC. The Union Internationale Contre le Cancer/American Joint Committee on Cancer (AJCC) staging system is the most commonly used, but it was developed to predict the risk of death rather than recurrence. To overcome this limitation, the American Thyroid Association (ATA) published guidelines to grade the risk of recurrence into 3 categories (low, intermediate, and high) based on tumour-related parameters (pathological tumour-node-metastasis and histological variant) integrated with other clinical features, including the result of the first post-therapy RAI whole-body scan and serum Tg measurement. Although the ATA risk stratification system has been shown to better predict short-term clinically relevant endpoints of persistent and recurrent disease than the AJCC system, it does not adequately predict longer-term outcomes because the risk of persistent or recurrent disease changes following initial therapy. In addition, the ATA intermediate risk category includes a wide variety of potential risk factors that can have a significant influence on both short term and long-term outcomes (any tumour size, N1a/N1b node status, vascular invasion, extrathyroidal extension, aggressive histology).

Recent evidence suggests that the likelihood of achieving remission varies depending on the size of the primary tumour, extent of invasion, or lymph node status as defined by number and size of affected nodes (refer to Table 1, Tuttle, unpublished sub-analysis of data from Tuttle et al 2010 and Vaisman et al 2012).

Table 1 Remission rates in 2 independent data sets of risk-categorised patients with differentiated thyroid cancer - based on tumour size and lymph node status

TNM status	Description	Remission rate[a] MSKCC[b] n=588 patients	Remission rate[a] Brazil[c] n=506 patients
T1	Tumour diameter 2 cm or smaller	40%	59%
T2	Tumour diameter 2 - 4 cm	47%	52%
T3	Tumour diameter > 4 cm or with minimal extrathyroidal extension	25%	37%
T4	Tumour of any size extending to invade subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia or encasing carotid artery or mediastinal vessels	13%	17%
N0	No metastatic nodes identified	62%	54%
N1a	Metastatic nodes in central neck (pretracheal, paratracheal, or prelaryngeal)	31%	30%
N1b	Metastatic nodes in lateral neck or superior mediastinum	16%	12%

[a] Remission rate within a 2 year follow up period
[b] unpublished sub-analysis of data from Tuttle et al 2010
[c] unpublished sub-analysis of data from Vaisman et al 2012

As can be seen patients with either T3 disease or N1a disease have remission rates that approximate 30%, while patients with T4 disease or N1b disease have remission rates that approximate 15%. From a clinical perspective, these findings are not surprising since T3 disease is very commonly associated with N1a disease, and T4 disease is often associated with N1b disease. Therefore, the similarity in remission rates in T3 and N1a disease, and in T4 and N1b disease, is consistent with observations in clinical practice.

It is important to note that in addition to the location of the lymph node metastases (N1a vs. N1b), the extent of lymph node metastases (size and number of involved nodes) is also a critical factor in assessing the risk of recurrence and risk of failing initial therapy (Randolph et al, 2012, Ricarte-Filho et al 2012). The complete remission rates from the MSKCC and Brazilian cohorts are based on patients with clinically significant, structurally evident N1a and/or N1b disease that required therapeutic neck dissections for clinically apparent metastatic disease (prophylactic neck dissections to remove sub-clinical disease were not performed in either the MSKCC or Brazilian cohorts). For example, in a MSKCC series of 246 papillary thyroid cancer patients who presented with lymph node metastases at the time of diagnosis, a median of 6 metastatic lymph nodes were identified with a median maximal diameter of 1.3 cm (Ricarte-Filho et al 2012). Furthermore, multiple studies have demonstrated that small volume lymph node metastases which are usually identified as incidental findings in the fibroadipose tissue surrounding the thyroid, or as a result of prophylactic central neck dissections, are associated with a low risk of recurrence (Randolph et al, 2012, Ricarte-Filho et al 2012), and these may not even require RAI adjuvant therapy (and therefore would not be

appropriate subjects for the proposed study). Therefore, to prevent patients with lower risk N1a or N1b small volume metastatic disease from enrolling into this study, a requirement is that subjects must have N1a or N1b disease involving 5 or more lymph nodes (of any size) or at least 1 lymph node ≥ 1 cm in the largest diameter.

Since only approximately 30% of patients presenting with any of the following features are expected to achieve clinical remission following total thyroidectomy and RAI remnant ablation, they are at high risk of failing their primary treatment:

- Primary tumour greater than 4 cm
- Primary tumours of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)
- N1a or N1b disease with at least 1 lymph node ≥ 1 cm
- N1a or N1b disease involving 5 or more lymph nodes (of any size)

Total thyroidectomy and RAI ablation is therefore very effective at inducing remission in low risk patients, however approximately 70% of patients with the above characteristics do not enter remission, and have an incomplete response to initial therapy with biochemical and/or structural evidence of persistent disease.

1.1.4 The benefits of achieving remission

Thyroid cancer deaths are exceedingly rare if remission is achieved, and studies have shown that nearly all deaths ultimately occur in the group of patients who do not achieve remission. For example, two recent studies reported disease-specific deaths in 6% and 8% of the patients who did not achieve remission compared to 0% in patients who achieved remission with median follow-up times of 7 and 10 years respectively (Tuttle RM, unpublished sub-analysis of data from Tuttle et al 2010, Vaisman et al 2012). This mortality rate continues to rise with longer periods of follow up with nearly all deaths from thyroid cancer being seen in the cohort of patients that failed to achieve remission.

The importance of a successful initial therapy is demonstrated by the excellent prognosis that even high-risk patients have if therapy results in negative imaging and negative thyroglobulin levels after stimulation by TSH. The majority of patients who achieve remission do not relapse; recurrence rates are typically 1% to 4% over median follow-up periods of 5 to 10 years for patients who achieve remission (Castagna et al 2011, Tuttle et al 2010, Vaisman et al 2012).

In patients that achieve remission, there are important clinical and psychological benefits. Patients that achieve remission are re-classified as low risk patients and require much less frequent follow-up. Thyroglobulin testing and imaging assessments are reduced in frequency, and less aggressive TSH suppressive therapy is required. This in turn reduces the longer-term risks of osteoporosis and atrial fibrillation that are known complications of supra-

physiological dosing of levothyroxine, and reduces the anxiousness and fatigue that can result from the mildly hyperthyroid state caused by TSH suppression.

If remission is not achieved with initial therapy, many patients will be subjected to additional therapies (eg, more RAI, surgery, external beam irradiation), in an effort to control disease progression and achieve a cure. Therapeutic RAI is associated with a cumulative dose-related risk of early and late-onset complications such as salivary gland damage, dental caries, nasolacrimal duct obstruction, and decreased fertility (Cooper et al 2009). Furthermore, a dose-dependent relationship is also seen between cumulative administered RAI activity and the subsequent occurrence of secondary malignancies (Rubino et al 2003, Sawka et al 2009). All of these risks and symptoms constitute significant quality of life issues for the patient. The inconvenience of repeating a low iodine diet, the associated radiation safety precautions and missed days of work are additional factors the patient must consider. Additional surgery carries associated risks related to anesthesia, nerve damage (resulting in hoarseness, permanent tracheotomy in rare occasions, drooping eye lid, loss of control of shoulder muscles and loss of sensation in the neck), increased scarring in the neck (resulting in discomfort and difficulty swallowing), and damage to the parathyroid glands (resulting in hypocalcemia and a lifetime need for vitamin D and calcium supplementation and frequent blood tests). Thus avoidance of further therapy is beneficial to the patient.

Unfortunately, additional therapy is often less effective, particularly in patients with persistent structural disease (Vaisman et al, 2011). Further RAI can be given to patients that have persistent biochemical evidence of disease, and although repeat RAI is often less effective than the initial RAI treatment (especially for patients with persistent structural disease), it can be effective at driving some patients with persistent biochemical disease into remission. Thus, strategies designed to improve the tumouricidal effect of the initial RAI dose should result in higher remission and cure rates.

An intervention that enhances the effectiveness of initial therapeutic RAI in higher risk patients (the target population for this study), should result in higher remission rates and remove the need for further therapy, and would thus be of clear benefit to patients.

1.1.5 Selumetinib

Selumetinib is a potent, selective, noncompetitive inhibitor of MEK, licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma. Selumetinib was discovered by Array Biopharma and had the designation ARRY 142886. Other laboratory code names used during the development of this molecule are AR00142886 and AR-142886-X (where X refers to a sequential lot number). Array BioPharma was responsible for the first-into-human study; the remainder of the clinical development programme for oncology indications is the responsibility of AstraZeneca. AZD6244 has now been assigned the international non-proprietary name selumetinib.

1.1.5.1 MEK and NIS expression

Papillary thyroid cancer (PTC), which is the most common form of the disease, is characterised by a set of genetic alterations, all of which result in the activation of

RAF/MEK/ERK signalling. Of these genetic lesions the most common is the typical V600E mutant of *BRAF* also found in other cancers, most notably melanoma. The other genetic lesions occur in receptor tyrosine kinases (RET and NTRK1), and in *RAS* (*N* and *HRAS*). In total these mutations in effectors of ERK signalling account for approximately 70% of papillary thyroid cancer (Kimura et al 2003, Soares et al 2003). *BRAF* itself is seen in at least 38% of PTC, and is also found in poorly differentiated and anaplastic thyroid carcinomas with a prevalence of 12% and 50%, respectively (Nikiforova et al 2003, Ricarte-Filho et al 2009). These genetic mutations are mutually exclusive and suggest the importance of RAF/MEK/ERK signalling in papillary thyroid cancer.

With regard to the impact on efficacy of RAI therapy, one of the primary effects of activation of the RAF/MEK/ERK signalling pathway is a significant and sustained down regulation of the sodium iodide symporter (NIS) which is responsible for the uptake of iodine into thyroid cells and is required for the uptake of therapeutic ^{131}I into thyroid cancer cells. Studies have demonstrated that the expression of NIS (and other genes typical of differentiated thyroid cells) is suppressed by activation of RAF/MEK/ERK signalling in mouse models of the disease (Franco A et al. 2011). In mice engineered to express V600E *BRAF* in thyroid cells, expression of NIS and other thyroid differentiation markers is reduced (Knauf et al 2005). These mice develop papillary thyroid cancers with dedifferentiated features. Further data using a mouse model of thyroid-specific inducible expression of V600E *BRAF*, show that V600E *BRAF* activation suppresses expression of NIS, thyroid peroxidase (TPO) and thyroglobulin (Tg), and blocks ^{124}I uptake, all of which are re-established once expression of oncogenic *BRAF* is turned off. Treatment of mice expressing the induced V600E *BRAF* with a MEK inhibitor also re-established NIS expression and ^{124}I uptake in the poorly differentiated thyroid carcinomas (PDTC) (Chakravarty D et al 2011). Constitutive activation of MAPK signalling also inhibits the expression of thyroid peroxidase and thyroglobulin in BRAF-induced murine thyroid cancers. Genetic or pharmacological blockade of the pathway restores their expression, and consequently the ability to incorporate iodine into tyrosine (iodine organification), which is associated with greater retention time of ^{131}I in cancer cells (Chakravarty D et al 2011). Other MAPK activating alterations common to thyroid cancer can also cause de-differentiation. Over-expression of either the G12V *HRAS* mutant or *RET/PTC* in thyroid cancer cells suppresses NIS, thyroglobulin and thyroid peroxidase expression, which is restored with MEK inhibitor treatment (Knauf et al 2003, De Vita et al, 2005). These experiments provide a pre-clinical proof of concept that inhibition of ERK signalling by MEK inhibitors can reverse the suppression of NIS, TG and TPO expression and re-establish iodine incorporation into PTC.

NIS expression in clinical thyroid cancer samples

Analysis of clinical tumour samples for NIS expression indicates a relative loss of NIS expression (and the expression of other thyroid specific genes) relative to normal thyroid tissue (Durante et al 2007; Espadinha et al 2009). Furthermore, NIS expression is lower in *BRAF* mutant tumours than in those without *BRAF* mutation (Durante et al 2007; Morai et al 2011; Romei et al 2008). In a well differentiated rat thyroid cell line model, expression of RET/PTC, mutant HRAS, or constitutively active MEK1, blocked TSH-induced expression of Tg and NIS; an effect that was reversed by MEK inhibition. These data are consistent with

the hypothesis that activation of MEK, regardless of the upstream activating mutation is a key factor in the loss of thyroid differentiation specific gene expression including NIS (Knauf et al 2003).

In summary, this data predicts that both an unselected and genetically selected population may benefit from treatment with a MEK inhibitor and RAI. This study will thus assess two populations for the primary endpoint of complete remission rate at 18 months; the genetic 'all comer' population, and also a population of patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that other patients may also benefit.

1.1.5.2 Clinical data in thyroid cancer

The preclinical data generated to date suggests the clinical hypothesis that MAPK pathway inhibition in patients with RAI-refractory tumours will result in reacquisition of RAI uptake and renewed susceptibility to therapeutic ^{131}I. To test this hypothesis, an investigator-sponsored selumetinib pilot study has been performed at MSKCC for patients with RAI-refractory recurrent or metastatic differentiated thyroid carcinoma of follicular cell origin entitled, "Reacquisition Of RAI Uptake Of RAI-Refractory Metastatic Thyroid Cancers By Pre-treatment With The Selective MEK Inhibitor Selumetinib: A Pilot Study" (Ho et al 2012). In this study, the RAI avidity of thyroid tumours was quantified by lesional dosimetry with ^{124}I PET imaging in patients, before and after 4 weeks of treatment with selumetinib. For patients whose tumours reacquired the ability to take up RAI, ^{131}I treatment was administered, and tumour response was assessed both radiographically and with measurement of the serum tumour marker thyroglobulin (Tg).

20 patients were treated with selumetinib in this pilot study. Of the 20 patients, 9 patients had tumours with the V600E *BRAF* mutation, 5 patients had tumours with *NRAS* mutations at codon 61, 3 patients had tumours with *RET/PTC* rearrangements, and the remaining 3 patients were wild-type for these alterations. Twelve of the 20 patients in the study demonstrated increased tumoural ^{124}I uptake, and 8 of these 12 patients achieved sufficient iodine reuptake to warrant treatment with ^{131}I. Interestingly, 5 of these patients were found to have *NRAS* mutations, one a *BRAF* mutation, one a *RET/PTC* rearrangement and one patient was wild-type. Further genotyping and cytogenetic analysis is ongoing to discover other potential oncogenic drivers that may have promoted susceptibility to this therapeutic strategy. The increased iodine incorporation as quantified on the ^{124}I scans translated to clinical efficacy with RAI therapy. Reduction in tumour size by RECIST criteria was achieved in all RAI-treated patients, with 5 confirmed partial responses and 3 patients with stable disease. Substantial decreases in serum thyroglobulin following RAI therapy were achieved in all 8 RAI-treated patients. The mean percent reduction in serum thyroglobulin achieved "post-RAI" (2 months after RAI treatment) compared to "pre-RAI" (within 3 weeks before RAI treatment) was 89%.

Data from the pilot study also suggests that pre-treatment with selumetinib selectively increased RAI uptake in tumoural lesions compared to non-thyroidal tissue (salivary gland).

This pilot study demonstrates that MAPK pathway inhibition can modulate RAI uptake in the most difficult clinical scenario: patients with resistance to RAI therapy. Most patients in the pilot clinical study described above had many metastatic lesions, some of which were refractory to RAI at baseline, and some of which were partially RAI avid at baseline. Importantly, selumetinib not only restored RAI uptake in previously refractory lesions, but also increased RAI uptake in most partially-avid lesions (typically by more than 100% compared to the baseline value; 3 to 7 fold increases in maximum SUVs in such lesions were consistently observed). This provides a strong rationale to develop this strategy in the adjuvant setting for RAI naïve patients, with the goal of further enhancing what is more likely to be RAI-susceptible disease for patients at high risk of primary treatment failure.

In addition to the pilot study described above, a phase II study of 100 mg bid selumetinib (previous mix-and-drink formulation) in 39 patients with RAI-refractory differentiated metastatic thyroid cancer has also been completed (Hayes et al 2012). This study involved continuous monotherapy dosing of selumetinib and no RAI treatment. The results demonstrated few clinical responses (one partial response in 32 evaluable patients), but demonstrated a 66% stable disease rate; median PFS in this poor-prognosis cohort was 33 weeks in patients with mutations in *BRAF* V600E, and 32 weeks in all-comers. Although this study was conducted with the mix and drink formulation (from which selumetinib exposure may be lower), the efficacy of selumetinib as monotherapy in this population was disappointing.

Taken together, these data suggest a strong rationale for investigating selumetinib with RAI in patients with DTC. Given the known prevalence of MEK pathway activation in patients with DTC, and both the pre-clinical and clinical data seen when selumetinib is added to RAI, increasing iodine uptake, specifically with respect to selumetinib's ability to upregulate NIS expression, adding selumetinib to standard of care RAI treatment has the potential to provide important clinical benefit. This benefit may extend to all patients regardless of their genotype, or it may be greater in those patients with tumours driven by mutations in the MEK pathway. This study will allow these hypotheses to be tested.

1.1.5.3 Safety profile of selumetinib

Array BioPharma was responsible for the first study of selumetinib into patients. The remainder of the oncology clinical development programme is the responsibility of AstraZeneca. Selumetinib is currently in phase II development, and has been used as both monotherapy and in combination with other anti-cancer agents, in a variety of adult solid tumour settings (eg, pancreatic cancer, colorectal cancer, melanoma and NSCLC), and paediatric cancer patients.

The formulation taken into the phase I clinical programme by Array Biopharma was an extemporaneous preparation of an oral suspension of selumetinib as the free-base in an aqueous solution of sulphobutylether β-cyclodextrin (SBE-CD, Captisol®), referred to as the free-base suspension formulation (mix and drink). The AstraZeneca phase II monotherapy

clinical programme also utilised this formulation. Subsequent formulation development resulted in a capsule formulation of selumetinib as the hydrogen sulphate salt (AZD6244 Hyd-Sulfate), which will be used in this study. The maximum tolerated dose (MTD) for the suspension formulation was determined to be 100 mg twice daily, whereas for the capsule, the MTD was determined to be 75 mg twice daily. The emerging safety and tolerability profile of the capsule formulation is broadly consistent with that of the suspension formulation, although a higher frequency of fatigue and nausea has been reported with the capsule formulation compared to the suspension formulation in the phase II monotherapy studies.

As of April 2012, over 1200 patients have received selumetinib as monotherapy or in combination with other anti-cancer agents in clinical studies (AstraZeneca and non AstraZeneca-sponsored studies, including investigator-sponsored studies).

Two phase I studies (D1532C00005, D1532C00020) were performed with the Hyd-Sulfate formulation. Comparison of the frequencies from Study D1532C00005 and the AZ-sponsored phase II monotherapy studies described below, shows that there are higher percentages of patients reporting the most frequent AEs such as fatigue, dermatitis acneiform, diarrhoea, nausea and peripheral oedema with the Hyd-Sulfate formulation. This may be due to the higher plasma exposures achieved with the capsule formulation, but may also be in part as a consequence of the more heavily pre-treated patient population in study D1532C00005 having lower tolerances to developing toxicity.

- The frequencies of common AEs observed in Study D1532C00020 were generally more similar to that of Study D1532C00003 (free-base suspension formulation in a phase II population), which may mean that some of the differences in frequencies observed just reflect variations in the study population as the selumetinib safety profile is established.

Two hundred and sixty nine (269) patients received selumetinib free base suspension 100 mg twice daily in 4 completed phase II monotherapy studies (D1532C00003, D1532C00008, D1532C00011, and D1532C00012).

- Rashes (including the preferred terms dermatitis acneiform, rash, rash maculopapular, rash macular, rash papular, acne, and folliculitis) were reported in approximately 70% of patients receiving treatment with selumetinib, and dermatitis acneiform was the most common AE term overall (54%). Other commonly reported AEs were diarrhoea (49%), nausea (33%) and vomiting (24%). Adverse events of peripheral oedema, periorbital oedema, and facial oedema were reported in 31%, 9%, and 4% of patients, respectively. The AEs of fatigue or asthenia were reported in approximately 30% of patients in this phase II population. Dyspnoea exertional or dyspnoea was reported in 13% of patients and, in individual studies, dyspnoea exertional was reported at a higher incidence in the selumetinib groups than in the comparator chemotherapy groups.

- Serious AEs were reported in 24% of patients receiving selumetinib monotherapy. The most frequently reported serious AEs were vomiting (1.5%), diarrhoea,

erysipelas, and pulmonary embolism (in 1.1% patients each). Serious AEs of infections (bacterial sepsis, sepsis, infection, and bacterial arthritis) were reported in 2.2% of patients. The most frequently related reported treatment-related SAE was vomiting (3 patients).

- In Study D1532C00003, small increases in blood pressure were observed after 1 week on selumetinib, with mean increases of 7.4 mmHg (systolic, SBP) and 5.3 mmHg (diastolic, DBP) at Week 8, compared with mean increases of 1.1 mmHg (SBP) and 0.5 mmHg (DBP) in the temozolomide comparator arm. The AE of hypertension was reported in 18 patients (6.7%) receiving selumetinib in phase II monotherapy studies; 6 of these patients had hypertension at entry to the study, and a further 5 patients had documented risk factors for hypertension.

- Reversible asymptomatic reduction in left ventricular ejection fraction (LVEF) to below 55% has been reported in a small proportion of patients with advanced cancers in the monotherapy and randomised placebo controlled studies in combination with standard chemotherapies, with both formulations of selumetinib. In both placebo controlled studies no patient treated with selumetinib had severe LVEF impairment (< 35%) or symptomatic heart failure. Evidence of reversibility on continuing treatment with selumetinib has been demonstrated in some patients. LVEF scheduled assessments were only included in one phase II study (D1532C00003) and in the selumetinib group to evaluate a possible cardiac aetiology of the peripheral oedema reported in earlier studies. The median change in LVEF at Week 4 was 1.2 percentage points, and the individual change from baseline ranged from –20 to +19 percentage points. Adverse events of ejection fraction decreased, left ventricular dysfunction, or ventricular dysfunction were reported in a total of 5 patients (3.3%) receiving selumetinib (including 1 patient who had switched from temozolomide treatment after disease progression) versus 1 patient (1%) in the comparator group.

- Review of clinical laboratory parameters in phase II monotherapy studies identified a trend toward increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels after starting treatment with selumetinib. An increase in serum phosphate was observed in some patients after initiation of selumetinib, compared with patients randomised to comparator treatments.There was a trend toward a small mean decrease in albumin relative to the comparator. No other reports of selumetinib-related changes in laboratory parameters were considered to be of clinical relevance at this time. There was no evidence of myelosuppression or renal impairment.

- Adverse events related to visual function have been reported across the programme with selumetinib. Most often there were no specific clinical findings reported from patients that underwent ophthalmological evaluation after reporting the AE of visual disturbance. AEs consistent with central serous retinopathy have been reported in a

small number of patients receiving treatment with selumetinib, generally in combination with other anti-cancer agents.

- There have been reports of pneumonitis-type events in a small number of patients receiving treatment with selumetinib. An association with selumetinib has not been established. An algorithm for investigation of dyspneoa is provided in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

- Weakness of neck extensor muscles in conjunction with creatine phosphokinase (CPK) increases (reversible on treatment interruption) have been reported in 3 out of 54 patients with uveal melanoma receiving selumetinib 75 mg twice daily in one non-AstraZeneca sponsored study. Increases in CPK levels have been recorded in a small number of patients receiving treatment with selumetinib. CPK elevations are present in some patients with muscle symptoms, although asymptomatic elevations have also been reported. A relationship between selumetinib and elevated CPK levels or myopathy has not been established.

In the DTC pilot study described in Section 1.1.5.2 (Ho et al 2012), where 20 metastatic thyroid cancer patients were treated with a 4 week course of selumetinib 75 mg twice daily, all events attributed to selumetinib were Grade 1 or 2, and included fatigue (80%), maculo-papular rash (70%), acneiform rash (25%), elevation in AST (70%; all Grade 1), elevation in ALT (45%; all Grade 1), diarrhea (45%), nausea (40%), limb edema (30%), oral mucositis (35%), constipation (20%), hypoalbuminemia (15%), decreased white blood cell count (15%), face edema (10%), scalp pain (10%), decreased platelet count (1 patient; Grade 1), eye disorder (1 patient; Grade 1 consisting of visual halos and slight blurriness that resolved after therapy stopped), hypertension (1 patient; Grade 1), periorbital edema (1 patient; Grade 1), and vomiting (1 patient, Grade 1). One patient who was treated with RAI was subsequently diagnosed with myelodysplastic syndrome 51 weeks after RAI administration which subsequently evolved into acute leukaemia (this was determined to be unrelated to selumetinib and likely related to cumulative RAI toxicity as well as previous external beam radiation therapy). All adverse events were readily managed with supportive mediations and were reversible upon discontinuation of selumetinib. None of the 20 patients required dose delays or reductions due to selumetinib toxicity.

In the only other study to specifically investigate selumetinib in differentiated thyroid cancer patients (the phase II study of 100 mg bid selumetinib, previous mix-and-drink formulation) in 39 patients with RAI-refractory differentiated metastatic thyroid cancer (Hayes et al 2012). In these patients with RAI-refractory disease, common drug-related AEs included rash (77%), fatigue (49%), diarrhea (49%), and peripheral oedema (36%). Grade 3 and 4 AEs were consistent with those across the selumetinib program and also included rash (18%), fatigue (8%), diarrhea (5%) and peripheral oedema (5%). Twelve patients required dose reductions for reported AEs across the length of the study (the duration of treatment was greater than 16 weeks for 69% of patients). Six patients (15%) discontinued treatment due to adverse events.

A study of selumetinib in combination with radiation in patients with non-small cell lung cancer has recently been opened but no safety or efficacy results are yet available from this study.

Selumetinib is not mutagenic or clastogenic in vitro but produced increases in micronucleated immature erythrocytes in mouse bone marrow micronucleus studies. Investigatory studies show that this is predominantly via an aneugenic mechanism which is consistent with disruption of normal spindle function as a consequence of the known pharmacological action of a MEK inhibitor. With selumetinib Hyd-Sulfate, a NOEL of 24 mg/kg/day (for 2 days) was established for induction of micronuclei, with plasma exposures significantly above those observed in cancer patients at the maximum tolerated dose of 75 mg twice daily. This suggests that selumetinib will have little potential to cause aneugenicity in dividing cell populations in patients at the proposed clinical dose. Thus, any additional aueugenic risk from a 5 week course (maximum 43 days) of twice daily 75 mg selumetinib dosing in this potentially curative patient setting, is considered to be negligible in comparison with the known and more substantial risk from radiation exposure following a therapeutic dose of ^{131}I (100 mCi) that patients will receive as part of standard of care.

In summary, selumetinib has been shown to have an acceptable profile of side effects, in an extensive safety database for a compound at this stage of development.

Further details regarding the safety profile of selumetinib can be found in the Investigator Brochure.

1.1.5.4 The pharmacokinetics of Selumetinib in subjects of Asian ethnicity

Plasma exposure of Selumetinib (Cmax and AUC) is higher, at a population level, in subjects of Asian ethnicity by approximately 1.5- to 2-fold in non-Japanese Asians and Japanese subjects, compared with Western subjects. However, the pharmacokinetics of Selumetinib show considerable variation and there is overlap in the range of exposure experienced by Asian and Western subjects (some individual Asian subjects have similar plasma levels to those in Western subjects). The higher average plasma exposure was not associated with a change in the tolerability profile of single dose Selumetinib.

The pharmacokinetics of Selumetinib were investigated in study D1532C00086, conducted in the UK involving healthy volunteers of Asian ethnicity (defined as being born in an Asian country, and expatriate for not longer than 5 years, and with maternal and paternal grandparents of Asian ethnicity). The subjects who received Selumetinib in Study D1532C00086 were of the following ethnicities: Japanese, Chinese, Filipino, Malay, Malaysian, Maldivian, Singaporean, Thai, Indian and Vietnamese, and it is not known in these groups whether Selumetinib exposure will be similar to Western subjects or to subjects of the specific Asian ethnicities included in Study D1532C00086.

The pharmacokinetic findings from study D1532C00086 do not support excluding subjects of Asian ethnicity from studies of Selumetinib. However, as it is possible that Asian subjects may experience higher Selumetinib plasma exposure (than would be expected in Western

subjects receiving the same dose of selumetinib), there could be a potential for a higher risk of adverse events.

The number of Asian patients with advanced cancer who have received treatment with Selumetinib is very low. Emerging information from ongoing study D1532C00067 of Japanese patients receiving selumetinib + docetaxel for second-line treatment of NSCLC suggests that febrile neutropenia may occur more commonly in Japanese patients (3 of 8 patients treated, although comparative data in Japanese patients receiving docetaxel monotherapy is not available) than might be predicted from studies conducted in Western subjects.

Patients of Asian ethnicity are not excluded from studies evaluating Selumetinib. However, when considering enrolling an individual of Asian ethnicity to a Selumetinib clinical study, investigators should make a clinical judgment as to whether the potential risk of experiencing higher Selumetinib plasma levels outweighs the potential benefit of treatment with Selumetinib. The Patient Information and Consent form for studies of Selumetinib includes information on the possibility of higher Selumetinib plasma levels and occurrence of adverse events in Asian subjects than in subjects who are not of Asian origin. Investigators should be aware of the potentially higher risk of adverse events when monitoring patients of Asian ethnicity receiving treatment in clinical studies of Selumetinib.

1.2 Research hypothesis

Pre-treatment with selumetinib enhances the uptake of radioactive iodine in differentiated thyroid cancer, resulting in a greater incidence of complete remission after adjuvant RAI therapy in patients at high risk of primary treatment failure.

1.3 Rationale for conducting this study

Unfortunately a significant proportion of thyroid cancer patients are not cured by their initial surgery and RAI therapy. This is often due to the inability of their cancer cells to adequately incorporate RAI (due to reduced expression of NIS). In such cases, repeated administration of RAI may be given (for RAI avid disease) with the aim of inducing remission and curing their disease. This outcome however is not guaranteed, and patients who subsequently develop refractory metastatic disease have a much poorer prognosis and may eventually succumb to their disease; at least one third of patients who develop metastatic disease have no or very low uptake and are thus not amenable to further RAI treatment. There is thus an urgent need for a medicine that can enhance the effectiveness of initial RAI treatment and increase the probability of achieving remission, thereby preventing more patients from developing distant metastatic disease.

1.4 Benefit/risk and ethical assessment

It is clear from the Investigator-sponsored study (Ho et al 2012), that a short course of selumetinib prior to RAI therapy, is effective in enhancing RAI uptake, reducing tumour

marker (Tg) levels, and reducing tumour size in heavily pre-treated patients with documented RAI-refractory disease. Most patients in the pilot clinical study had numerous metastatic lesions, some of which were refractory to RAI at baseline and some of which were partially RAI avid at baseline. Importantly, selumetinib pre-treatment not only restored RAI uptake in previously refractory lesions, but also increased RAI uptake in the majority of partially avid lesions (typically by more than 100% compared to the baseline value; 3- to 7-fold increases in maximum SUVs in such lesions were consistently observed). This pilot data not only supports the preclinical hypothesis that inhibiting the MAPK pathway can convert non-RAI avid lesions to RAI avid tumours, but also demonstrates that iodine uptake in previously iodine sensitive lesions can be significantly increased with selumetinib. This observation broadens the potential clinical applicability of this approach beyond just RAI-refractory thyroid cancer, to the use of selumetinib and RAI as part of upfront adjuvant treatment of RAI-naïve and susceptible DTC.

The potential benefit to patients in this study is therefore high, with an increased chance of complete remission. The toxicity risk from a short course (approximately 5 weeks) of selumetinib treatment has been carefully considered for this potentially curative population; the side effect profile of selumetinib in the short timeframe (maximum 6 weeks of exposure) is considered to be predictable, manageable and reversible (mainly rash and fatigue). The long term risk of secondary malignancies associated with RAI is considered low from a single 100 mCi dose, as these are rare and more typically develop following cumulative RAI treatments and exposure. Patients under the age of 18 years will be excluded to minimise any risk of increased radioactivity exposure in a younger population. The side effect profile of both selumetinib and RAI will be monitored over the entire 3 year study duration for each patient.

2. STUDY OBJECTIVES

2.1 Primary objective

To compare the efficacy of selumetinib with radioactive iodine therapy (RAI), versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in the intention to treat (ITT) study population. Complete remission is defined in Section 6.4.1.

2.2 Secondary objectives

1. To compare the efficacy of selumetinib with RAI, versus placebo with RAI, by assessment of complete remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Complete remission is defined in Section 6.4.1.

2. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in the ITT study population. Clinical remission is defined in Section 6.4.6.

3. To compare the efficacy of selumetinib with RAI, versus placebo with RAI by assessment of clinical remission rate at 18 months post RAI treatment in a sub-group of patients with tumours known to be mutation positive for *BRAF* or *NRAS* (defined in Section 6.10.1). Clinical remission is defined in Section 6.4.6.

4. To assess the safety and tolerability of selumetinib with RAI compared to placebo with RAI.

5. To investigate the pharmacokinetics (PK) of selumetinib and N-desmethyl selumetinib when administered to patients with differentiated thyroid cancer.

2.3 Exploratory objectives

1. To explore subsequent thyroid cancer therapy given to patients who receive selumetinib with RAI, or placebo with RAI.

2. To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, AEs and/or safety parameters.

3. To collect tumour, plasma and serum samples for potential future research on biomarkers relevant to DTC and response and resistance to study treatments.

4. To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to selumetinib or RAI and/or susceptibility to cancer.

The exploratory analysis will be reported separately from the CSR.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is a double-blind, randomised, placebo-controlled study to assess the efficacy and safety of a short course (approximately 5 weeks) of selumetinib (75 mg, orally twice daily) in combination with adjuvant RAI therapy compared to placebo and adjuvant RAI therapy, in patients with differentiated thyroid cancer at high risk of primary treatment failure.

Approximately 228 patients will be randomised 2:1 selumetinib to placebo.

This will be a multi-centre, international study; it is anticipated that approximately 50 centres will recruit patients in South and/or North America and Europe.

3.1.1 Treatment Plan

Following randomisation, patients will take their assigned study treatment (selumetinib or placebo) for a period of approximately 5 weeks, twice daily. Study treatment will begin approximately 4 weeks prior to the planned day of RAI therapy. Refer to Table 2 for an example study treatment plan. The following treatment criteria must be adhered to:

1. Day 1 of study treatment must occur:
   - no earlier than 6 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy), and
   - no later than 16 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).
2. Patients should remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be rescheduled at the discretion of the Investigator to allow the patient to receive study treatment for a minimum of 7 consecutive days beforehand.
3. Study treatment with selumetinib or placebo will typically last for 36 days, but must be for no longer than 43 days. The planned RAI can be postponed by up to 1 week if absolutely necessary.
4. Patients will be required to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI treatment. Refer to Section 5.1.1 and the example diet in Appendix F for further details.
5. For each of the 2 days immediately prior to their planned RAI therapy, patients will receive a recombinant human TSH injection (rhTSH, Thyrogen), in order to stimulate iodine uptake (refer to Section 5.5.4 for details).
6. Following the 2 days of rhTSH injections, patients will receive their planned RAI therapy the immediate next day (refer to Section 5.5.4 for further RAI dosing information).
7. Twice daily dosing of selumetinib/placebo should continue for 5 days following RAI therapy.
8. If a patient suspends study drug (selumetinib or placebo) treatment for more than 14 days they are no longer eligible to re-start the treatment but will be followed according to the study plan.

Table 2 Example study treatment plan

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Day 1 X	Day 2 X	Day3 X	Day 4 X	Day 5 X	Day 6 X	Day 7 X
Day 8 X	Day 9 X	Day 10 X	Day 11 X	Day 12 X	Day 13 X	Day 14 X
Day 15 X	Day 16 X	Day 17 X	Day 18 X	Day 19 X	Day 20 X	Day 21 X
Day 22 X	Day 23 X	Day 24 X Low I diet	Day 25 X Low I diet	Day 26 X Low I diet	Day 27 X Low I diet	Day 28 X Low I diet
Day 29 X Low I diet **Thyrogen**	Day 30 X Low I diet **Thyrogen**	Day 31 X Low I diet **RAI**	Day 32 X Low I diet	Day 33 X	Day 34 X	Day 35 X
Day 36 X **last day of study treatment**		Day 38 (Day 36-41) WBS scan (3-10 days after RAI dose)				

X: Study treatment administration (selumetinib or placebo, twice daily)
RAI: radioactive iodine therapy (^{131}I) refer to Section 5.5.4.2 for details
This suggested treatment plan is an example only. The treatments may be planned for different days as long as all criteria in Section 3.1.1 are met.

3.1.2 Follow-up plan

Following completion of RAI therapy and planned discontinuation of study treatment (randomised selumetinib or placebo); patients will be followed up as follows:

1. 3-10 days after RAI therapy, patients will undergo a post-therapy whole body RAI (^{131}I) nuclear medicine scan to determine where the RAI has localized in the body (refer to Section 6.4.4.2 for further detail).

2. Patients will be monitored for TSH and thyroxine (T4) levels as per local standard of care (refer to Section 6.4.3.3 for further detail). Note that T4 levels will not be collected in the study database.

3. At 9 months (±3 months) following RAI treatment, patients will be assessed for:

   (a) TSH-suppressed Tg and Tg antibody levels (TgAb). Refer to Section 5.9.1.1 for further details.

(b) Neck ultrasound (US). Refer to Section 5.9.1.2 for further details.

It is important that these assessments are not performed earlier than 6 months after RAI treatment.

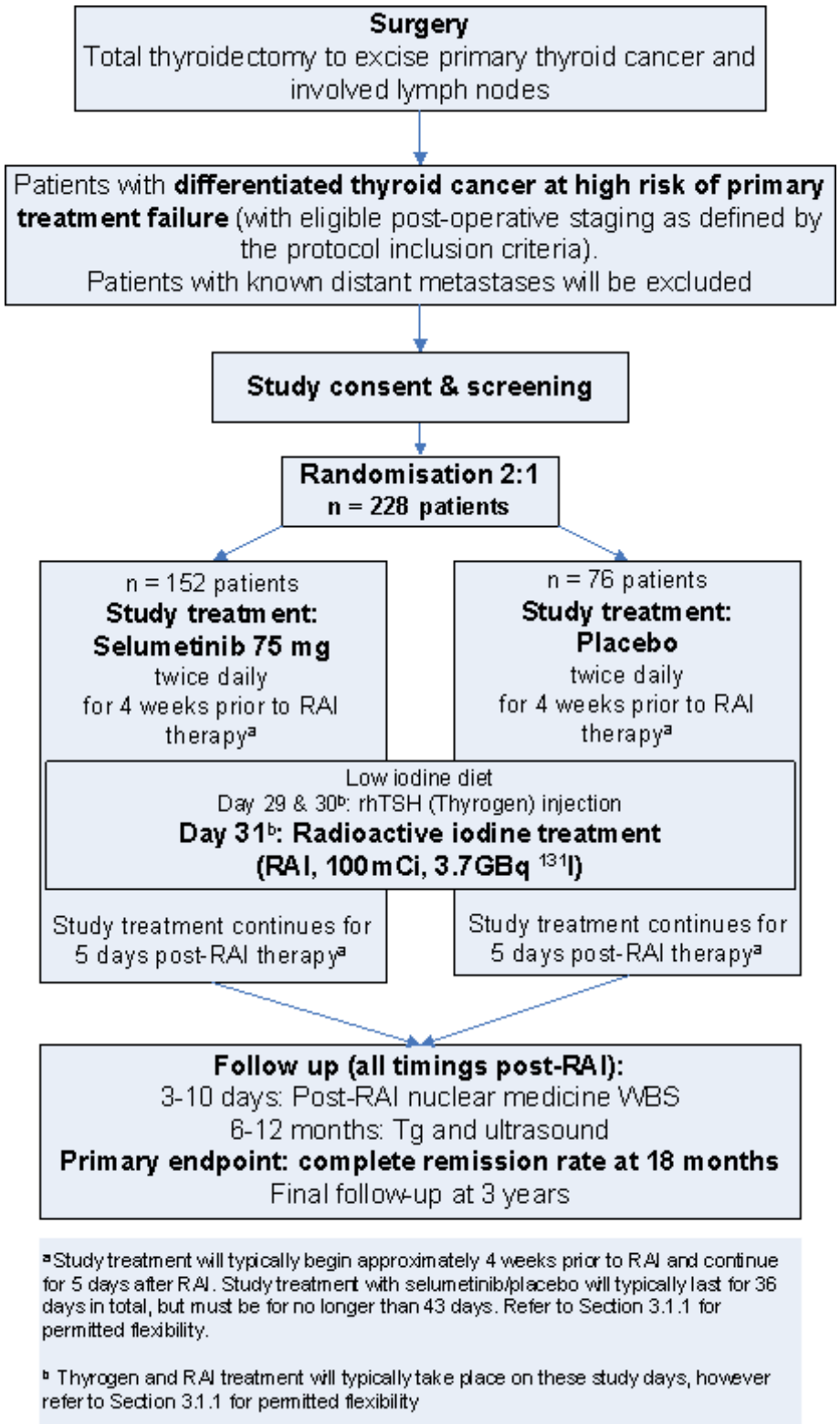
4. Patients will be assessed for their complete remission status at the primary endpoint 18 months following their RAI treatment. A staged approach to the primary endpoint assessments will be used in this study in order to determine remission status (presence or absence of thyroid cancer), such that each patient may not require all assessments. Refer to Section 6.4, Table 4 and Figure 3 for further details. The primary endpoint assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within an 8 week period.

   Further thyroid cancer therapy (eg, additional surgery, RAI re-treatment, external beam radiotherapy or systemic therapy) should only be given during the initial 18 month follow-up period according to the re-treatment criteria in Section 5.9. Any patient that is re-treated in the 18 month period following their RAI therapy will not require any primary endpoint assessments performing (they will be determined not to be in complete remission for the purpose of the study and will enter standard of care follow up, remaining in the study until the 3 year follow up).

5. Following the primary endpoint assessments (or re-treatment), all randomised patients will be further followed-up at 3 years following their RAI treatment. It is the responsibility of the study investigator to ensure they conduct follow-up as described in this protocol if patients transfer to non-study hospitals, or if patients are discharged for routine follow up at other institutions (eg, family doctor or local non-specialist hospital).

Assessments planned at each visit are detailed in Table 3, Table 4 and Section 6.

Figure 1 Study flow chart



[a] Study treatment will typically begin approximately 4 weeks prior to RAI and continue for 5 days after RAI. Study treatment with selumetinib/placebo will typically last for 36 days in total, but must be for no longer than 43 days. Refer to Section 3.1.1 for permitted flexibility.

[b] Thyrogen and RAI treatment will typically take place on these study days, however refer to Section 3.1.1 for permitted flexibility

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post RAI (visit 5)	9 months post RAI (visit 5)	18 months post RAI (visit 5)	27 months post RAI (visit 5)	3 years post RAI (visit 5)	
Visit Window	N/A	N/A	±1wk	+1wk	+1wk	+1wk	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Informed consent	X												
Physical examination	X		X	X (Day 29 or 30)			X						6.5.6
Additional screening procedures	X												6.2
Provision of archival tumour[b]		X											6.10.1.1
Plasma/serum sample for exploratory analysis[b]		X (pre-dose)											6.10.2
Pregnancy test	X				X					X[a]			6.5.9.1
Optional genetic consent & sample (whole blood)		X (pre-dose)											6.9
Adverse events[c]	X →	→	→	→	→	→	→	→	→	→	→	→	6.5.3
Concomitant medications	X →	→	→	→	→	→	→	→	→	→	→	→	5.6

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post RAI (visit 5)	9 months post RAI (visit 5)	18 months post RAI (visit 5)	27 months post RAI (visit 5)	3 years post RAI (visit 5)	
Visit Window	N/A	N/A	±1wk	+1wk	+1wk	+1wk	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Telephone follow up for safety[d]								X			X		6.5.3
Vital signs (including height at screening), weight	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.8
Clinical chemistry	X	X (pre-dose)	X	X (Day 29 or 30)			X						6.5.5
Haematology	X	X (pre-dose)	X	X (Day 29 or 30)			X			X		X	6.5.5
Urinalysis	X		X				X						6.5.5
ECG[e]	X	X		X[e] (Day 29 or 30)			X						6.5.7.2
ECHO/MUGA[f]	X						X						6.5.7.1
Ophthalmologic examination[f]	X						X						6.5.9.2

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post RAI (visit 5)	9 months post RAI (visit 5)	18 months post RAI (visit 5)	27 months post RAI (visit 5)	3 years post RAI (visit 5)	
Visit Window	N/A	N/A	±1wk	+1wk	+1wk	+1wk	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Selumetinib/placebo dosing[g] twice daily		→	→	→	→	→							5.5.2
PK blood samples[h]		X		X[h] (Day 29 or 30)									6.7
Low iodine diet[i]				X	X					X[a]			5.1.1
Thyrogen injection				Xx2 (Day 29 and 30)						Xx2[a]			5.5.4.1
^{131}I (RAI) treatment single 100 mCi dose					X								5.5.4.2
^{131}I 5 diagnostic dose for WBS single 5 mCi dose										X[a]			5.5.4.2
^{131}I nuclear medicine WBS scan						X[j]				X[a]			6.4.4.2
Re-treatment assessment[k]									X	X		X	5.9

Table 3 Study Plan

Visit	1	2	3	4	5	6	7	8	9	10	11	12	
Visit Description	Screening	Randomisation	On-treatment safety visit	Thyrogen	RAI therapy	Last day of treatment	30 days post treatment	4 Month safety follow up	9 Month FU	Primary endpoint assessments[a]	27 Month safety follow up	3 Year FU	Protocol Section
Timing	Day -28 to –1	Day 1	Day 14	Days 29 & 30	Day 31	Day 36	Week 10	4 months post RAI (visit 5)	9 months post RAI (visit 5)	18 months post RAI (visit 5)	27 months post RAI (visit 5)	3 years post RAI (visit 5)	
Visit Window	N/A	N/A	±1wk	+1wk	+1wk	+1wk	± 2 days	± 2 weeks	± 3 months	Refer to **Table 4**	± 2 months	± 1 month	
Blood sample for TSH									X	X			6.4.3.3
Blood sample for suppressed Tg									X[n]	X			6.4.3.1
Blood sample for TgAb	X								X	X			6.4.3.4
Blood sample for rhTSH-stimulated Tg										X[a]			6.4.3.2
Neck ultrasound	X[l]								X	X			6.4.4.1
Neck MRI	X[l]									X[a]			6.4.4.3
Chest CT without contrast	X[l]									X[a]			6.4.4.4
Final follow-up assessment of clinical status												X	6.4.8
Biopsy/FNA for disease confirmation									X[m]	X[m]			6.4.4.5
Tumour biopsy on progression (optional)	Optional sample on disease progression (for example, if the patient is re-treated for persistent or recurrent thyroid cancer, or has further surgery). Note that both a plasma and serum sample for exploratory analysis should also be taken on disease progression.												6.10.3 6.10.2

Study Plan Table 3 Footnotes

[a] Refer to Table 4 and Section 6.4.2.

[b] Provision of these samples is mandatory in this study. Samples should also be obtained on progression (refer to Section 6.10.2).

[c] All AEs/SAEs should be collected from the day of consent until 30 days following the last dose of study treatment. From then on, all SAEs (regardless of causality), and all AEs related to either RAI, or the combination of RAI and study treatment, should be collected until the last study visit 3 years following the patient's RAI dose. The same AE collection scheme applies for any re-treated patient.

[d] The Investigator (or delegate) is required to contact the patient by telephone to follow up for any safety information (according to the collection scheme detailed in Section 6.5). For re-treated patients, safety follow-up should continue according to the protocol-scheduled visits, but may be collected by telephone if necessary at each visit (refer to Section 5.9).

[e] Single ECG assessments 1-2 hours following the first dose on Day 1 and Day 29 or Day 30 of study treatment. A single ECG assessment is also required whenever an ECHO/MUGA is performed, on any cardiorespiratory AE, and for premature discontinuation.

[f] These assessments must also be performed on symptomatology according to the relevant protocol section.

[g] Study treatment must be initiated no earlier than 6 weeks after the patient's thyroid cancer surgery, and no later than 16 weeks after the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).

[h] Each patient will be asked to contribute 8 PK blood samples, one from each of the four pre defined time windows on both Day 1 and Day 29 or Day 30. The Day 29 or Day 30 PK blood samples may be taken earlier, from Day 22 onwards of study treatment if preferred, but it is essential that all PK blood samples are collected before the RAI dose is administered. (a) Pre-dose (within 15 minutes of dosing), (b) between 15 minutes and 1 hour post-dose, (c) between 1.5 and 2.5 hours post-dose, and (d) between 3 and 8 hours post-dose.

[i] All patients must adhere to a low iodine diet (an example diet is provided in Appendix F).

[j] The post-RAI WBS may be performed any time from 3-10 days following the patient's RAI dose (thus it does not have to be on the same day as the last dose of study treatment).

[k] The re-treatment assessment will establish whether the patient has received any further treatment for thyroid cancer. Refer to Section 5.9 for the study criteria for re-treatment in the initial 18 months following the patient's RAI dose.

[l] The post-operative imaging assessments must be performed no sooner than 4 weeks post-surgery, and after all other screening assessments have been performed (ie, they should not be performed for any patient that is otherwise ineligible).

[m] Only if required (refer to Section 6.4.4.5)

[n] A repeat sample for suppressed Tg may be required 2-4 weeks later, refer to Section 5.9.1.1.

For imaging data that is required to be sent to the central imaging CRO at any point in the study refer to Section 6.4.4.5.

Table 4 Study Plan for the 18 month Primary Endpoint Assessments

A staged approach to the primary endpoint assessments will be used in this study in order to determine remission status (absence of thyroid cancer), such that each patient may not require all assessments. Full details are outlined in Section 6.4.2.

	Stage 1	**Stage 2**	**Stage 3**	Protocol Section
Time window	Stage 1 assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within an 8 week period.			6.4.2
Thyroid cancer re-treatment assessment[a]	X[a]			5.9
Suppressed Tg	X			6.4.3.1
TSH	X			6.4.3.3
TgAb[b]	X[b]	X[b]		6.4.3.4
Neck US[f]	X			6.4.4.1
Biopsy or FNA[d]	X[d]			6.4.4.5
Haematology	X			6.5.5
Low iodine diet[e]		X[e]		5.1.1
Thyrogen injection[c]		X x 2[c]		5.5.4.1
Stimulated Tg[c]		X[c]		6.4.3.2
Pregnancy test		X		6.5.9.1
Diagnostic 5mCi ^{131}I dose[c]		X[c]		5.5.4.2
WBS (nuclear medicine scan)[c, f]		X[c]		6.4.4.2
Neck MRI with contrast[f]			X	6.4.4.3
Chest CT without contrast[f]			X	6.4.4.4
Selumetinib/RAI-related AE/SAEs	→	→	→	6.5.3

Footnotes for Table 4: Study Plan for the 18 month Primary Endpoint Assessments

[a] Patients that have been re-treated for thyroid cancer between their initial RAI dose and the primary endpoint assessments 18 months later (refer to Section 5.9 for re-treatment criteria), will not have any primary endpoint assessments performed, they will remain in the study and enter standard of care follow up according to local practice. They should still be followed up for safety information at 18 m, 27 m and 3 years following their initial RAI dose.

[b] For decision making purposes at any time in the study, standardised central analysis results must be used. If the stage 1 blood sample is positive for TgAb, but the stage 2 blood sample is negative for TgAb, then a third blood sample 10 days later (± 3 days) is required to confirm absence of TgAb.

[c] Patients will receive 2 Thyrogen injections on consecutive days (day 1 and 2), followed by a diagnostic dose (5mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5.

[d] Only if required to prove absence of disease for suspicious lesions (refer to Section 6.4.4.5).

[e] Patients will be required to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI treatment. Refer to Section 5.1.1 and the example diet in Appendix F for further details.

[f] For imaging data that is required to be sent to the central imaging CRO refer to Section 6.4.4.5.

3.2 Rationale for study design, doses and control group

This study is designed to determine the efficacy of a 5-week course of selumetinib or placebo, and adjuvant RAI therapy, by assessing the rate of complete remission at 18 months post-RAI therapy.

The dose and duration of selumetinib treatment in this study (75 mg twice daily for 5 weeks) is selected to be consistent with the pilot study, which has previously demonstrated enhanced RAI uptake following selumetinib treatment, reduction in Tg levels, and reduced tumour size following RAI therapy, in patients with RAI-refractory metastatic thyroid cancer (Ho et al 2012). In addition to the effects of selumetinib on the sodium iodine transporter (refer to Section 1.1.5.1), selumetinib may also increase levels of thyroid peroxidase and thyroglobulin in any remaining thyroid cells. These proteins are required to organify and retain iodide in thyroid cells, thus facilitating greater retention of ^{131}I, and a higher dose of radiation to cancer cells. For this reason, patients will remain on selumetinib treatment for 5 days after receiving the therapeutic dose of RAI.

Since RAI is the standard of care for this patient population, the selumetinib/RAI treatment group will be compared to a placebo/RAI control group for all study endpoints.

The population who will participate in this study will be patients with differentiated thyroid cancer at high risk of primary treatment failure that would routinely require RAI adjuvant therapy as standard of care. This risk-stratified population has been selected because it is known that they are at an increased risk of failing to achieve remission following standard initial therapy, and therefore require more effective treatment strategies (refer to Section 1.1.3). This study is intended to be an adjuvant therapy trial for patients without known structural persistent disease; patients with known distant metastases at screening will be excluded in order to minimise heterogeneity of the efficacy recorded.

A secondary efficacy endpoint will be assessed in patients with tumours carrying *BRAF* or *NRAS* mutations, as these are known to constitutively activate the MEK signalling pathway. Treatment with a MEK inhibitor may thus be hypothesised to deliver a greater treatment effect in these patients. However, the pathway can be activated in many ways such that these patients are not likely to be the only population to benefit. Incorporation of a genetically predefined study population enables this hypothesis to be examined (mutation analysis of samples to identify the genetically predefined study population will be performed post-randomisation, and prior to data base lock for the primary endpoint data analysis).

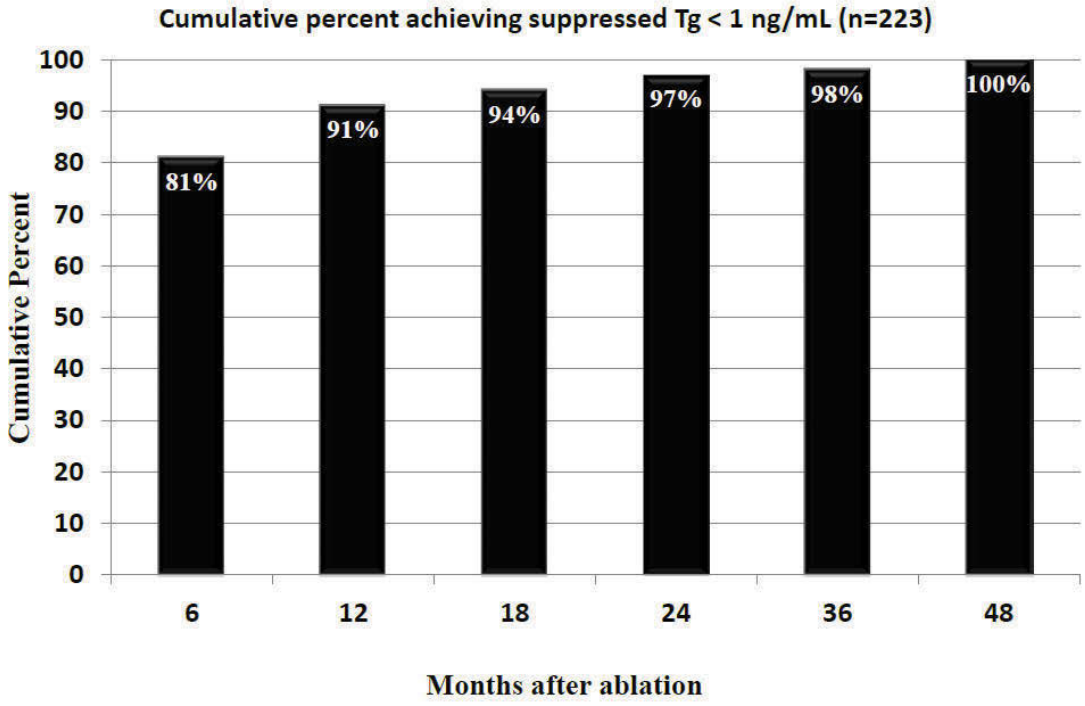
Enhancing RAI uptake into thyroid cancer cells has the potential to increase the incidence of complete remission following RAI treatment. It has been shown that the incidence of complete remission following initial RAI treatment correlates with long-term outcome, and if complete remission has not been achieved, further treatment is frequently administered (Castagna et al 2011, Tuttle et al 2010).

A study has retrospectively evaluated the time to nadir Tg in 299 patients who did not receive additional therapy after total thyroidectomy and RAI (Padovani et al 2012). This patient

population includes both patients with no evidence of disease (remission) and patients with low level disease who are being observed (median follow up time is 7 years). Figure 2 illustrates that 94% of the 223 patients with no evidence of disease achieved a suppressed Tg level of < 1 ng/mL (the biochemical component of remission) by 18 months after initial RAI therapy. Therefore, it is expected that most patients who are likely to achieve remission in both arms will have done so by this time (for the purpose of this study both biochemical and structural absence of disease will be assessed). Longer follow-up would not be expected to change the conclusions regarding an efficacy difference between the two study arms. In patients with similar characteristics to those planned in this study, a similar pattern and extent of Tg decline is also seen (Tuttle RM, unpublished sub-analysis of data from Padovani et al 2012). Previous studies have used time-points ranging from 8 to 24 months to assess remission rates after primary treatment of surgery and RAI (Castagna et al 2011, Tuttle et al 2010, Vaisman et al 2012).

Taking all the data into consideration, the incidence of complete remission at 18 months following initial RAI therapy has been selected as the primary endpoint for the proposed study. Each randomised patient will be followed beyond their 18 month primary endpoint assessment, until 3 years after their RAI treatment, in order to further assess both the clinical status of patients, and the safety profile of selumetinib and RAI beyond the primary analysis (refer to Section 6.4.8).

Figure 2 **Time course to achieving a suppressed Tg<1 ng/mL in patients receiving total thyroidectomy and RAI therapy**



4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, (eg, patient screening log), of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures. The main study consent will include mandatory consent to provide a sample of archival tumour material.

2. Males and females aged 18 years or above.

3. Patients with histologically or cytologically confirmed follicular cell derived differentiated thyroid cancer including papillary thyroid cancer and all variants, follicular thyroid cancer and all variants, and poorly differentiated thyroid cancer.

4. Note: Patients with a diagnosis of Hürthle cell carcinoma should be excluded. These are defined as having an invasive tumour composed of >75% of oncocytic (Hürthle) cells lacking the nuclear features of papillary carcinoma, tumor necrosis and marked mitotic activity. Patients with oncocytic (Hürthle cell variants) of papillary thyroid carcinoma defined as a tumour composed of a majority of oncocytic (Hürthle) cells having the nuclear features of papillary carcinoma are eligible to participate.

5. Patients presenting with any one of the following staging categories post-surgery:

   (a) Primary tumour greater than 4 cm

   (b) Primary tumour of any size with gross extrathyroidal extension outside the thyroid gland (T4 disease)

   (c) N1a or N1b disease with at least 1 lymph node ≥ 1 cm

   (d) N1a or N1b disease involving 5 or more lymph nodes (of any size)

   Note: Patients with known metastatic disease at screening will be ineligible for this study as per the exclusion criteria.

6. Patients must have had a one or two-stage total thyroidectomy with therapeutic neck dissection of any clinically apparent metastatic lymph nodes (levels I to VII of the lateral and central neck). All known tumour must have been resected.

Note, the optimal surgical procedure is based on the findings from preoperative ultrasound, to identify the extent of lymph node metastases and thereby facilitate compartment-oriented neck dissection for complete surgical removal of all gross disease. Prophylactic neck dissection is not required or encouraged, but may be performed at the discretion of the treating surgeon. As the surgical procedure(s) will have been performed before study consent, any patient for whom a total thyroidectomy cannot be verified must be excluded from the study (note that patients having undergone a robotic or endoscopic thyroidectomy, or any other novel or remote access surgical technique must also be excluded). For patients who have had a two-stage thyroidectomy, the second surgical procedure must have taken place no later than 12 weeks after the first procedure, otherwise the patient is not eligible.

7. Patients must have all of the following post-operative assessments performed no sooner than 4 weeks post-surgery (post their last surgery if it was a 2-stage thyroidectomy) and the results from each must verify the absence of macroscopic disease:

   (a) Neck US exam

   (b) Neck MRI with contrast

   (c) Chest CT without contrast

   Refer to Section 6.3 for further details. These assessments must be performed within the 28 day screening period (but ideally after all other screening assessments have been performed, ie, they should not be performed for any patient that is otherwise ineligible).

8. Patients must be suitable for radioactive iodine therapy.

9. Patients must be suitable for TSH suppression with a goal of ≤0.5 mIU/L TSH for the duration of the study (this may exclude some patients with cardiac conditions or osteoporosis).

10. Patients must be willing and able to start study treatment within 16 weeks of their thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy). Note that study treatment must not be initiated within 6 weeks of the patient's last surgery.

11. WHO or ECOG Performance Status 0 or 1.

12. Females must:

   (a) be using adequate contraceptive measures (refer to Section 5.1.2),

(b) not be breast feeding (breast feeding must be discontinued in order to participate in this study),

(c) have a negative pregnancy test prior to the start of dosing if they are of child-bearing potential,

(d) or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

(i) Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.

(ii) Women under 50 years old will be considered postmenopausal if they have been amenorrheic for at least 12 months following cessation of exogenous hormonal treatments, and with LH and FSH levels in the post-menopausal range for the institution.

(iii) Documentation of irreversible surgical sterilisation by hysterectomy and/orbilateral oophorectomy and/or bilateral salpingectomy but not tubal ligation.

13. Male patients with sexual partners who are pregnant or who could become pregnant (ie, women of child-bearing potential) must agree to use acceptable methods of contraception until 12 weeks after completing study therapy, or longer if required for standard RAI administration restrictions and in accordance with local labels, to avoid pregnancy and/or potential adverse effects.

14. Adequate organ function as defined by following lab values before randomization:

(a) ANC $\geq 1.5 \times 10^9$/L (1500 per mm^3)

(b) Platelets $\geq 100 \times 10^9$/L (100,000 per mm^3)

(c) Hemoglobin ≥ 9 g/dL

(d) ALT/SGOT and AST/SGPT < 2.5 X upper limit of normal (ULN).

(e) Bilirubin ≤ 1.5 X ULN (with the exception that patients with elevated unconjugated bilirubin due to a pre-existing diagnosis of Gilbert's syndrome are eligible for the study)

(f) Serum creatinine clearance > 50mL/min by either Cockcroft-Gault formula (see Appendix E) or 24hr urine collection analysis.

15. Patients must be able to swallow selumetinib/placebo capsules for the duration of the study treatment period. This may exclude some patients with swallowing

dysfunction due to the specific technique required for their thyroid surgery. Functional assessment of swallowing ability may be made by the treating Investigator.

4.1.1 Genetics research study (optional blood sample)

1. For inclusion in the optional genetics research study patients must provide optional genetics research informed consent.

2. If a patient declines to participate in the genetics research, there will be no penalty or loss of benefit to the patient. A patient who declines genetics research participation will not be excluded from any other aspect of the main study.

4.1.2 Biomarkers research study on tumour progression biopsy

For inclusion in the optional progression tumour sample study, patients must provide optional consent for this sample to be obtained.

If a patient declines to provide consent to obtain optional tumour sample on progression, there will be no penalty or loss of benefit to the patient, and the patient will not be excluded from any other aspect of the main study.

4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Known distant metastatic disease at study entry. Investigators are not required to specifically screen patients for distant metastasis beyond their normal Standard of Care practices and the protocol-specific post-operative imaging assessments, but any patient with known distant metastatic disease at screening must be excluded.

2. Diagnosis of anaplastic thyroid cancer, medullary thyroid cancer, or Hürthle cell carcinoma (refer to inclusion criterion 4 for further details on Hürthle cell eligibility).

3. Presence of anti-Tg antibodies at screening (as determined by standardised central methodology, refer to Section 6.4.3.4).

4. Previous treatment with ^{131}I (RAI) at any time in the past or external beam radiation therapy (EBRT) within 6 months before randomization.

5. Any unresolved toxicity ≥ CTCAE Grade 2 from previous anti-cancer therapy including the patient's recent thyroid cancer surgery.

6. Having received an investigational drug during the last 4 weeks prior to first dose of study treatment.

7. Receiving herbal supplements or medications known to be strong inhibitors or inducers of the CYP1A2, CYP2C19 and CYP3A4 enzymes unless such products can be safely discontinued at least 14 days before the first dose of study medication.

8. Recombinant human TSH (rhTSH, Thyrogen):

   (a) Patients with known hypersensitivity to rhTSH will be excluded.

   (b) Patients not willing to use rhTSH prior to their RAI treatment will also be excluded (ie, patients or clinicians choosing withdrawal of thyroid hormone treatment prior to their RAI treatment will be ineligible for this study).

9. Patients requiring medication with high content in iodide (amiodarone), or patients receiving IV iodine containing contrast as part of radiographic procedure within the last 3 months prior to the planned RAI treatment (unless a urine measurement demonstrates that urinary iodide level has returned to normal range earlier than 3 months following administration of a contrast agent).

10. Patients with clinically significant cardiovascular disease as defined by the following:

    (a) Uncontrolled hypertension (at randomization: BP ≥150/95 despite optimal therapy)

    (b) LVEF < 55% measured by echocardiography (or MUGA)

    (c) Symptomatic heart failure (NYHA grade II-IV), prior or current cardiomyopathy, or severe valvular heart disease

    (d) Uncontrolled angina (Canadian Cardiovascular Society grade II-IV despite medical therapy)

    (e) Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest

    (f) Acute coronary syndrome within 6 months prior to starting treatment

    (g) Mean QTc interval >470 ms

11. Patients with the following ophthalmological findings/conditions:

    (a) Intraocular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intraocular pressure)

    (b) Current or past history of central serous retinopathy or retinal vein occlusion

12. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to agents used in the study.

13. Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

14. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

15. Pregnant women will be ineligible (breast feeding should be discontinued if the mother is treated with study therapy).

16. Male or female patients of reproductive potential who are not employing an effective method of contraception (refer to Section 5.1.2).

17. Refractory nausea and vomiting, chronic gastrointestinal diseases, or significant bowel resection that in the Investigator's opinion would preclude adequate absorption of study therapy.

18. History of another primary malignancy within 5 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ and the disease under study.

19. Clinical judgement by the investigator that the patient should not participate in the study.

20. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

21. Previous treatment with any MEK or BRAF inhibitor.

22. Previous treatment in the present study.

4.2.1 Genetics research study (optional blood sample)

1. Exclusion criteria for participation in the optional genetics research component of the study:

(a) Previous allogeneic bone marrow transplant

(b) Whole blood transfusion within 120 days of the date of genetic sample collection (except for leukocyte depleted blood transfusion, which is allowed)

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

5.1.1 Low-iodine diet

Published data and opinion regarding the necessity for a low iodine diet prior to RAI therapy or a diagnostic whole body scan is variable. For the purpose of this study a low iodine diet will be mandated in order to standardise patient care and study data as best as possible. Compliance to the low iodine diet will not be recorded or assessed, and all randomised patients will receive RAI treatment as planned. Refer to Table 2 and the Study Plan (Table 3) for further details. An example low iodine diet is provided as Appendix F to this protocol.

A low iodine diet is necessary at two occasions in the study:

Prior to RAI adjuvant treatment

All patients must be willing to adhere to the low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI therapy.

Prior to the primary endpoint Stage 2 assessments

All patients must be willing to adhere to the low iodine diet for a period of 1 week before the diagnostic ^{131}I dose used prior to the primary endpoint WBS assessment (^{131}I nuclear medicine scan), until the diagnostic WBS assessment is completed. This is only relevant for patients who pass Stage 1 primary endpoint assessments (refer to Section 6.4.2).

5.1.2 Other study restrictions

The following restrictions also apply while the patient is receiving selumetinib or placebo:

1. Female patients of child-bearing potential will be required to use reliable methods of contraception until 4 weeks after the last dose of selumetinib/placebo or longer if required for standard RAI administration restrictions and in accordance with local labels. Male patients will be required to use reliable methods of contraception until 12 weeks after the last dose of the last study treatment, or longer if required for standard RAI administration restrictions and in accordance with local labels. Reliable methods of contraception should be used consistently and correctly. Acceptable methods include implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception), some IUDs and vasectomised partner. Sexual abstinence is also an acceptable method of contraception according to ICHM3.

2. Fasting restrictions for the study are described in Section 5.5.2.

3. Patients should avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.

4. Patients should avoid large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study treatment period.

5. Selumetinib/placebo capsules contain vitamin E in form of D-α-tocopheryl polyethlen glycol 1000 succinate (TPGS), a water-soluble form of vitamin E which acts as a formulation excipient. The maximum daily dose of vitamin E that a study subject may receive from selumetinib /placebo is approximately 261.6 mg/day. Therefore:

   - Patients should not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interrupt blood coagulation processes.

   - Selumetininb/placebo should be administered with caution in patients who are also receiving concomitant coumarin anticoagulant medications, e.g. warfarin. These patients should have their INR monitored/anticoagulant assessments conducted more frequently and the dose of anticoagulant should be adjusted accordingly.

6. Permitted and excluded antiemetic medications in this study are described in Section 5.6.

7. Permitted and excluded medications for management of skin toxicities (eg, rash) are described in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib." All patients will be given prophylactic provision of emollient cream to take home and to start using when starting study treatment.

8. Unless patients require re-treatment, they should not be enrolled in other studies evaluating novel therapies for thyroid cancer for the entire study duration.

5.2 Patient enrolment, randomisation and initiation of investigational product

The Principal Investigator or delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 4.1 and 4.2

3. Call IVRS/IWRS to assign the eligible patient a unique enrolment number (beginning with 'E#'), and randomisation code (subject number). Randomisation codes will start at 001 and go up.

Randomisation codes will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for randomisation.

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused.

If a patient withdraws from the study, after they have received study treatment then they cannot re-enter the study.

If a patient is re-screened, a new E-code will always be assigned.

5.2.1 Procedures for randomisation

Patients who satisfy all the entry criteria will be centrally assigned by the IVRS/IWRS, according to the randomisation scheme generated by the Biostatistics Group, AstraZeneca, to selumetinib or placebo in a ratio of 2:1.

Every effort should be made to minimise the time between randomisation and starting treatment. Patients must not be randomised unless all eligibility criteria have been met.

IVRS/IWRS will be used for allocation of enrolment number, allocation of randomisation number, study medication assignment, discontinuation from study treatment, emergency code breaks and study drug shipment confirmation.

5.3 Procedures for handling patients incorrectly enrolled, randomised or initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the study criteria are enrolled in error, incorrectly randomised a discussion must occur between AstraZeneca Study Physician and the Investigator regarding the patient's safety and well-being and whether to continue or discontinue the patient from the study treatment. The AstraZeneca Study Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their therapy stopped, then followed up for the primary endpoint assessments and safety. Those patient randomised in error should remain in the study and be followed for the primary endpoint assessments and safety where possible.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The active and placebo capsules will appear identical and presented in the same packaging to ensure blinding of the medication. Medication will be labelled using a unique material pack code which is linked to the randomisation scheme. IVRS/IWRS will allocate randomisation numbers sequentially when sites call IVRS/IWRS to randomise an eligible patient. IVRS/IWRS will allocate the medication pack code to be dispensed to the patient.

All patients must remain blinded until after the 18 month primary endpoint data analysis has been conducted for the study; most patients will thus remain blinded for longer periods of time than their initial 18 month follow up period. Any patient that is re-treated prior to the 18

month primary endpoint time-point (refer to guidelines in Section 5.9), must not be unblinded until after the primary analysis of 18 month primary endpoint data from all patients in the study.

The personnel analyzing the PK samples will be unblinded to treatment allocation in order to organise the appropriate sample analysis. The treatment allocation information will be kept in a secure location until the end of the study.

Once the 18 month primary endpoint data analysis has been conducted for the study, patients may be unblinded for the remaining study follow up.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Procedures for emergency unblinding will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Selumetinib	25 mg Hyd-Sulfate capsule	AstraZeneca
Placebo to match selumetinib	Capsule	AstraZeneca

5.5.2 Doses and treatment regimens

Patients will be randomised on a 2:1 basis, via IVRS/IWRS, to receive either selumetinib 75 mg twice daily, or matching placebo.

Patients will be instructed to take 3 capsules orally on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing), twice a day approximately 12 hours apart according to the Study Plan. Capsules should be taken with

water only. On clinic days when PK samples are scheduled to be taken, dosing should be delayed until arrival at the clinic and until the pre-dose PK sample has been taken.

Selumetinib/placebo will be supplied in bottles of 60 capsules of 25 mg strength. At Randomization visit, selumetinib/placebo for the entire treatment period will be dispensed (5 bottles). Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Day 1 of study treatment must occur within 16 weeks of the patient's thyroid cancer surgery (their last surgery if it was a 2-stage thyroidectomy).

5.5.3 Management of study treatment related toxicity

The immediate management of any adverse event should be according to standard clinical practice for that event. Subsequent management of treatment related adverse events should be guided by the Investigators' assessment of causality.

5.5.3.1 Selumetinib dose interruption or reduction

Patients should remain on study treatment continuously for a minimum of 7 consecutive days prior to their planned RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. If necessary, RAI therapy may be postponed up to 1 week at the discretion of the Investigator to allow the patient receive study treatment for a minimum of 7 consecutive days (as long as the total duration of study treatment does not exceed 43 days)

For all adverse events reported in this study that are considered at least partly causal to administration of selumetinib, the following dose modification guidance should be applied.

Study treatment with selumetinib/placebo should be temporarily interrupted if one of the following AEs are observed (and considered causal to study treatment), **despite optimal supportive care** (ie, supportive treatment may be given prior to withholding study treatment):

- Any intolerable adverse event regardless of Grade
- Any adverse events ≥ CTCAE Grade 3

On improvement of the adverse event to Grade 1 (Grade 2 for rash) or baseline, study treatment may be restarted at the original dose or may be reduced at the discretion of the investigator. One dose reduction of study treatment to 50 mg twice daily is permitted before permanent discontinuation.

- If a further episode of the same AE subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the AE.
- If a different AE subsequently requires dose interruption, selumetinib may be restarted at the same dose or at the next dose level down on improvement of the AE.

- Selumetinib should not be re-escalated to an earlier dose level on improvement of an AE.

- The schedule of assessments described in Table 3 should continue relative to Day 1 in the event of selumetinib dose interruption or reduction.

Therefore, the dose reduction/adjustment algorithm in the study allows for 2 steps only:

75 mg twice daily (initial dose)
↓
50 mg twice daily
↓
permanent discontinuation

If a patient suspends study treatment (selumetinib or placebo) for more than 14 days they are no longer eligible to re-start the study treatment.

All dose delays, reductions and adjustments will be recorded in the appropriate electronic Case Report Form (eCRF).

The guidance above should also be followed for dose interruptions or reductions for adverse events of rashes or diarrhoea. Guidance for interruption or reduction of treatment with selumetinib may be considered for particular events, as indicated in the algorithms provided as a separate study aid in the "Guidance for Management of Specific Adverse Events in Studies of Selumetinib" (refer to Section 5.5.3.2).

5.5.3.2 Management and investigation of specific selumetinib related AEs

Recommendations for the management or investigation of the following specific AEs is provided in Appendix G: Guidance for Management of Adverse Events in Studies of Selumetinib.

- Rash: early initiation of treatment for rash is strongly recommended to minimise the duration and severity of the adverse event. All patients should be given prophylactic provision of emollient cream to take home and to start using when starting study treatment as indicated in the algorithm for management and investigation of rash included in Appendix G.

- Visual disturbances: symptoms, including blurred vision, have been reported during treatment with selumetinib. Events consistent with central serous retinopathy have been reported in a small number of patients receiving treatment with selumetinib, generally in combination with other novel targeted anti-cancer agents. AEs of central serous retinopathy and retinal vein occlusion have been reported in studies of other MEK inhibitors (Lemech & Arkenau 2012). Investigation to determine the underlying cause of visual disturbance is recommended.

- Diarrhoea: early initiation of treatment for diarrhoea is strongly recommended to minimise the duration and severity of the adverse event. Treatment provision will be according to Investigator discretion according to local practice and regulations.

- Dyspnoea: new or worsening dyspnoea has been reported during treatment with selumetinib; investigation to determine the underlying cause is recommended.

5.5.4 Additional study drugs

5.5.4.1 Thyrogen (rhTSH, thyrotropin alfa for injection)

Thyrogen use prior to the RAI ablative dose

Effective use of RAI therapy requires stimulation by TSH in order to maximise RAI uptake by thyroid cells. Recombinant human TSH (rhTSH or Thyrogen) will be used to stimulate iodide uptake according to the manufacturer's recommendation (0.9 mg intra-muscular injection for 2 days immediately prior to the RAI treatment according to the Study Plan Table 3). rhTSH is approved for use in routine clinical care as a diagnostic tool to stimulated serum thyroglobulin and RAI uptake for diagnostic scanning and as an adjunct to RAI ablation in many countries. This allows patients to avoid the hypothyroidism state, since they can maintain their routine thyroid hormone supplementation. Patients or clinicians choosing withdrawal of thyroid hormone treatment for this purpose will be ineligible for this study. All randomised study patients will receive Thyrogen twice prior to their RAI treatment dose.

Thyrogen use for the primary endpoint assessments (18 months post-RAI)

For those patients that progress to Stage 2 of the primary endpoint assessments (refer to Section 6.4.2), Thyrogen will be used to stimulate iodide uptake immediately prior to administering the diagnostic ^{131}I dose for the primary endpoint WBS assessment. Patients will receive a 0.9 mg intra-muscular Thyrogen injection for two consecutive days. Refer to Section 6.4.2.2 for further details.

5.5.4.2 Radioactive iodine (RAI)

All RAI for the study will be locally provided at each site.

Therapeutic RAI dose (^{131}I)

A single oral RAI dose of 100 mCi (3.7 GBq) ^{131}I (+/- 10% at the time of administration) will be administered to all patients according to the Study Plan Table 3, according to standard practice at each site.

Diagnostic WBS dose (^{131}I)

For those patients that progress to Stage 2 of the primary endpoint assessments (refer to Section 6.4.2), a single oral RAI dose of 5 mCi (185 MBq) ^{131}I (+/- 10% at the time of administration) will be administered for the primary endpoint WBS (nuclear medicine scan) 18 months following the ablative treatment dose of RAI. Refer to the Study Plan Table 3, and Section 6.4.4.2 for further details.

5.5.4.3 Thyroid hormone supplementation (TSH suppression)

Routine thyroid hormone supplementation (levothyroxine, LT4) is required during the study as per standard clinical practice. The purpose of this is both to correct resulting hypothyroidism using a dosage appropriate to achieve normal blood levels of thyroid hormone, and to inhibit TSH-dependant growth of residual thyroid cancer cells. Thyroid hormone supplementation will be adjusted in individual patients with the aim of achieving suppressed TSH levels of <0.5 mIU/L for the duration of the study.

5.5.5 Study drug labelling

Each bottle of selumetinib and matching placebo capsules will be labelled by Pharmaceutical Development Supply Chain, AstraZeneca or its designee.

All labels will comply with good manufacturing practice (GMP) regulations, and will state that the drug is for clinical use only or that it is the investigational drug and is to be used by qualified investigators only and should be kept out of reach of children. The labels will have blank spaces for the site personnel to complete the following at the time of drug dispensing: enrolment code, visit number and dispensing date.

Label text will be translated into local language.

Each bottle of selumetinib/placebo capsules will have a tear-off portion that will be removed at the time of dispensing and attached to the Drug Label Accountability Log.

5.5.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle specifies the appropriate storage.

5.6 Concomitant medications

The use of antiemetic medication for the prevention of nausea caused by administration of radioactive iodine is permitted in this study according to local clinical practice (with the exception of aprepitant which is an excluded medication in this study, due to the potential for modification of selumetinib exposure via CYP3A4). The administration of any antiemetic medication must be recorded in the appropriate sections of the Case Report Form.

All patients will be given prophylactic provision of emollient cream to take home and to start using when starting study treatment as indicated in the algorithm for management and investigation of rash included in Appendix G: “Guidance for Management of Adverse Events in Studies of Selumetinib.”

The following treatments/drugs are restricted in this study:

- No other anti-cancer agents, or investigational drugs should be administered whilst patients are receiving study medication or are in follow-up in this study (unless the patient withdraws from the study, or meets the re-treatment criteria in Section 5.9).

- Patients who are taking coumarin anticoagulants should increase the frequency of assessment of anticoagulation, such as INR measurements, during the study treatment period with selumetinib/placebo.

- The maximum dose of vitamin E patients may receive from selumetinib is approximately 261.6 mg/day. The concomitant intake of excessive (supratherapeutic) doses of vitamin E should be avoided in patients receiving the capsule formulation.

- Throughout the study, patients should avoid changes to, or the addition of all other concomitant medications, in particular any that may affect the metabolism of selumetinib (eg, CYP1A2 or 3A4 inhibitors/inducers), unless considered clinically indicated.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the Case Report Form.

All concomitant medications will be recorded on the CRF until 30 days after the last dose of study treatment, and after this time a study-specific record must be kept of any further treatment for thyroid cancer (including surgery), or treatment for RAI-related AEs/SAEs until the last study visit for all patients (refer to Section 5.9).

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Where appropriate facilities and procedures for drug destruction exist, and prior approval from the site monitor has been received, site personnel will account for all unused drugs and for appropriate destruction.

Where such facilities do not exist study site personnel/study monitor will return all unused drugs to AstraZeneca or its designee according to country rules.

The AstraZeneca monitors will ensure that all drug-handling procedures at sites are appropriate, and that all certificates of delivery and return are completed and signed by the site, AstraZeneca, or its delegate, as appropriate. In addition, the monitor will check that the certificate of destruction has been signed by the site, if study drug destruction is performed at the site.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Risk to patients as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- A female patient becoming pregnant

5.8.1 Procedures for premature discontinuation of a patient from investigational product

A patient that decides to prematurely discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.5.3 and 6.5.4), and all study drugs should be returned by the patient. In this situation, a treatment discontinuation visit will be conducted as soon as possible after the patient received the last dose of study drug (selumetinb/placebo). A single 12-lead ECG, physical examination, vital signs measurement, clinical chemistry, haematology is also required at premature discontinuation of treatment. As long as the patient does not withdraw consent, study visits will be continued according to study plan. RAI treatment will be administered as soon as possible after last dose of investigational product and WBS will be performed 3-10 days following the RAI dose.

RAI treatment must be preceded by 0.9 mg intra-muscular injection of thyrogen administered 2 days immediately prior to RAI.

30 days post treatment visit will be conducted 30 days (+/- 2days) after last dose of investigational product or RAI (whatever latest). The schedule of follow – up assessments described in Table 3 should continue relative to RAI treatment in the event of selumetinib premature discontinuation.

A patient that decides to prematurely discontinue investigational product and has not received RAI treatment should continue study visits according to study plan. The schedule of follow – up assessments described in Table 3 should continue relative to planned date of RAI treatment.

If a patient is withdrawn from the study (ie, withdraws consent for follow-up procedures), see Section 5.10.

Any patient with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (±7days) after discontinuation.

5.9 Criteria for further thyroid cancer therapy during the study

5.9.1 Re-treatment prior to the 18 month primary endpoint assessments

It is acknowledged that there is variability in thyroid cancer re-treatment clinical practice. The study-specific criteria below are designed to standardise re-treatment prior to the primary endpoint assessments for the purpose of this study as best as possible. Thus, further thyroid cancer therapy (eg, additional surgery or RAI treatment) prior to the primary analysis of complete remission at 18 months post-RAI, must not be administered unless any of the following criteria are met.

Patients meeting the following re-treatment criteria do not have to be re-treated, they can instead be followed expectantly without re-treatment at the discretion of the treating Investigator.

5.9.1.1 Biochemical disease re-treatment criteria

The first scheduled post-RAI follow up for serum Tg will be assessed 9 months after the RAI dose (± 3 months). Tg assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (**but not before 6 months**).

All biochemical sample analysis for study re-treatment criteria must be performed by standardised central laboratory methodology (for further details refer to the Laboratory Manual).

Patients must not be re-treated for thyroid cancer unless any of the following biochemical criteria are met:

1. If a serum Tg level ≥ 5 ng/mL on central analysis is measured **during TSH suppression**, then a repeat Tg sample must be assessed by central analysis 2-4 weeks later. The patient must not be re-treated unless both centrally analysed samples demonstrate the suppressed Tg level to be 5 ng/mL or higher.

2. If a serum Tg level ≥ 10 ng/mL is measured **following TSH stimulation**, the patient may be re-treated (a repeat sample for confirmation is not necessary). Note, a stimulated Tg assessment is not part of the study-specific follow up plan for patients prior to the 18 month primary endpoint assessments (thus it is not recommended or required, and is not included in the Study Plan). However, if a stimulated Tg assessment is performed due to local practice, this re-treatment criterion applies.

3. If an increase (delta change) in serum Tg level of 3 ng/mL or more is determined between two Tg assessments taken 2-4 weeks apart (due to a repeat sample), the patient may be re-treated.

Thus, in the absence of structurally identifiable disease, patients in this study should have continued observation without additional thyroid cancer treatment (eg, additional RAI, surgery) until the study primary endpoint (18 months after RAI treatment), if the serum Tg level remains below 5 ng/mL during TSH suppression, below 10 ng/mL following TSH stimulation (if assessed), and is either stable/declining, or rising less than 3 ng/mL between samples 2-4 weeks apart.

Note: If a patient has Tg levels below the above re-treatment criteria, but TgAb are detected (ie, the patient is TgAb positive; refer to Section 6.4.3.4), the patient should not be re-treated unless new structural disease is detected according to Section 5.9.1.2 (ie, it is recommended that patients are not re-treated on the basis of new antibodies alone, in the absence of structural disease).

Unscheduled samples and local analysis

It is acknowledged that Investigators may wish to also perform their own local biochemical analysis according to local standard of care. In general, unscheduled samples that are taken either outside of the visit window specified, or in addition to the scheduled study samples, should not be sent for standardised central analysis. Only if such unscheduled local analysis leads the Investigator to wish to administer further therapy for thyroid cancer, should a sample ideally be sent for central analysis and the above criteria applied before the patient is re-treated.

5.9.1.2 Structural disease re-treatment criteria

The first post-RAI ultrasound follow up will be assessed 9 months after the RAI dose (± 3 months). Ultrasound assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (but not before 6 months).

Patients must not be re-treated for thyroid cancer unless any of the following structural criteria are met:

1. In the absence of any biochemical evidence of thyroid cancer, structural DTC should be confirmed prior to re-treatment, by positive histology/cytology from a biopsy/FNA of ultrasonographically suspicious lesions or lymph nodes ≥ 5 mm in the smallest diameter (refer to Section 6.4.4.5).

2. Identification of new distant metastases (these do not need to be confirmed by biopsy). Assessment of potential distant metastases is not required, but may be performed if clinically indicated at the discretion of the treating Investigator.

5.9.1.3 Patient management on study (up to the primary analysis at 18 months post-RAI)

At the required follow up visits, the following questions should be answered for each subject:

1. Does the patient have a suppressed Tg ≥ 5 ng/mL, a TSH stimulated Tg ≥ 10 ng/mL or a rising Tg level (increase of 3 ng/mL or more) according to the guidelines in Section 5.9.1.1?

2. Does the patient have new loco-regional structural thyroid cancer according to the guidelines in Section 5.9.1.2?

3. Does the patient have new distant metastatic lesions according to the guidelines in Section 5.9.1.2?

If the answer is yes to any of the questions, the patient is unlikely to enter remission and may be re-treated for thyroid cancer (but does not have to be).

Full details of any thyroid cancer re-treatment must be recorded on the appropriate eCRF.

Any re-treated patients will remain in the study and should enter standard of care follow up according to local practice until 3 years after their initial RAI therapy (refer to Section 6.4.8). Patients who are re-treated prior to the primary endpoint at 18 months post-RAI do not require primary endpoint disease assessments performing, however these patients should continue to follow all protocol-scheduled visits for safety (AE/SAE follow-up) as described in the Study Plan Table 3 and in Section 6.5. Patients do not need to attend these follow up visits in person (telephone contact is permitted), however when local follow-up visits coincide with protocol-specified visits, these should ideally be in person where possible.

If the answer is no to all questions, the patient should continue the study follow-up as per protocol without additional thyroid cancer re-treatment.

5.9.2 Re-treatment after the 18 month primary endpoint assessments

Following completion of all assessments for complete remission at the primary endpoint 18 months post-RAI, patients may receive re-treatment for thyroid cancer as per clinically indicated according to local standard of care. Any re-treated patients will remain in the study and should enter standard of care follow up according to local practice until 3 years after their initial RAI therapy (refer to Section 6.4.8).

Full details of any thyroid cancer re-treatment must be recorded on the appropriate eCRF.

5.10 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and follow-up assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.5.3 and 6.5.4); any remaining study drug should be returned by the patient.

5.11 Replacement of patients

There will be no replacement of randomised patients in this study for any reason.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

6.2 Data collection at enrolment

The following data will be collected & procedures performed for each patient:

1. Informed consent (to include consent for archival tumour sample provision)
2. Demography (date of birth, sex, race)
3. Histological/cytological confirmation of thyroid cancer, including post-operative disease staging
4. Medical and surgical history
5. Concomitant medications and previous anti-cancer therapy
6. Assessment of WHO or ECOG performance status (refer to Section 6.2.1)
7. Collection of AEs will start after signing the consent form
8. Physical examination
9. Vital signs (resting blood pressure (BP), pulse rate), weight and height
10. Single ECG
11. Blood samples for clinical chemistry and haematology
12. Blood sample for determination of interfering Tg antibodies (central standardised analysis)
13. Local derived *BRAF* and/or *NRAS* mutation status (where available)
14. Urinalysis (at sites where the local laboratory is able to determine the required parameters, see Section 6.5.5)

15. Pregnancy test for female pre-menopausal patients

16. Full ophthalmologic examination, including slit-lamp fundoscopy and intraocular pressure examination

17. ECHO or MUGA

18. The following imaging assessments must be performed within the 28 day screening period but only after all other screening procedures have confirmed eligibility status (refer to Section 6.3):

    (a) Neck ultrasound (US)

    (b) Neck MRI with contrast

    (c) Chest CT scan without contrast

19. Overall assessment of patient eligibility for the study

20. Upon confirmation of patients' eligibility, patients will be invited to attend the randomisation visit. Patients must not be randomised unless all eligibility criteria have been met.

21. Call interactive voice response system (IVRS)/interactive web response system (IWRS) to randomise the patient

6.2.1 Performance status definitions

Performance status will be assessed at screening according to either the WHO or ECOG criteria as follows:

0 = Fully active, able to carry out all pre-disease performance/activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light housework, office work

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair.

6.3 Post-operative imaging assessments for eligibility

The post-operative imaging assessments of US, neck MRI and chest CT are performed during screening to determine study eligibility. These assessments must determine the absence of macroscopic persistent disease post-surgery for a patient to be eligible prior to randomisation.

The post-operative imaging assessments must be scheduled once all other screening assessments and eligibility criteria have been verified.

The screening chest CT procedure must be performed **without iodine containing contrast agent**.

Eligibility will be determined by the local investigational site.

Acquisition guidelines for the post-operative imaging assessments will be provided separately to this protocol.

In addition to information recorded on the eCRF for US, the post-operative images for chest CT and neck MRI must be collected and sent to the central imaging CRO.

6.4 Efficacy

6.4.1 Complete remission

The primary endpoint for this study is **complete remission rate at 18 months** (following RAI treatment).

Definition of complete remission:

Patients will be defined to be in complete remission if all of the following criteria can be demonstrated:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer[a] on neck US, as assessed by investigator site review.

3. No confirmed radiological evidence of thyroid cancer[a], as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

There are two main components to complete remission: biochemical remission and structural remission. Biochemical remission is measured by Tg and structural remission is assessed by the imaging assessments US, MRI, CT and WBS in conjunction with biopsy/FNA.

A staged approach will be taken for performing assessments contributing to the primary endpoint, to avoid unnecessary assessments for individual patients who received further

therapy prior to the primary assessment, and for those patients not in biochemical remission (as determined by serum Tg levels in the absence of interfering Tg antibodies).

[a]Confirmation of evidence of structural DTC will be either histopathological (from a biopsy/FNA; as criterion 4 above), or RAI-avid disease (refer to Section 6.4.4.2). In this disease setting, structural abnormalities that are not RAI-avid and do not have confirmed histopathology consistent with DTC (ie are not biopsy proven) are considered benign in the absence of biochemical DTC.

6.4.2 Staged approach to primary endpoint assessments

Full details of the staged approach to the primary endpoint assessments are outlined below.

There will be 3 stages of assessments. Patients that have been re-treated for thyroid cancer will not have any primary endpoint assessments performed. All patients who have not been re-treated for thyroid cancer will have stage 1 assessments performed. The decision on whether to proceed to stage 2 and 3 assessments for patients that have not been re-treated will be based on centrally analysed biochemical data (Tg and TgAb data).

Sites will receive results from standardised central laboratory analysis of the biochemical data and make a decision to proceed based on these results. Patients identified as not in biochemical remission will not be required to have all imaging assessments described in Section 6.4.1 performed.

For patients that have imaging assessments performed, the appropriate data will be sent to the imaging CRO for blinded independent central review to identify presence or absence of structural disease. Note: results from the central imaging review will not be reported to clinical sites.

Briefly:

In stage 1, suppressed Tg will be determined together with neck US assessment for all patients who did not require re-treatment for thyroid cancer during the first 18 months of follow up (refer to Section 6.4.2.1).

In stage 2, rhTSH stimulated Tg and diagnostic WBS will be performed (refer to Section6.4.2.2).

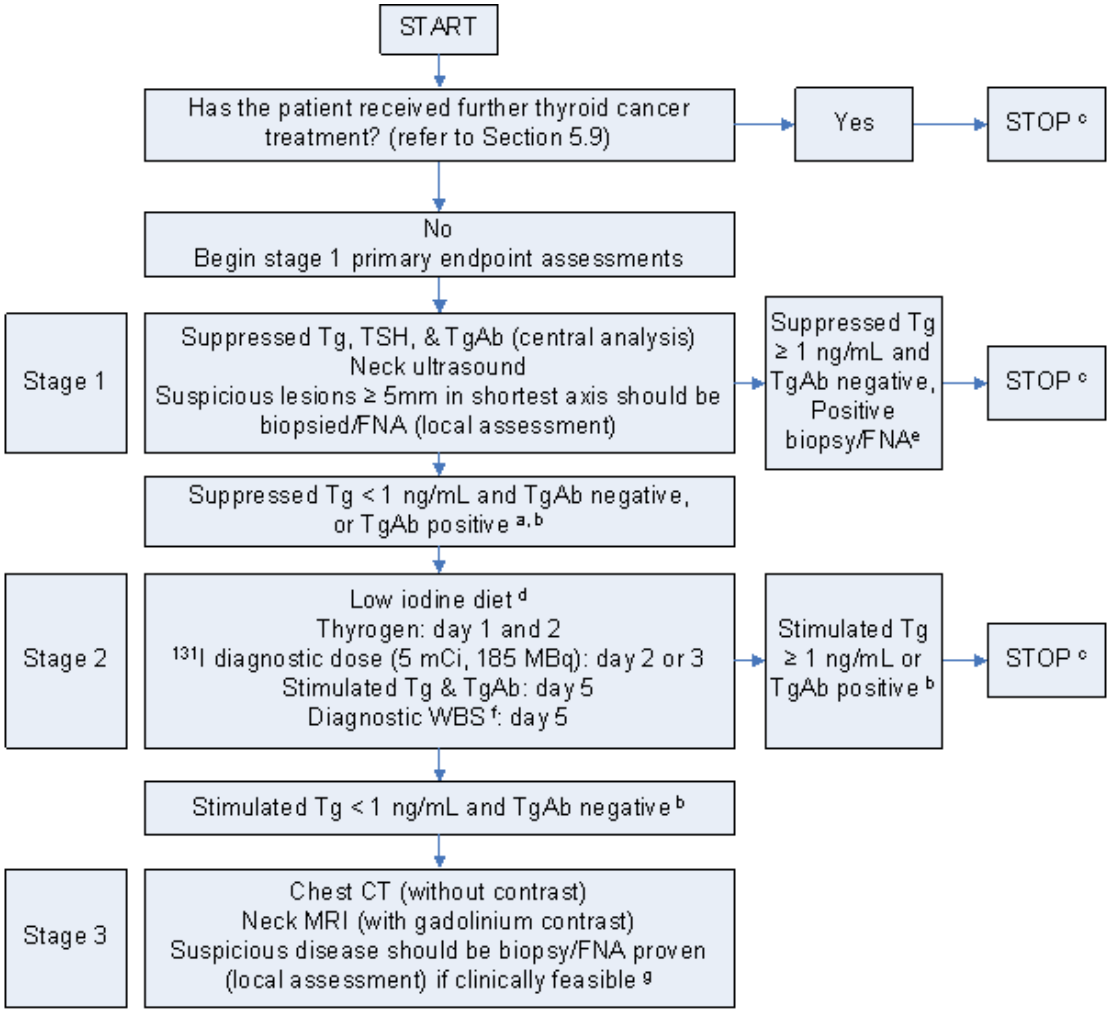
In stage 3, additional radiological imaging (chest CT and neck MRI) will be performed (refer to Section 6.4.2.3).

Stage 1 assessments must be started 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments (all 3 stages if required) must be completed within an 8 week period (refer also to Table 4).

Refer to the flowchart Figure 3 for a visual representation of the staged approach for primary endpoint assessments.

Refer to Section 6.4.5 for the process of determining complete remission from the primary endpoint assessment data.

Figure 3 Flow chart for staged primary endpoint assessments



[a] Patients should progress to stage 2 assessments based on biochemical data only (regardless of US results). Any TgAb positive patients should progress to stage 2 regardless of their suppressed Tg result.
[b] If both stage 1 and stage 2 blood samples are positive for TgAb, then the stimulated Tg result will be deemed to be uninterpretable, and for the purpose of this study the patient will be classified as not in complete remission. No further primary endpoint assessments are required. The patient will remain in the study for follow up until 3 years following their initial RAI treatment. If the stage 1 and stage 2 samples are discordant for TgAb status, then a third blood sample 10 days later (± 3 days) is required to confirm TgAb status.
[c] For the purpose of this study, patient will be classified as not in complete remission. The patient should remain in the study for follow up until the final study visit 3 years following their initial RAI treatment, and enter standard of care treatment/follow up according to local clinical practice.
[d] Low iodine diet is required from 1 week before the diagnostic dose of ^{131}I is administered, until completion of the WBS assessment. Refer to Appendix F.
[e] If a patient has a biopsy/FNA result available that confirms the presence of structural DTC then no further assessments are required. If a biopsy/FNA was taken, but the result is not yet available, then the patient should not delay moving to stage 2 assessments (even if the biopsy/FNA is subsequently confirmed to be positive for structural DTC).
[f] For study endpoint purposes the WBS will evaluated by blinded independent central review. Even if local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).
[g] For the size criteria for biopsy/FNA from MRI/CT assessments, refer to Sections 6.4.4.3 and 6.4.4.4 respectively.

6.4.2.1 Primary endpoint assessments Stage 1

Patients that have been re-treated for thyroid cancer between their initial RAI dose and the primary endpoint assessments 18 months later (refer to Section 5.9 for re-treatment criteria), will not have any primary endpoint assessments performed. For the purpose of the primary endpoint, such re-treated patients will be determined not to be in complete remission.

In stage 1, all patients that have not previously been re-treated for thyroid cancer will have:

- Suppressed Tg level determined by standardised central laboratory analysis.
- TSH and TgAb (using the same blood draw for suppressed Tg) determined by standardised central laboratory analysis. Refer to Section 6.4.3.
- Neck US assessment for structural disease to be assessed by investigator site review. Refer to Section 6.4.4.1.

Suspicious lesions identified by US ≥ 5 mm in the shortest diameter should be biopsied or aspirated by fine needle. All biopsy/FNA samples will be assessed locally at each site. Lesions identified by US < 5 mm in the shortest diameter do not require a biopsy.

All neck US and biopsy/FNA samples will be assessed locally at each site. The relevant US information with any biopsy findings will be provided to the imaging CRO as part of the blinded independent central review.

When to proceed to stage 2 assessments

All patients in the following situations should proceed to stage 2 assessments:

1. Patients with suppressed Tg < 1 ng/mL. These patients should proceed to stage 2 regardless of the TgAb or US results.
2. Patients who are TgAb positive in stage 1 (regardless of the suppressed Tg level, and US results).
3. Patients who fulfil either of the 2 above criteria, and have a biopsy/FNA result pending (ie, Investigators should not wait for the biopsy/FNA result before performing stage 2 assessments).

When not to proceed to stage 2 assessments

All patients in the following situations will be classified not in complete remission and should not proceed to stage 2 assessments:

1. Patients who have suppressed Tg level ≥ 1 ng/mL in the absence of TgAb (unequivocal biochemical disease).

2. Patients with a positive biopsy/FNA that confirms the presence of structural DTC. Note that if the biopsy/FNA results are not yet available, the patient should not delay proceeding to stage 2 assessments.

Patients who demonstrate presence of disease and do not proceed to stage 2 assessments will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, **and will continue to be followed in this study** until 3 years following their initial RAI dose (refer to Section 6.4.6).

6.4.2.2 Primary endpoint assessments Stage 2

In stage 2, patients will have:

- rhTSH stimulated Tg level determined by standardised central laboratory analysis.
- TgAb (from the same blood draw for rhTSH stimulated Tg) determined by standardised central laboratory analysis. TSH will not be analysed from this sample. A repeat (third) sample for TgAb analysis may be required 10 days ± 3 days later if the stage 1 and 2 TgAb status is discordant (refer to Table 5).
- Diagnostic nuclear medicine ^{131}I scan (WBS) to be evaluated by blinded independent central review.

These assessments will require the patient to follow a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose, until the diagnostic WBS assessment is completed (refer to Section 5.1.1 and Appendix F). Patients will also receive two Thyrogen injections (refer to Section 5.5.4.1) on consecutive days (day 1 and 2), followed by a diagnostic dose (5 mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5.

When to proceed to stage 3 assessments

Patients should proceed to stage 3 assessments in the absence of biochemical disease. Patients with stimulated Tg < 1 ng/mL and TgAb negative (for the definition of TgAb negativity refer to Section 6.4.3.4) should proceed to stage 3 **regardless of the WBS results**.

- Note that if the stage 1 and 2 blood samples are discordant for TgAb, a repeat (third) blood sample for central analysis is required 10 days (±3 days) later. Only if the third sample is negative for TgAb will the stimulated Tg level from stage 2 be considered to be interpretable and valid for decision making. Refer also to Table 5.
- Note also that for study purposes the WBS will evaluated by blinded independent central review, and even if local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).

When not to proceed to stage 3 assessments

All patients in the following situations will be classified not in complete remission and should not proceed to stage 3 assessments:

1. Patients who have stimulated Tg level ≥ 1 ng/mL in the absence of TgAb (unequivocal biochemical disease by standardised central laboratory analysis).

2. Patients confirmed to be TgAb positive (regardless of all other data):

   (a) When both the stage 1 and 2 blood samples are TgAb positive (refer to Section 6.4.3.4).

   (b) When the repeat (third) blood sample confirms positive TgAb following a discordant TgAb status from stage 1 and 2.

In these situations the stimulated Tg value will be deemed to be uninterpretable, and the patient will be deemed not to be in complete remission because absence of biochemical disease cannot be proven.

These patients will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, and will continue to be followed in this study until 3 years following their initial RAI dose (refer to Section 6.4.6).

Note that for study purposes the WBS will evaluated by blinded independent central review. If local interpretation of WBS scan data indicates uptake suspicious for DTC, any biochemically negative patients must still be sent for stage 3 assessments (in case the local and central WBS results are discordant).

Table 5 Criteria for biochemical decision making (based on standardised central analysis results)

Scenario	Stage 1		Stage 2		Repeat 3rd TgAb sample[b]	Biochemical remission?
	Suppressed Tg	TgAb[a]	Stimulated Tg	TgAb[a]		
1	≥ 1ng/mL	Negative	Not required	Not required	Not required	No. Stop.[c]
2	< 1 ng/mL	Negative	< 1 ng/mL	negative	Not required	Yes. Proceed to stage 3
3	< 1 ng/mL	Negative	≥ 1 ng/mL	negative	Not required	No. Stop.[c]
4	Any	Positive	< 1 ng/mL	negative	negative	Yes. Proceed to stage 3
5	Any	Positive	< 1 ng/mL	negative	positive	No. Stop.[c]
6	< 1 ng/mL	Negative	< 1 ng/mL	positive[d]	negative	Yes. Proceed to stage 3
7	< 1 ng/mL	Negative	< 1 ng/mL	positive	positive	No. Stop.[c]
8	Any	Positive	Any	positive	Not required	No. Stop.[c]

[a] Standardised central methodology will be used to define TgAb negative/positive status, refer to Section 6.4.3.4.
[b] When the TgAb results from stage 1 and 2 are discordant, a repeat (third) blood sample for TgAb is required 10 days (± 3 days) after the stage 2 blood sample.
[c] For the purpose of the study, the patient will be deemed not to be in complete remission and no further stage 3 assessments are required. These patients will enter standard of care treatment/follow up at each centre as determined by the treating Investigator, and will continue to be followed in this study until 3 years following their initial RAI dose (refer to Section 6.4.6).
[d] Although this stimulated Tg blood sample is positive for TgAb, the patient will be declared to be in biochemical remission if the other two TgAb samples are both negative by standardised central analysis. It is not feasible to repeat a second stimulated Tg assessment.

6.4.2.3 Primary endpoint assessments Stage 3

In stage 3, patients with biochemically-negative disease will have:

- Neck MRI with gadolinium contrast to be evaluated by blinded independent central review.
- Chest CT without contrast to be evaluated by blinded independent central review.
- If clinically indicated, a biopsy/FNA should be performed as follows:
  - For any suspicious lymph nodes on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter.
  - For any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter should be biopsied/FNA.

6.4.3 Blood sample assessments for efficacy

All protocol-scheduled samples for serum Tg (suppressed and stimulated), TSH and TgAb assessment, will be sent for central laboratory analysis using standardised methodology. All decision making for study purposes will be based on the standardised central analysis results; values obtained from different assay methods may be different and cannot be used interchangeably.

Full details of the sample collection, shipment and analytical methodology is provided in the Laboratory Manual.

Unscheduled samples and local analysis:

Investigators may also perform local biochemical analysis for these parameters as per standard site practice if desired, however this data will not be used for study-related decision making. If local analysis is performed, Investigators must ensure that the maximum permissible blood volumes for individual patients at their institutions are not exceeded.

In the case that an investigator performs additional assessment of Tg (and TSH, TgAb) outside of the protocol scheduled visits, such samples should not be sent for central laboratory analysis. Only if such unscheduled local analysis leads the Investigator to wish to administer further therapy for thyroid cancer, should an additional sample ideally be sent for central analysis and the protocol-specified re-treatment criteria applied (Section 5.9.1.1) before the patient is re-treated.

6.4.3.1 Suppressed Tg

Prior to the 18 month primary endpoint assessments:

A blood sample for TSH-suppressed serum Tg is required at 9 months after the RAI dose (± 3 months) in order to assess whether thyroid cancer re-treatment is clinically indicated;

refer to the thyroid cancer re-treatment guidelines in Section 5.9.1.1. Tg assessment for this purpose may take place at any time from 6 months after the patient's RAI treatment (but not before 6 months). A second blood sample 2-4 weeks later may also be required to verify the biochemical re-treatment criteria (refer to Section 5.9).

Stage 1 primary endpoint assessments:

For all patients that have not been re-treated for thyroid cancer prior to the primary endpoint assessments 18 months following their RAI dose, a blood sample to centrally analyse the TSH-suppressed serum Tg level will be taken.

Anytime that a Tg blood sample is taken, the same sample will also be centrally analysed for TSH and TgAb (refer to Sections 6.4.3.3 and 6.4.3.4 respectively).

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

6.4.3.2 Stimulated Tg

Prior to the 18 month primary endpoint assessments:

Prior to the 18 month primary endpoint assessments, stimulated Tg levels are not recommended and not included as part of the patient follow up for this study.

Stage 2 primary endpoint assessments:

Serum Tg measured during TSH suppression is not sufficiently sensitive to confirm that a patient is free of thyroid cancer. For this reason, rhTSH (Thyrogen) stimulated serum Tg level will also be assessed at the primary endpoint, only for patients proceeding to stage 2 of the primary endpoint assessments.

For patients that require stimulated Tg assessment, 0.9 mg of rhTSH will be administered IM for 2 consecutive days (refer to Section 5.5.4.1), with the blood sample taken for stimulated Tg central analysis on day 5.

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

Each time that a blood sample is taken for central stimulated Tg analysis, the same sample will also be centrally analysed for TgAb (refer to Sections 6.4.3.4 respectively).

6.4.3.3 TSH

Thyroid hormone supplementation will be adjusted in individual patients with the aim of achieving suppressed TSH levels of 0.5 mIU/L or less for the duration of the study. Each time that a suppressed Tg sample is taken, TSH should also be assessed (by central standardised methodology).

The volume of blood for biochemical assessments is detailed in the Laboratory Manual for this study.

6.4.3.4 Tg antibody (TgAb)

Each time that a blood sample is taken for central Tg analysis, the same sample will also be centrally analysed using standardised methodology for TgAb. Full details of the sample collection, shipment and analytical methodology to be used will be provided in the Laboratory Manual.

TgAb cut-off for decision making

For decision making purposes at any time in the study, standardised central analysis results must be used. The cut-off value for positive/negative TgAb status according to the standardised central methodology will be provided to sites prior to the start of recruitment.

At screening:

Patients with TgAbs present at screening will be ineligible for the study (refer to the exclusion criterion in Section 4.2, screening samples must be sent for standardised central analysis).

Prior to the 18 month primary endpoint assessments:

If TgAbs are detected in the follow-up Tg blood sample (at 9 months ±3 months), the patient should not be re-treated unless new structural disease is detected according to Section 5.9.1.2 (ie, it is strongly recommended that patients are not re-treated on the basis of new antibodies alone, in the absence of structural disease). Refer to Section 5.9.

Primary endpoint assessments (Stage 1 and 2)

The TgAb status of the stage 1 blood sample will not be taken into consideration alone. The following rules will apply (refer also to Table 5):

1. If both stage 1 and stage 2 blood samples are negative for TgAb, then the Tg results will be valid for decision making.

2. If both stage 1 and stage 2 blood samples are positive for TgAb, then the stimulated Tg result will be deemed to be uninterpretable, and for the purpose of this study the patient will be classified as not in complete remission. No further primary endpoint assessments are required.

3. If the stage 1 and 2 blood samples are discordant for TgAb status, then a repeat (third) blood sample is required 10 days later (± 3 days). Only if the repeat sample is confirmed negative for TgAb, will the stimulated Tg level in stage 2 be considered to be interpretable and valid for decision making.

6.4.4 Imaging assessments for efficacy

6.4.4.1 Neck ultrasound (US)

Neck US assessments will take place at the times indicated in the Study Plan Table 3. Refer also to Section 6.4.2 and Table 4 for further details of US assessment at the primary endpoint.

Any suspicious lymph nodes or lesions in the neck ≥ 5 mm in the smallest diameter identified by US during the study should be biopsied/FNA.

Note: for a lesion to be suspicious it must be new or enlarged compared to the previously obtained imaging data, and be consistent with the biological characteristics of DTC.

Biopsy/FNA samples, where performed, will be assessed at each site. Needle washout may be analysed locally for Tg according to local standard practice. The totality of the information obtained from a biopsy/FNA (including washout Tg data where analysed), will be assessed locally to determine presence or absence of thyroid cancer in the sample.

US definition of structural DTC

Any soft tissue or lymph node lesions that are new or enlarged compared to previous ultrasound assessment (either post operatively and/or at 9 months) that are consistent with the biological characteristics of DTC and fulfil the following criteria will be considered as structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is subsequently shown to be RAI avid/positive on central review of WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on US that is non-RAI avid on the subsequent WBS, will be considered benign even in the absence of a biopsy.

The assessment of neck US and biopsy/FNA sample will be made by investigator site review.

The local ultrasound information will be recorded in the eCRF (with FNA/biopsy results if performed) and provided to the central imaging CRO if necessary as supporting clinical data (refer to Section 6.4.4.6).

Guidelines for standardised acquisition, defining suspicious lesions and reporting of US assessments required for this study will be provided to each study site.

6.4.4.2 Whole body diagnostic ^{131}I nuclear medicine scan (WBS)

Pre-RAI treatment

There is no pre-ablation WBS in this study. This is a fixed RAI dose study (100mCi, 3.7GBq) with Thyrogen stimulation. Study-specific post-operative imaging will be used to ensure that enrolled patients do not have overt macronodular disease remaining in the neck or distant metastatic disease in the lungs.

Post-RAI treatment

All randomised patients will have a WBS performed 3-10 days following their RAI treatment dose to assess where the administered ^{131}I has localised.

It is acknowledged that this assessment may identify a small number of patients with distant metastatic disease that was not previously identified (patients with known metastatic disease at study entry will be excluded). Such patients will continue in the study and should not be withdrawn; they will continue to be followed according to the protocol and will be included in both the Intention To Treat (ITT) efficacy and safety analysis sets for the study.

Primary endpoint (stage 2)

If required according to Section 6.4.2, the diagnostic WBS to assess the primary endpoint will be performed following a diagnostic dose of 5 mCi ^{131}I (refer to Section 5.5.4.2). Patients will receive 2 Thyrogen injections on consecutive days (day 1 and 2), followed by a diagnostic dose (5 mCi) of ^{131}I on either day 2 or day 3, and a blood draw for stimulated Tg central assessment and WBS both on day 5. Patients will be required to adhere to a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose, until the diagnostic WBS assessment is completed.

Standardised acquisition and submission guidelines for every WBS procedure will be provided separately to this protocol.

WBS definition of structural DTC

The WBS evaluation will be made by blinded, independent central review.

If the central review determines no visible ^{131}I uptake then the WBS for that patient will be considered normal/negative (no disease). Areas considered to be anatomically normal (for example uptake in the salivary glands, stomach, gastrointestinal, urinary tract and bladder) will not be considered disease.

If the central review determines there is a low level of visible uptake in the thyroid bed:

- Uptake must be < 0.1% to be considered normal/negative (no disease).
- If uptake in the thyroid bed region is ≥ 0.1%, the patient will be deemed not to be in remission due to the presence of iodine-avid DTC.

The % uptake in the thyroid bed will be assessed by the Investigator site according to the local clinical practice and entered into the eCRF to be made available to the central reviewer.

If an abnormality identified by US is subsequently shown to be RAI avid on WBS, the WBS data takes precedent over a negative biopsy/FNA.

6.4.4.3 Neck MRI

Post-operative (screening)

This baseline assessment is performed to determine study eligibility according to Section 4.1). The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Primary endpoint (stage 3)

Neck MRI to define the primary endpoint will be performed in stage 3 of the assessments in patients deemed to be biochemically-negative for thyroid cancer. Refer to Section 6.4.2.3 and Figure 3.

The neck MRI must be performed using T1 weighted image sequences with and without gadolinium contrast agent, and T2 weighted image sequences.

If clinically indicated, any suspicious lymph nodes on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter, should be biopsied/aspirated by fine needle.

MRI definition of structural DTC

New lesions (nodal or non-nodal) or significantly enlarged lymph node lesions compared to previous post operative (screening) MRI which are consistent with the biological characteristics of DTC and fulfil either of the following criteria will be considered to represent structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is shown to be RAI avid/positive on WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on MRI that is non-RAI avid on the WBS, will be considered benign even in the absence of a biopsy.

This assessment will be made by blinded, independent central review.

6.4.4.4 Chest CT

In this study all chest CT procedures should be performed without iodine containing contrast agent.

Post-operative (screening)

This baseline assessment is performed to determine study eligibility according to Section 4.1). The baseline post-operative images will be available at the central imaging CRO to aid interpretation of the primary endpoint image central read if necessary (refer to Section 6.3).

Primary endpoint (stage 3)

Chest CT to define the primary endpoint will be performed in stage 3 of the assessments in patients deemed to be biochemically-negative for thyroid cancer. Refer to Section 6.4.2.3 and Figure 3.

If clinically indicated, any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter should be biopsied/FNA.

CT definition of structural DTC

New lesions (nodal or non-nodal) or significantly enlarged lymph node lesions compared to previous post operative (screening) CT which are consistent with the biological characteristics of DTC and fulfil either of the following criteria will be considered to represent structural thyroid cancer:

- Lesions of any size confirmed to be structural DTC by positive biopsy/FNA (ie, biopsy proven).
- Any suspicious lesion or lymph node of any size that is shown to be RAI avid/positive on WBS (in this situation the positive WBS data takes precedent over a negative biopsy/FNA from the same lesion/lymph node if performed).

Note, any abnormality on CT that is non-RAI avid on the WBS, will be considered benign even in the absence of a biopsy.

This assessment will be made by blinded, independent central review

6.4.4.5 Biopsy or fine needle aspirate (FNA)

A biopsy or FNA should be performed in the following situations:

- **US:** For any suspicious lymph nodes or lesions in the neck ≥ 5 mm in the smallest diameter identified by US during the study.
- **MRI:** If clinically indicated, for lymph nodes suspicious on MRI ≥ 15 mm in the smallest diameter (≥ 10 mm for level II, III or IV lymph nodes in the neck), or non nodal lesions ≥ 10 mm in the smallest diameter.

- **CT**: If clinically indicated, for any chest abnormalities suspicious on CT ≥ 10 mm in the smallest diameter.

Note: for a lesion to be suspicious it must be new or enlarged compared to the previously obtained imaging data, and be consistent with the biological characteristics of DTC.

All biopsy/FNA samples taken during the study will be assessed at each site according to local standard practice. Needle washout may be analysed locally for Tg according to local standard practice (this is not a mandatory requirement). The totality of the information obtained from a biopsy/FNA (including washout Tg data where analysed), will be assessed locally to determine presence or absence of thyroid cancer in the sample. This information will be provided to the central imaging CRO.

Refer to Section 6.10.3 for details regarding tumour sample acquisition on disease progression.

6.4.4.6 Information to be sent to the central imaging CRO

The following information will be sent to the central imaging CRO (further details are provided in the imaging charter/guidelines for this study).

1. Post-operative screening assessments (refer to Section 6.3): images for chest CT and neck MRI. This data must be sent for all patients as soon as possible after each patient is randomised.

2. Post-RAI WBS images taken 3-10 days after each patient's RAI dose. This data must be sent for all patients as soon as possible after each patient has their post-RAI WBS assessment.

3. Primary endpoints assessments stage 1: site ultrasound and biopsy information. The required data must be entered into the clinical database for each patient as soon as possible after completion of the assessment (NOTE: this information is not sent to the central imaging CRO, but instead must be entered into the database directly using eCRF).

4. Primary endpoint assessments stage 2: diagnostic WBS images. This data must be sent for all patients as soon as possible after completion of the assessment.

5. Primary endpoint assessments stage 3: chest CT and neck MRI images and biopsy information (if performed). This data must be sent for all patients as soon as possible after completion of the assessments. Biopsy data must be entered into the clinical database for each patient as soon as possible after completion of the assessment.

6.4.5 Derivation of primary endpoint of complete remission

The complete remission status of each patient will be determined programmatically by AstraZeneca, by incorporating data on re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, and structural disease assessment from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in complete remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer, all available imaging data will be sent to the imaging CRO. Determination of presence or absence of structural thyroid cancer will be made by the imaging CRO only for biochemically negative patients. A list of biochemically negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

The imaging CRO will assess the WBS, MRI and CT and also review the site assessment of neck US to provide an overall assessment: presence or absence of structural thyroid cancer, or not evaluable based on all of the available information. For the derivation of the complete remission endpoint, patients that are not evaluable for structural disease assessment will be considered as not achieving complete remission, regardless of the result of other assessments.

AstraZeneca will programmatically combine information on further therapy, biochemical data, and the determination of structural disease from the central imaging CRO, to determine the complete remission status of each patient as shown in Table 6.

The dates on which assessments were performed will be incorporated into the derivation of the primary endpoint to ensure patients are assessed within a time window around the scheduled 18 month post-RAI treatment. The first assessment must be started at 18 months ± 2 weeks following the patient's RAI dose, and all necessary primary endpoint assessments must be completed within a 8 week period. If a patient has assessments/scans that fall outside of these time windows, the patient will be considered not to be in complete remission, regardless of the assessment of disease status.

Table 6 Programmatic derivation of complete remission status

Scenario	Further thyroid cancer therapy[a] (re-treatment)	Biochemical data[b]		Structural disease assessment[c]	Complete remission
		Stimulated Tg[b]	TgAb[b]		
1	Yes	N/A	N/A	N/A	No
2	No	< 1 ng/mL	Negative[d]	Absence of disease	Yes
3	No	≥ 1ng/mL	Any	Any	No
4	No	Any	Positive[d]	Any	No
5	No	Any	Any	Presence of disease	No
6	No	NE	Any	Any	No
7	No	Any	NE	Any	No
8	No	Any	Any	NE	No

[a] As assessed by investigator at site.
[b] As assessed by standardised central laboratory analysis.
[c] As assessed by blinded, independent central review.
[d] If the stage 1 and 2 blood samples are discordant for TgAb status, then a third blood sample 10 days later (± 3 days) is required. Only if the third sample is negative for TgAb will the overall TgAb result be considered negative for the primary endpoint assessments. Refer also to Table 5.
N/A primary endpoint assessments are not required for patients that have received further treatment for thyroid cancer in the previous 18 months.
NE Not evaluable (for example due to missing samples or assessments).

6.4.6 Clinical remission

The secondary efficacy endpoint for this study is **clinical remission rate at 18 months** (following RAI treatment). This is designed to more typically reflect clinical practice. As such, the definition of clinical remission will exclude the additional radiological assessments performed for the purpose of complete remission in this study.

Definition of clinical remission:

Patients will be defined to be in clinical remission if all of the following criteria can be demonstrated:

1. Serum Tg levels < 1ng/mL during rhTSH stimulation, in the absence of interfering Tg antibodies, as assessed by standardised central laboratory analysis.

2. No confirmed evidence of thyroid cancer on neck US, as assessed by investigator site review.

3. No evidence of thyroid cancer on diagnostic WBS, as assessed by blinded independent central review.

4. No histopathological evidence of thyroid cancer on FNA/biopsy when performed to clarify equivocal US findings, as assessed by investigator site review.

5. No further thyroid cancer therapy was administered in the first 18 months following the initial RAI treatment.

6.4.7 Derivation of clinical remission status

The clinical remission status of each patient will be determined programmatically by AstraZeneca, by incorporating data on re-treatment provided by the site, biochemical data from the standardised central laboratory analysis, structural disease assessment based on US by investigator site review and structural disease assessment based on WBS from the blinded, independent central review.

If a patient has received further therapy for thyroid cancer prior to the primary endpoint assessment, the patient will be classified as not in clinical remission and no further data will be considered.

For patients that have not received further therapy for thyroid cancer:

A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the investigator based on US.

A determination of presence or absence of structural thyroid cancer or not evaluable will be made by the central imaging CRO based on WBS for only biochemically negative patients. Information on US will not be reviewed as part of this assessment. A list of biochemically

negative patients (based on standardised central laboratory analysis) will be provided by AstraZeneca to the imaging CRO to enable them to identify which patients to assess.

AstraZeneca will programmatically combine information on further therapy, biochemical data, determination of structural disease from the investigator site assessment of US and determination of structural disease from the central imaging CRO of WBS, to determine the clinical remission status of each patient.

Full details of the programmatic derivation of clinical remission will be provided in the SAP.

6.4.8 Final study follow up at 3 years

The final study follow-up will take place 3 years post-RAI for each patient, and will include:

1. The clinical status of each patient, for example: remission, persistent disease, recurrent disease, survival status.

2. The incidence of further therapy (re-treatment) for thyroid cancer, for example, additional RAI or surgery.

3. Final assessment of selumetinib or RAI-related AEs and SAEs.

Note, following the primary endpoint assessments until the final study visit at 3 years following each patient's initial RAI treatment, each patient will enter standard of care treatment or follow up according to local practice. No study-specific assessments will be performed, and locally performed assessments and data will not typically be collected as routine in the clinical study database (except for safety data, refer to Section 6.5.3). The patient's clinical status at the final study follow up will be collected (along with any relevant supporting local assessment data). For example, remission status will be defined by the Investigator on the eCRF based on the relevant local standard of care assessments (eg, locally assessed Tg and no evidence of thyroid cancer on locally assessed US).

6.5 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.5.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.5.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.5.3 Recording of adverse events

All adverse events will be graded according to NCI CTCAE Version 4.

Time period for collection of adverse events

All AEs/SAEs will be collected from informed consent until 30 days following the last dose of study treatment (selumetinib or placebo).

After this time:

- all SAEs regardless of causality will be collected until the final study follow-up (3 years post-RAI for each patient, refer to Section 6.4.8)
- only AEs considered causal to RAI or the combination of RAI and study treatment will be collected until the final study follow-up (3 years post-RAI for each patient, refer to Section 6.4.8).

Follow-up of unresolved adverse events

Any AE or laboratory change occurring during the study treatment period should be followed up by the investigator for as long as medically indicated (resolution or stabilisation), and follow up information recorded in the eCRF.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade information
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no) and/or RAI (yes or no)
- Action taken with regard to investigational product
- AE caused patient's withdrawal from study treatment
- Treatments patient received for AE
- Outcome
- Whether event constitutes an SAE.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death (if applicable)
- Date of death (if applicable)
- Autopsy performed (if applicable)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.5.2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The Investigator will assess causal relationship between Investigational Product and RAI and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication, study procedures and additional study drug (eg, RAI). Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient, or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation, will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs etc should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

After the 30 day follow up visit, AEs associated with RAI or the combination of study treatment and RAI, should continue to be collected by AE reporting, these would include abnormalities, for example, white blood cell count or Hb reductions.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law,' for further instructions. All patients with an AST, ALT or bilirubin value above ULN at time of the last dose of selumetinib/placebo should have a further liver chemistry profile (AST, ALT, bilirubin and ALP) performed 30 days (± 7 days) later for follow-up.

6.5.3.1 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.5.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.5.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (Table 3). For samples taken after Day 1 during the study treatment period, the sample may be taken any time of day (ie, it does not matter whether it is pre-dose or post-dose). Day 1 samples should be taken pre-dose.

The following laboratory variables will be measured:

Table 7 Laboratory safety assessments

Clinical chemistry	Haematology	Urinalysis [a]
s, p-Albumin	Erythrocyte count	u-Albumin
s, p-ALT	Haemoglobin	u-Creatinine
s, p-AST	Platelet count	
s, p-ALP	Leucocyte cell count	
s, p-Total Calcium	Leucocyte differential count (absolute count or percentage):	
s, p-Creatinine	Neutrophils	
s, p-Gamma glutamyl transferase (γGT)	Eosinophils	
s, p-Glucose	Basophils	
s, p-Magnesium	Lymphocytes	
s, p-Phosphate	Monocytes	
s, p-Potassium		
s, p-Sodium		
s, p-Total protein		
s, p-Total bilirubin		
s, p-Urea nitrogen		
s, p-Creatine kinase		

[a] A single-spot urine specimen will be collected on the day of scheduled visit, at sites where the local laboratory is able to determine the concentration of urine albumin and urine creatinine from a single-spot urine specimen. Investigational sites unable to report these parameters will perform routine urinalysis according to the local standard of care.
s, p serum, plasma
u urine

All laboratory safety assessments will be analysed by the local laboratory.

Clinical chemistry, haematology and urinalysis testing will be repeated as clinically indicated as part of the routine management of the patient on the occurrence of AEs.

For blood volume see Table 9.

6.5.6 Physical examination

A complete physical examination will be performed at the times indicated in the Study Plan Table 3.

6.5.7 Cardiac monitoring

Note: troponin assessment in this study is only required for cardiac AE follow up as clinically indicated.

6.5.7.1 ECHO or MUGA

An ECHO or MUGA assessment (according to site preference) will be conducted at the timepoints indicated in the Study Plan (Table 3). A further assessment should be performed as part of the assessment package for any cardiorespiratory adverse event with no obvious diagnosis. Medical management of the event should follow local clinical practice. Selumetinib interruption should be considered until resolution of the event or until return to baseline.

LVEF can be measured in many different ways but echography is the preferred choice when possible. The same modality should be used as baseline for any ECHO/MUGA follow up. Recommendations include having complete high quality standardized 2-D with Doppler echocardiographic examinations performed by an experienced sonographer (preferably with the same operator performing all studies for a given patient), according to a specified protocol including evaluation of both systolic and diastolic left ventricular function. Ejection fraction determinations should be assessed quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.

6.5.7.2 Resting 12-lead ECG

ECGs will be analysed locally at each site. Patients should be supine and at rest 10 minutes prior to recording the ECG.

Parameters including heart rate, duration of QRS complex, PR and QT intervals will be collected. R-R interval and QTcF will be calculated by AstraZeneca from the data provided.

The investigator should review the paper copy of the ECGs on each study day and may refer to a local cardiologist if appropriate.

Any symptoms from the patient should be registered as a comment and if AE criteria are met, recorded as an AE.

At screening all patients will have a single 12-lead ECG performed. The screening ECG can be conducted up to 28 days prior to randomisation.

During the treatment phase of the study, patients will have single 12-lead ECGs assessments at the following timepoints:

- 1-2 hours after the first dose of study treatment on Day 1

- 1-2 hours after the morning dose of study treatment on Day 29 or 30
- At the 30-day follow up visit following completion of study treatment
- Single ECGs must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event
- A single 12-lead ECG is also required at premature discontinuation of treatment

6.5.8 Vital signs

Resting blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size. Vital sign assessments, including weight, will be performed at the times indicated in the Study Plan Table 3. Pulse and blood pressure must also be performed at the time of any ECHO/MUGA assessment, and on occurrence of any cardiorespiratory adverse event. Height will be assessed at Visit 1 only.

Any changes in vital signs should be recorded as an AE if applicable.

6.5.9 Other safety assessments

6.5.9.1 Pregnancy test

A serum or urine pregnancy test (according to local practice) will be performed at the times indicated in the Study Plan Table 3. Following the RAI treatment, monitoring for pregnancy will be performed according to standard clinical practice at each centre.

6.5.9.2 Ophthalmologic examination

An ophthalmologic examination (best corrected visual acuity, intraocular pressure, slit lamp fundoscopy) should be performed at the timepoints indicated in the Study Plan (Table 3), and if a patient experiences a visual symptoms (including blurring of vision) with additional tests if clinically indicated e.g. consider OCT scans.

Patients who have a retinal abnormality prior to discontinuation of selumetinib/placebo should have a follow up eye examination performed within 30 days after discontinuation of selumetinib/placebo in order to document reversibility.

An algorithm for management and investigation of visual symptoms is provided in Appendix G: "Guidance for Management of Adverse Events in Studies of Selumetinib."

6.6 Patient reported outcomes (PRO) – not applicable

Patient reported outcomes will not be collected in this study.

6.7 Pharmacokinetics

6.7.1 PK samples required

Blood samples (2 mL) for determination of plasma concentrations of selumetinib and N-desmethyl selumetinib will be collected from every patient according to the time points below. Other metabolites (eg, selumetinib amide) may also be determined in the PK analysis. Each patient will be asked to contribute 8 blood samples, one from each of the pre defined time windows below on both Day 1 and Day 29 or Day 30. The Day 29 or Day 30 PK blood samples may be taken earlier, from Day 22 onwards of study treatment if preferred, but it is essential that all PK blood samples are collected on a visit day **prior** to the RAI dose being administered.

- Pre-dose (within 15 minutes of dosing)
- Between 15 minutes and 1 hour post-dose
- Between 1.5 and 2.5 hours post-dose
- Between 3 and 8 hours post-dose

Depending on emerging data/information, the timings and number of the PK samples may be altered, but the maximum total blood volumes given in Table 9 will not be exceeded. The actual sample date and time of all PK samples must be recorded in the eCRF.

Samples will be collected, labelled, stored and shipped as detailed in Laboratory Manual.

6.7.2 Determination of drug concentration

Samples for determination of selumetinib and N-desmethyl selumetinib concentrations in plasma will be analysed by Covance on behalf of Clinical Bioanalysis Alliance, AstraZeneca R&D, using an appropriate bioanalytical method. Other metabolites (eg, selumetinib amide) may also be determined in the PK analysis. Full details of the bioanalytical method used will be described in a separate bioanalytical report.

For each placebo patient, samples will only be analysed on a ‘for cause’ basis, for example, if no quantifiable concentrations were observed in a patient’s samples when the drug was expected to be present.

All samples still within the known stability of the analytes of interest (ie, selumetinib, N-desmethyl selumetinib and its metabolites) at the time of receipt by the bioanalytical laboratory will be analysed.

6.8 Pharmacodynamics – not applicable

Pharmacodynamic samples will not be taken during this study.

6.9 Pharmacogenetics

6.9.1 Genetic blood sample at study entry

An optional blood sample for genetic research will be obtained from eligible patients at Visit 1 or 2 ideally. If for any reason the sample is not drawn at Visit 1 or 2, it may be taken at any visit **before the RAI dose is administered** (radioactive samples for this purpose will not be accepted). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. Only one sample should be collected per patient for this purpose. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volumes see Section 7.1.

6.10 Biomarker analysis

6.10.1 *BRAF* and *NRAS* patient population

Archival tumour sample from each patient will be analysed for *BRAF* and *NRAS* mutational status centrally using standardised methodology. Analysis may include, but is not limited to, *BRAF* V600E and *NRAS* Q61R, Q61K, Q61L.Full analytical methodology details will be provided in the CSR.

The genetic analysis of archival tumour samples to identify the *BRAF* and *NRAS* patient population will be performed retrospectively in the study (after randomisation but prior to the primary endpoint data analysis).

BRAF/NRAS positive = mutations in *BRAF/NRAS* have been detected

BRAF/NRAS not detected = no mutation in *BRAF/NRAS* has been detected

BRAF/NRAS unknown = mutation status in *BRAF/NRAS* cannot be confirmed

6.10.1.1 Archival tumour sample

All patients will be required to provide consent for AstraZeneca to collect and analyse samples of their previously obtained tumour material (ie, from their recent surgery) for analysis of biomarkers relevant to DTC. Archival tumour sample provision is mandatory in this study, and each Investigator should make every effort to collect a sample from all randomised patients. It is accepted that it may not be possible to obtain all samples prior to commencement of study treatment (which should continue as planned). However, it should be established during the screening period that sufficient sample exists and is available. Samples are expected to be made available as soon as possible. Note, no replacements will be made for patients where an archival tumour sample is not provided.

These samples will be analysed for the biomarkers necessary for the definition of the second primary objective patient population (*BRAF* and *NRAS* mutational status), and may also be

used for exploratory analyses on residual material. Such analyses may include (but are not restricted to):

- Mutational status of *BRAF* and *NRAS* genes, *RET* rearrangements, and other known MAPK and PI3K effector oncogenes.
- Baseline expression of pathway and thyroid differentiation specific genes such as *NIS*, *Tg*, *TPO*, and *PAX8*.
- Comprehensive genetic analysis to ensure coverage of the major mutational events in DTC.

The exploratory analyses from tumour material may include but are not limited to mRNA expression profiling, microRNA expression profiling, gene copy number analysis and protein expression by immunohistochemistry for any markers relevant to DTC, either known at the time of analysis, or identified in the future.

For the tumour samples detailed below, each site will be asked to provide one of the following for each randomised patient:

– Formalin-fixed, paraffin-embedded tumour tissue block,

or

– 20 pre-cut sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 μm thick.

Sites should ship the tumour sample as soon as it is available. If mutational status cannot be adequately determined from the initial tumour biopsy sample, and histopathological review shows it to be a poor quality sample, a second sample should be submitted for re-testing.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

If requested, unused tumour samples will be repatriated. For further details see the Laboratory Manual.

6.10.2 Collection of plasma and serum for exploratory biomarker research

All randomised patients will be required to provide a blood sample at or before randomisation, and disease progression (for example, when the patient is re-treated for persistent or recurrent thyroid cancer) for exploratory biomarker research.

All patients will be required to provide:

– 1x 10ml blood sample for preparation of serum at randomisation (any time before the first dose of study treatment for eligible patients) and disease progression.

– 1x 10ml blood sample for preparation of plasma at randomisation (any time before the first dose of study treatment for eligible patients) and disease progression.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Residual material may be used for exploratory biomarker research.

6.10.3 Collection of disease progression tumour sample

Patients will be asked to provide a tumour sample removed during the study when the patient's cancer is deemed to have progressed (for example, when the patient is re-treated for persistent or recurrent thyroid cancer, or has had further surgery). This is an optional sample.

This will enable a comparison to be made of (for example) tumour genetics and relevant signal transduction pathways between the randomisation and the disease progression tumour sample and also the evolution of the tumour biology in response to treatment with selumetinib can be explored. Such changes may reflect an evolution in phenotype of the tumour, which ultimately may guide future treatment decisions post progression on selumetinib.

Samples can be of any type (such as FNA, or tumour sample taken from a surgical procedure performed as part of the patient’s disease management plan), and will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Table 8 Biomarker summary table

Biomarker sample	Time point	Protocol Section
Archival tumour for *NRAS* and *BRAF* analysis[a]	Randomisation	6.10.1.1
Plasma sample for exploratory biomarker analysis	Randomisation and disease progression	6.10.2
Serum sample for exploratory biomarker analysis	Randomisation and disease progression	6.10.2
Disease progression tumour biopsy (optional)	Disease progression	6.10.3
Blood sample for genetic analysis (optional)	Randomisation	6.9.1

[a] Residual tissue sample material will be stored for potential retrospective biomarker analysis, which will be performed in an AstraZeneca laboratory or AstraZeneca approved laboratory.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood (maximum) that will be drawn from each patient in this study is as follows:

Table 9 Volume of blood to be drawn from each patient

Assessment		Maximum sample volume [a] (mL)	Typical number of samples (over 18+ months)	Total volume (mL)
Safety	Clinical chemistry (local analysis)	5	5	25
	Haematology (local analysis)	3	7	21
Efficacy	Tg, TSH, TgAb (central analysis)	10	4[b]	40
PK		2	8	16
Genetics at randomisation (optional)		10	1	10
Exploratory biomarkers at randomisation, serum		10	1	10
Exploratory biomarkers at randomisation, plasma		10	1	10
Exploratory biomarkers on progression, serum		10	1	10
Exploratory biomarkers on progression, plasma		10	1	10
Total				152 [b]

[a] All volumes presented are maximums. The actual volume requirements will be detailed in the Laboratory Manual.

[b] For efficacy samples up to 2 repeat samples may be required, this would result in 10-20 mL additional blood and bring the maximum total to 172 mL.

7.2 Handling, storage and destruction of biological samples

Biological samples for future research may be retained at or on behalf of AstraZeneca for a maximum of 25 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report or Scientific Publication.

7.2.1 Pharmacokinetic samples

Samples will be anonymised by pooling or will be disposed of after the Bioanalytical report finalisation or six months after issuance of the draft Bioanalytical report (whichever is earlier), unless requested for future analyses. Pooled, anonymised samples may be used for analytical method development and/or validation. Anonymised samples will be retained for no more than 5 years after the CSR is finalised. Samples may also be disposed of earlier, pending further notification.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical report.

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 25 years, from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document.'

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of any optional donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central and bioanalytical laboratories holding the samples are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

In the USA the Principal Investigator is also responsible for providing the Ethics Committee with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the Ethics Committee according to local regulations and guidelines.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of

AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study.' All patients in this study will be followed for 3 years following their RAI treatment.

The study is expected to start in 2013 and to end in 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with selumetinib.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the principal investigator has signed the eCRF electronically as per eCRF instructions, the subject's data will be locked.

Medical coding will be performed using the AstraZeneca Autocoder application. The Data Management Centre Coding Team will perform coding using agreed coding conventions. AEs and medical and surgical history will be coded using the standard dictionary – Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medication will be coded using the AstraZeneca Drug Dictionary.

SAEs will be entered into a global patient safety database for regulatory reporting purposes and be reconciled with the AEs in the clinical database.

Data associated with biological samples will be transferred to the data manager as an electronic file and merged with study data as appropriate.

Data from external providers (eg, central laboratory) will be validated as appropriate to ensure that it is consistent with the clinical data and included in the final database.

Clean file will be declared for the database once all data have been received, entered, validated and all queries resolved. The database will be locked after clean file has been declared. Treatment codes will not be broken until after clean file. Following database lock, all data will be extracted as SAS (Statistical Analysis Software) data sets for the statistical analysis to be performed by AstraZeneca.

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate. Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. The results from this genetic research will be reported separately from the Clinical Study Report for the main study.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Complete remission rate at 18 months post-RAI treatment

Patients will be considered to be in complete remission if they are alive and all of the criteria in Section 6.4.1 are met at 18 months post-RAI treatment.

Complete remission rate at 18 months post-RAI treatment is defined as the proportion of patients who have achieved complete remission at this time point. The complete remission rate will be calculated using all randomized patients as the denominator.

11.1.2 Clinical remission rate at 18 months post-RAI treatment

Patients will be considered to be in clinical remission if they are alive and all of the criteria in Section 6.4.6 are met at 18 months post-RAI treatment.

Clinical remission rate at 18 months post-RAI treatment is defined as the proportion of patients who have achieved clinical remission at this time point. The clinical remission rate will be calculated using all randomized patients as the denominator.

11.1.3 Thyroid cancer recurrence

The occurrence and date of any thyroid cancer recurrence will be recorded for patients who have previously entered either complete or clinical remission (at any point during the study or follow up periods). The rate of thyroid cancer recurrence will be calculated using only patients who have achieved remission as the denominator.

11.1.4 Survival status

The survival status and survival assessment date of all patients will be recorded. Survival time will be calculated as the time from the date of randomisation to the date of death. Patients who have not died at the time of the final study follow up will be censored at the last date the patient was known to be alive.

11.1.5 Further therapy

The dates and type of any further therapy for thyroid cancer will be recorded during the study and follow up periods.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Adverse events

Adverse events will be listed for each patient and summarised by treatment received according to the System Organ Class (SOC) and preferred term assigned to the event using the MedDRA. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs Version 4. The CTC Grade will be assigned by the Investigator.

AE summaries will include all of the following:

- Any AEs occurring after commencement of study treatment and within 30 days of the last dose of study medication
- AEs related to RAI or the combination of RAI and study treatment occurring between 30 days after the last dose of study medication and the final study visit at 3 years following the initial RAI dose
- All SAEs occurring after commencement of study treatment until the final study visit at 3 years following the initial RAI dose

AEs occurring before commencement of study treatment will not be included in AE summaries but will be included and identified in the patient listings.

11.2.2 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2.3 Vital signs, laboratory data, ECGs, ECHO/MUGA, physical examination and ophthalmologic examination

For change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF (Fredericia) will be calculated programmatically by AstraZeneca using the reported ECG values (RR and QT).

QTcF = QT / RR^ (1/3) where RR is in seconds

The denominator used in laboratory summaries will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality. For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded

The denominator in vital signs data should include only those patients with recorded data.

11.3 Calculation or derivation of PK variables

The final PK analyses will be the responsibility of Clinical Pharmacology and Pharmacometrics, AstraZeneca.

Using appropriate PK software the available PK data will be used to derive PK parameters such as, but not restricted to, C_{max}, AUC for Selumetinib, N-desmethyl selumetinib and any other metabolites determined.

The selumetinib, N-desmethyl selumetinib and metabolite concentration-time profiles, along with the derived PK variables, will be listed for each patient per dose and dosing day and summarised appropriately, as described in the SAP.

Population PK models may be used to derive the PK parameters and will aim to characterise variability in the population by investigating the influence of covariates such as weight, age, sex, and/or concomitant medications. In addition, if the data are suitable, potential relationships between plasma selumetinib and N-desmethyl selumetinib concentrations will be investigated using a graphical approach and/or appropriate PK/PD modelling techniques. A detailed PK analysis plan will be produced prior to any such investigations and will be reported separately.

11.4 Calculation or derivation of pharmacogenetic variables

Genetic data (except *BRAF* and *NRAS* data) will be reported separately to the CSR for this study.

11.5 Calculation or derivation of biomarker variables

11.5.1 Analysis of *NRAS* and *BRAF*

Tumour samples will be collected as outlined in the study plan and assessed for *BRAF* and *NRAS* mutational status (as detailed in section 6.10.1) to identify patients for this patient population.

11.5.2 Further biomarker research analysis

Methods of analysis for all other biomarker research may include investigation of genetic variability, gene expression profiling, protein expression profiling.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Intention to treat (ITT) analysis set

The ITT analysis set will include all randomised patients. The ITT analysis set will be used for all efficacy analyses and treatment groups will be compared on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment will be included in the ITT analysis set.

12.1.2 *BRAF/NRAS* mutation positive analysis set

For the analysis of the *BRAF* and *NRAS* mutation positive population (secondary objective), only those patients from the ITT population with genetic samples that are positive for *BRAF* or *NRAS* will be included.

12.1.3 Treatment-compliant (TC) analysis set

The treatment-compliant analysis set will be a subset of the ITT population containing patients that adhered to the minimum study treatment requirements specified in Section 3.1.1, i.e. patients who take study treatment twice daily for a **minimum** of 7 consecutive days prior to RAI therapy, on the day of RAI therapy, and for 5 consecutive days afterwards. Patients must also have had their RAI dose.

The TC analysis set will be used as a sensitivity analysis for the primary endpoint.

12.1.4 Safety analysis set

The safety analysis set will consist of all patients who received at least one dose of randomised treatment. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment combination received, ie, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be summarised according to the treatment they actually received.

12.1.5 PK analysis set

PK data will be analysed according to treatment received. This population will comprise all patients who receive study treatment as per protocol and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the AstraZeneca Study Team Physician, Pharmacokineticist and Statistician prior to any analyses being performed.

12.2 Methods of statistical analyses

A comprehensive SAP will be prepared prior to start of recruitment (first subject in).

Since there is only one primary endpoint/comparison of interest (complete remission rate at 18 months for selumetinib vs. placebo in the ITT population) the primary endpoint will be considered statistically significant if the two-sided p-value is less than 0.05.

12.2.1 Complete remission rate at 18 months post-RAI treatment

The primary endpoint of complete remission rate at 18 months will be compared between selumetinib in combination with RAI, and placebo in combination with RAI in the ITT population using a logistic regression model including treatment as the only covariate. Results will be presented in terms of the odds ratio, 95% confidence interval and associated p-value. A sensitivity analysis will be performed using a logistic regression model including treatment and adjusted for the covariates histology status (papillary, follicular, poorly differentiated), mutation status (*BRAF/NRAS* positive, *BRAF/NRAS* not detected) and age, provided there are enough data points for a meaningful analysis.

A secondary analysis of complete remission rate will be performed to compare selumetinib in combination with RAI vs. placebo in combination with RAI in the *BRAF*/*NRAS* mutation positive population using a logistic regression model including treatment as the only covariate. A sensitivity analysis will be performed using a logistic regression model adjusted for the covariates histology status (papillary, follicular, poorly differentiated) and age, provided there are enough data points for a meaningful analysis.

For the sensitivity analyses using each covariate adjusted logistic regression models, the following missing data approach for each covariate will be adopted:

- Missing age; impute the mean of observed ages
- Missing histology status; add an additional ‘unknown’ category to make 4 categories (papillary, follicular, poorly differentiated, and unknown)
- Missing mutation status; add an additional ‘unknown’ category to make 3 categories (*BRAF/NRAS* positive, *BRAF/NRAS* not detected and unknown)

The results of the analyses, in terms of treatment effects, will be presented as odds ratios together with their associated 95% profile likelihood confidence intervals and 2-sided p-values. The p-value will be based on twice the change in log-likelihood resulting from the

addition of a treatment factor to a model that contains the covariates defined above. The complete remission rate and 95% confidence interval will be estimated for each treatment arm.

Sensitivity analyses for the primary endpoint

The primary endpoint analysis, a logistic regression model including treatment as the only covariate for complete remission rate at 18 months, will be repeated:

- using the treatment-compliant population.
- to allow patients that were identified as being in complete remission outside of the specified time windows to be classed as being in complete remission, in order to investigate time bias between arms.
- excluding patients with high TSH. Elevated TSH can be caused by poor compliance and can mean a patient is less likely to achieve remission, therefore this sensitivity analysis excludes patients with high TSH, which is defined as a value >10 mIU/L recorded at any point by standardised central laboratory analysis.

Treatment by covariate interactions

The extent to which the treatment effect is consistent across the subgroups histology status, mutation status (ITT population only), gender, race and age will be assessed in the ITT population and in the *BRAF*/*NRAS* mutation positive population. The presence of a quantitative interaction will be assessed by means of an overall global interaction test. This will be performed by comparing the fit (likelihood ratio test) of a model including all covariate-by-randomised treatment interaction terms, treatment and covariate terms with a model that excludes the interaction terms. If the global interaction test is found to be statistically significant at the 10% significance level, an attempt to determine the cause and type of interaction will be made. Stepwise backward selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

For quantitative interactions identified, the presence of any qualitative interactions will be assessed using the approach of Gail and Simon (Gail & Simon 1985). For categorical covariates the test statistics, based on the appropriate degrees-of-freedom, can be taken directly from the paper. For the continuous covariate, the approach will be adapted as follows:

Identify the cut-point ($-\beta_1/\beta_3$) of the covariate where the odds ratio for the treatment effect is 1, where β_1 is the treatment parameter estimate and β_3 is the treatment-by-covariate parameter

estimate. Re-analyse the data separately for the values of the covariate above and below the cut-point and use the separate chi-square values in the Simon and Gail test.

Subgroup data

Subgroup data (histology status, *BRAF* or *NRAS* mutation status, gender, race and age) will be summarised by a forest plot where the odds ratio is plotted on the log scale. For this, age will be categorised as ≤45 or >45 years. The treatment effect and 95% confidence intervals for each level of the subgroup will be obtained from a single logistic regression model that contains a treatment, factor and treatment-by-factor interaction term.

12.2.2 Clinical remission rate at 18 months post-RAI treatment

The secondary endpoint of clinical remission rate will be analysed as described in Section 12.2.1, except for primary endpoint specific sensitivity analyses and treatment by covariate interaction testing.

12.2.3 Thyroid cancer recurrence

Very few thyroid cancer recurrences are expected on this study, therefore no formal analysis of thyroid cancer recurrence data will be performed; data will be listed and summarised.

12.2.4 Survival status

Very few deaths are expected on this study therefore no formal analysis of survival data will be performed; data will be listed and summarised. Kaplan-Meier plots of survival may produced if appropriate.

12.2.5 Further therapy

No formal analysis of further therapy data will be performed; data will be listed and summarised. Kaplan-Meier plots of time to further therapy may produced if appropriate.

12.2.6 Safety data analysis

Safety data will not be formally analysed. All patients who commenced study treatment will be included in the assessment of safety and will be summarised by treatment received.

12.2.7 PK data analysis

The selumetinib, N-desmethyl selumetinib and metabolite concentration-time profiles, along with the derived PK variables, will be listed for each patient per dose and dosing day and summarised appropriately.

12.2.8 Genetics

Any genetic data analysis (other than *BRAF* and *NRAS*) will be reported outside the CSR for this study.

12.2.9 Biomarker data

BRAF and *NRAS* mutation assessment of tumour biopsy will be used to identify patients for this primary patient population.

The results of any other exploratory biomarker investigations will be reported outside of the CSR.

12.2.10 Interim analyses

There are no interim analyses planned for this study.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

The primary objective of the study is to compare the efficacy of selumetinib with RAI versus placebo with RAI, by assessment of the complete remission rate at 18 months post-RAI treatment in the ITT study population. Assuming the true complete remission rates in the overall study population are 30% and 50% for the placebo and selumentinib-containing arms, respectively, a total of 228 patients, randomised in a 2:1 ratio (152 and 76 patients in the selumentinib and placebo-containing arms, respectively) provides at least 80% power to show statistical significance, based on a two-sided 5% significance level.

12.4 Data monitoring committee

Due to the short treatment duration in this study there will not be a data monitoring committee for this study.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.5.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Physician. If the Study Delivery Team physician is not available, contact the Study Delivery Team Leader.

Name	Role in the study	Address & telephone number
PPD	AstraZeneca Physician responsible for the protocol at central R&D site	PPD
PPD	AstraZeneca Study Delivery Team Leader responsible for the protocol at central R&D site	PPD
24-hour emergency cover at central R&D site.	24-hour emergency cover at central R&D site.	PPD

13.2 Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.5.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.5.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

The outcomes of any conception occurring from the date of the first dose, until 30 days after last dose, must be followed up and documented in the "Pregnancy Outcome Report" form.

Male patients must refrain from fathering a child for 12 weeks following the last dose of study treatment, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated. Restrictions from fathering children should also take into account local recommendations following therapy with RAI.

Pregnancy of the patients' partner is not considered to be an AE. However, the outcome of all pregnancies (including spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

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Clinical Study Protocol Appendix B	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
Edition Number	1
Date	24th January 2013

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C	
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Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample

containment standards are encouraged wherever possible when road or rail transport is used.

Clinical Study Protocol Appendix D	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
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Appendix D

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. ACTIONS REQUIRED IN CASES OF AST OR ALT ≥ 3X ULN OR TBL ≥ 2X ULN

The Investigator is responsible for, without delay, determining whether the subject meets potential Hy's law (PHL) criteria; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of Alkaline Phosphatase (ALP). The AST or ALT and total bilirubin values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN **or** TBL ≥ 2x ULN, please follow the instructions below.

- Review each laboratory report and if a subject has an increase in AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit:
  - Notify the AstraZeneca representative
  - Promptly enter the laboratory date into the laboratory CRF.

1.2 Determination and Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the subject **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP

- Inform the AZ representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

1.2.2 Potential Hy's Law Criteria met

If the subject **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- Notify the AZ representative who will then inform the central ST

The Study Physician (SP) contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data.

The Investigator:

- Follows the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigates the etiology of the event and perform diagnostic investigations as discussed with the SP
- Completes the Liver CRF Modules.
- If at any time (in consultation with the SP) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

1.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

For the purpose of this process a Hy's Law case is defined as:

Any subject with an increase in both Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) and Total Bilirubin (TBL) ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum Alkaline Phosphatase (ALP) indicating cholestasis, viral hepatitis, another drug

If there **is** an agreed alternative explanation for the AST or ALT **and TBL** elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** other explanation that would explain the AST or ALT and TBL elevations:

- Report an SAE (report term Hy's Law') according to AZ standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

– As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

2. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm

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Clinical Study Protocol Appendix E

Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
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Appendix E
Cockcroft-Gault Formula

COCKCROFT-GAULT FORMULA

The Cockcroft-Gault formula has been provided for reference, as the protocol allows for the serum creatinine clearance to be calculated using the Cockcroft-Gault formula (see Section 4.1, Inclusion criteria):

For serum creatinine values in µmol /L:

Estimated creatinine clearance rate (eCCr) (for men) = [(140 – age) x weight (kg) x 1.23] / creatinine (µmol/L)

eCCr (for women) = [(140 – age) x weight (kg) x 1.04] / creatinine (µmol/L)

For serum creatinine values in mg/dL:

eCCr (for men) = [140 – age] x weight (kg) / [72 x creatinine (mg/dL)]

eCCr (for women) = 0.85 x ([140 – age] x weight (kg) / [72 x creatinine (mg/dL)])

Reference: Cockcroft D, Gault MD. Nephron 16: 31-41, 1976.

Clinical Study Protocol Appendix F	
Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00065
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Appendix F
Low Iodine Diet

LOW IODINE DIET

Published data and opinion regarding the necessity for a low iodine diet prior to RAI therapy or a diagnostic whole body scan is variable. For the purpose of this study a low iodine diet will be mandated in order to standardise patient care and study data as best as possible. Compliance to a low iodine diet will not be recorded or assessed, and all randomised patients will receive RAI treatment as planned.

A low iodine diet is necessary at two occasions in the study:

Prior to RAI adjuvant treatment

All patients must be willing to adhere to a low iodine diet for a period of 1 week before their planned RAI adjuvant treatment, until the day after their RAI therapy.

Prior to the primary endpoint Stage 2 assessments

All patients must be willing to adhere to a low iodine diet for a period of 1 week before the diagnostic ^{131}I dose used prior to the primary endpoint WBS assessment (^{131}I nuclear medicine scan), until the diagnostic WBS assessment is completed. This is only relevant for patients who progress to Stage 2 primary endpoint assessments (refer to Section 6.4.2 of the main protocol).

What is Iodine?

Iodine is a mineral. It plays an important role in several processes that take place in the body. One is the production of a hormone called thyroxine, which occurs in the thyroid gland.

Where is Iodine Found?

The amount of iodine found in food varies. Much of the iodine we get comes from iodized salt and breads. Adults need 150 micrograms of iodine a day. This appendix describes an example of a low iodine diet typically used in this treatment setting. This is a diet with less than 50 micrograms of iodine per day. A local low iodine diet may be used instead, as long as it is equivalent to this appendix.

Why is a Low Iodine Diet Necessary?

The iodine in your diet can block the uptake of radioactive iodine by the thyroid gland.

What Should You Avoid?

Read all food labels to check for iodine content. Do NOT eat or use:

- Iodized salt.
- Sea salt in any form.
- Onion salt.

- Celery salt.
- Garlic salt.
- Seasoned salt.
- Kelp (seaweed).
- Any food that has:
  - **Iodates**
  - **Iodides**
  - **Algin**
  - **Alginates**
  - **Carrageen**
  - **Agar**
- Commercial breads and bakery products, because they often contain iodate.
- Milk (except for 1 ounce a day), egg yolks, and seafood.
- Vitamins and food supplements if they have iodine. If you have any doubt, do not take them.
- Food, pills, or capsules with food dyes or that are orange, red, or brown in color. Examples include red or pink cereals or candies/sweets.
- Antiseptics, such as tincture of iodine (Betadine®) applied on a cut.
- Cough medicines (especially those with red coloring).
- Supplements such as:
  - **Ensure®**
  - **Boost®**
  - **Commercial shakes**
  - **Nutrament®**.

- Restaurant and processed foods, because they are often high in iodine content.
- Soy products such as edamame, tofu, soy burgers etc.
- All canned foods, because the lining of the can contains iodine.

Do not stop taking any of your medicines unless your doctor tells you.

Ask your doctor about drinking alcohol during a low iodine diet.

This low iodine diet does not meet the suggested daily allowance for all nutrients. You will be on it for a short time only.

Drink Plenty of Fluids

Note: Unless your doctor tells you differently, you must drink at least 8 to 10, 8-ounce cups of fluid a day. This includes the drinks in the diet guidelines and as much water as you want.

LOW IODINE DIET GUIDELINES

Breads and Cereals **Total number of servings per day:** 6-8 (1 serving equals 1 slice of bread or 1/2 cup of cooked pasta)	
Include	**Avoid**
Plain cooked barley, oats, millet, buckwheat, bulgur wheat, quinoa; unsalted unprocessed preservative-free boxed cereals such as puffed rice and shredded wheat; rice, plain macaroni, spaghetti, noodles; unsalted grits, cream of rice or cream of wheat hot cereals; unsalted rice cakes, unsalted plain crackers, English muffins, plain unsalted popcorn, homemade breads prepared without commercial dough.	All commercial breads and rolls, processed boxed cereals, salted crackers, potato chips/crisps, pretzels, bagels, Melba toast, egg noodles, packaged rice and pasta mixes.

Meat and Meat Substitutes **Total number of servings per day:** Two–three (1 serving equals 3 ounces of meat, fish, poultry, or 2 Tablespoons of unsalted peanut or almond butter)	
Include	**Avoid**
Fresh beef, veal, pork, lamb, chicken and turkey; unsalted peanut or almond butter; freshwater fish such as carp, riverbass, lake trout, and river perch; fresh egg white.	Egg yolks and whole eggs, foods made with eggs; all fast foods; all canned fish such as salmon and tuna; seafood, shellfish (clams, crabs, oysters, lobsters), or any food made with fish stock; all processed meats; liver and all organ meats; all canned, dried, salted, or cured meats such as bacon, sausage, ham, frankfurters, chipped beef, luncheon meats (salami, bologna, pastrami); spicy meats such as chili, beef jerky, liverwurst; all canned or processed poultry such as turkey or chicken roll; tofu and soy products, such as soy burgers (e.g., Boca); salted peanut butter.

Milk and Milk Products **Total number of servings per day:** Zero	
Include None allowed Exception: Only 1 ounce of milk a day in your coffee or tea.	**Avoid** All milk (except for one ounce daily) and milk products such as condensed or evaporated milk, cheese, yogurt, puddings, ice cream, custard; any cream such as heavy/double or light/single cream, whipped cream, sour cream; any foods made with cream or milk or cheese such as soup, pizza, macaroni and cheese.

Fruits **Total number of servings per day:** Five (1 serving equals 1 small piece of fruit or 3/4 cup of juice)	
Include All fresh fruit, exception: limit bananas to 1 serving per day; fresh apple sauce; all natural frozen fruits; fresh fruit juices (including bottles or cartons of fruit juice without artificial coloring or preservatives); white grape juice.	**Avoid** Cranberries, all dried fruits, all canned fruits and canned fruit juices; jarred applesauce; cranberry and grape juice, canned or bottled cherries; rhubarb.

Vegetables **Total number of servings per day:** Four (1 serving equals 1/2 cup of cooked or 1 cup raw vegetable)	
Include All fresh vegetables except spinach, fresh potatoes without skin, all plain frozen vegetables without added salt, fresh or dried lentils and peas.	**Avoid** All canned vegetables and all canned vegetable juices, fresh or dried beans such as red kidney beans, lima beans, navy beans, pinto beans; canned legumes (such as beans, peas, and lentils); canned soups; sauerkraut, celery; commercially prepared potatoes (e.g., instant mashed potatoes); frozen vegetables with added salt; spinach.

Fat **Total number of servings per day:** Suggest four to six servings a day (1 serving equals 1 teaspoon of butter or oil)	
Include Unsalted margarine or sweet butter **(not more than 1 teaspoon of each per day),** oils, vegetable shortening, plain oil and white vinegar dressing.	**Avoid** Salted nuts and seeds, mayonnaise, commercial salad dressings and salad cream, and lard.

Beverages **Total number of servings per day:** No restrictions One serving equals 12 ounces of a carbonated beverage or 1 cup (8 ounces) of any of the other beverages listed	
Include	**Avoid**
Water; bottled carbonated beverages without added coloring (such as Sprite®, 7Up®, sodium-free seltzer); brewed coffee, tea steeped from tea leaves; white tea bags; fresh lemonade or fresh orangeade.	Mineral water containing sodium; all bottled, canned, or powdered: iced tea, lemonade, instant coffee, instant tea, instant iced-tea, fruit punch, and other powdered or commercial drinks, such as Hi-C® and Kool-Aid®; tea steeped from tea bags; soy milk and rice milk (which contain sea salt); ginger ale, Coke®, Pepsi® or any other carbonated beverages with added coloring.

Desserts and sweets **Total number of servings per day:** Two (See below for serving equivalents)	
Include	**Avoid**
Each of the following equals 1 serving: • 1 cup Knox® or equivalent clear gelatin • 2 tablespoons (T) sugar • 2T honey • 2T maple syrup • 2 regular size marshmallows • 1/2 cup natural sorbets with no coloring or added salt	All bakery products such as pies, cakes, pastries, danishes, muffins, doughnuts and cookies; sweet crackers/biscuits; Jell-O® (or equivalent jelly), colored gelatins; chocolate and chocolate desserts; candy.

Miscellaneous **Total number of servings per day:** Unlimited	
Include	**Avoid**
Pepper, spices such as cinnamon; herbs such as oregano; white vinegar, and non-iodized salt (contains trace amounts of iodine, use sparingly).	All salted foods such as salted nuts, Chinese food, soy sauce, catsup, Worcestershire sauce, chili sauce, all commercial sauces, tomato sauce, all gravies, olives, pickles, relish, bouillon cubes, soup bases, iodized salt, sea salt, onion salt, garlic salt, celery salt, seasoned salt, kelp (seaweed); molasses; any food containing food coloring, iodates, iodides, iodate dough conditioners or stabilizers, algin, alginate, carrageens, agar, or nori (seaweed); all sushi; red wine vinegar, balsamic vinegar (with caramel coloring); all additives, preservatives, or artificial colorings.

EXAMPLE MENU FOR A LOW IODINE DIET

BREAKFAST

1 Fruit	½ cup orange juice
3 Breads	½ cup oatmeal (no milk) 1-2 plain unsalted cracker/crispbreads
1 Meat	1 egg white omelet
Misc.	2 teaspoons sugar
1 Beverage	1 cup brewed coffee

MID MORNING SNACK

1 Bread	2 rice cakes
1 Fat	1 teaspoon unsalted butter
1 Beverage	1 cup water

LUNCH

1 Meat	3 oz fresh turkey breast
2 Fats	2 tsp oil
2 Breads	2 slices homemade white bread
1 Vegetable	1 cup Romaine lettuce
1 Beverage	1 cup fresh lemonade

MID AFTERNOON SNACK

1 Fruit	1 fresh apple
1 Meat	2 tablespoons unsalted peanut butter

DINNER

1 Meat	3 oz roast beef
2 Breads	1 baked potato (no skin)
2 Vegetables	1 cup fresh broccoli
2 Fats	2 tsp oil (used in cooking)
1 Fruit	1 orange
1 Beverage	1 cup white tea

BEDTIME SNACK

1 Fruit	1 small pear
1 Beverage	1 cup tea made from fresh tea leaves

Clinical Study Protocol Appendix G	
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Appendix G
Guidance for Management of Adverse Events in Studies of Selumetinib

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LIST OF TABLES

LIST OF FIGURES

1. GUIDANCE FOR THE MANAGEMENT OF PATIENTS WITH RASH

Recommendations to start on day 1 of treatment with selumetinib‡ and for the duration of treatment

- Use skin moisturiser (thick, alcohol-free) at bedtime
- Avoid excessive exposure to sunlight
- Use sunglasses/sunscreen (PABA-free, SPF ≥15; UVA and UVB protection) as needed
- Use of topical retinoids or benzoyl peroxide is not recommended

CTC Grade 1 rashes

Mild or moderate strength topical steroid

and/or topical antibiotic

CTC Grade 2 rashes

Moderate strength topical steroid

and oral antibiotic

CTC grade ≥3 rashes
CTC grade 2 rashes considered by the patient to be intolerable

Moderate strength topical steroid

and oral antibiotic
(consider broad spectrum/Gram negative cover if infection suspected)

Consider referral to a dermatologist: manage rash per recommendation

Interrupt selumetinib‡ until rash improves to grade 2 or less

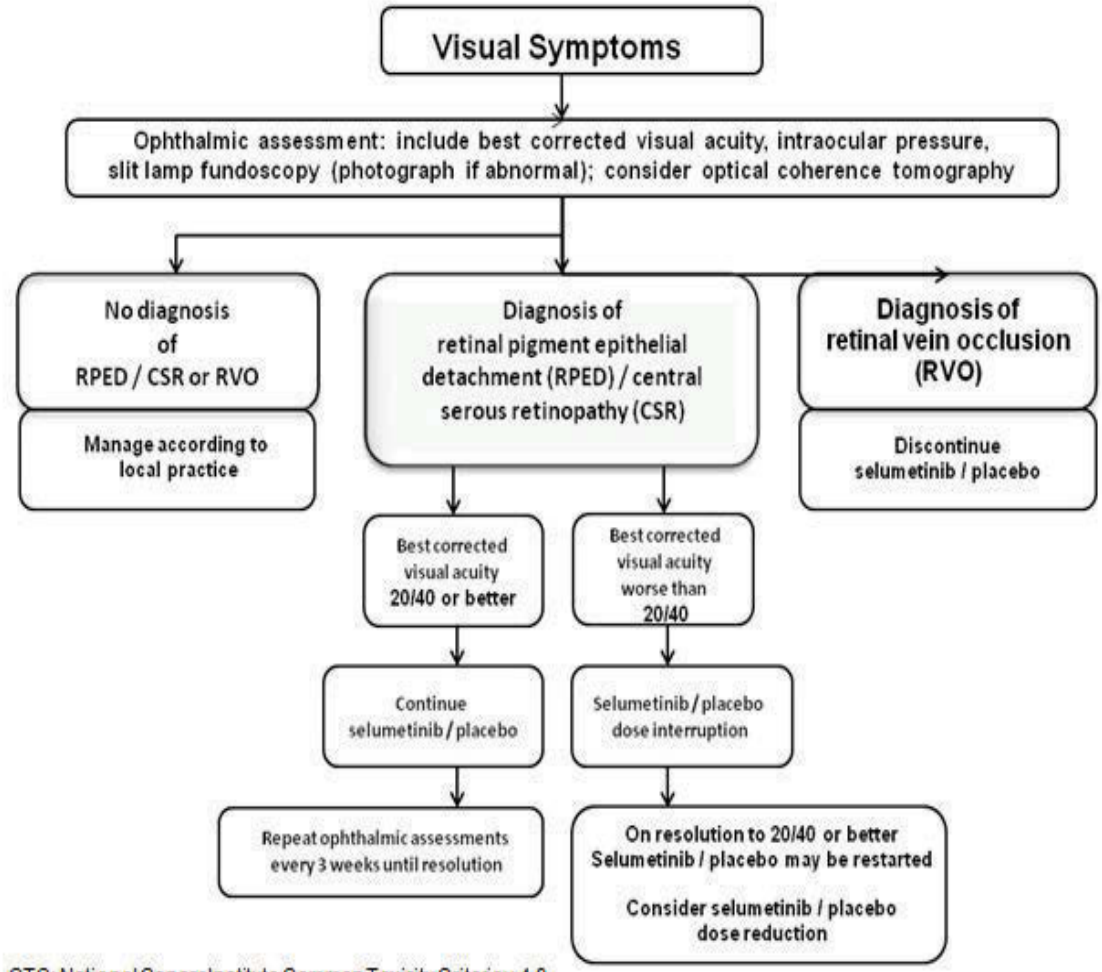
Selumetinib‡ may be restarted at original dose or reduced at the discretion of the investigator

‡ selumetinib or matching placebo
Version: Final 2.0 28Sep2012

Table 1 Example topical steroids and antibiotics (use according to local guidelines)

Topical steroids moderate strength	Triamcinolone acetonide 0.025% Fluticasone proprionate 0.05% Desonide 0.05% Aclometasone 0.05%
Topical antibiotics	Clindamycin 1 - 2% Metronidazole 1% Erythromycin 1% - 2% Silver sulphadiazine 1%
Oral antibiotics	Doxycycline 100 mg bd Minocycline 100 mg bd Oxytetracycline 500 mg bd

2. GUIDANCE FOR MANAGEMENT OF VISUAL SYMPTOMS OR ABNORMAL FINDINGS



CTC: National Cancer Institute Common Toxicity Criteria v 4.0
RVO: Retinal vein occlusion
CSR: Central serous retinopathy
‡ selumetinib or matching placebo
Version 3.1 16-Dec-2013

3. RECOMMENDATIONS FOR DIARRHOEA MANAGEMENT

Diarrhoea may occur during treatment with selumetinib (AZD6244) and action should be taken as soon as symptoms develop. The recommendations for diarrhoea management are based on guidelines from the American Society of Clinical Oncology (J Clin Oncol 2004; 22:2918-26). These guidelines recommend that treatment-induced diarrhoea should be carefully monitored and treated aggressively to ensure that severe complications are avoided and that treatment is not delayed.

- Patients should be made aware that they may experience diarrhoea and be encouraged to record the number of stools and report possible associated symptoms
- Patients should be given loperamide (in accordance with local regulation and local practice) to take home with them and be advised to start immediately after the first episode of unformed stool.
- Patients should be given dietary advice in case of diarrhoea (eg. BRAT [bananas, rice, apple sauce, toast, plain pasta] diet; readily digestible food; avoidance of lactose-containing products, fried, fatty or spicy food) and increase fluid intake (8 to 10 glasses of clear fluids daily, including water and fluids containing salt and sugar, such as sports drinks and clear broth).
- Patients should seek advice early, from their physician or study nurse, if:

  (a) Persistent Grade 1 or 2 diarrhoea (refer to Section 3.2), or

  (b) Grade 3 or 4 diarrhoea, or

  (c) Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension.

Table 2 CTCAE (version 4) grading for diarrhoea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 1	Increase in number of stools per day (<4)	Mild increase in loose watery colostomy output compared with pre-treatment
Grade 2	Increase in number of stools per day (4-6) or nocturnal episodes	Moderate increase in loose watery colostomy output compared with pre-treatment, not interfering with normal activity
Grade 3	Increase of more than 7 stools per day or incontinence or needing support for dehydration.	Severe increase in loose watery colostomy output compared with pre-treatment and interfering with normal activity

Table 2 CTCAE (version 4) grading for diarrhoea

CTCAE Grade	Patients without colostomies	Patients with colostomies
Grade 4	Life-threatening consequences (eg, hemodynamic collapse)	

3.1 Initial management of uncomplicated Grade 1 or 2 diarrhoea

- Patients should immediately start loperamide after the first episode of diarrhoea (4 mg initially) and continue loperamide (2 mg every 4 hours or after each unformed stool) until they have been free from diarrhoea for at least 12 hrs
- If after 12 hours of loperamide treatment the diarrhoea is not improving or resolved, the patient should be instructed to contact the centre and to increase to high dose loperamide (2 mg every 2 hours, or 4 mg every 4 hours at night) and continue to take loperamide until they have been free from diarrhoea for at least 12 hrs. Additional treatment may be considered according to local practice.

3.2 Management of persistent (>24h) Grade 1 or 2 diarrhoea despite loperamide at high dose

The patient should be seen by the physician or study nurse for full evaluation and the following should be considered:

- Rehydration and electrolytes replacement as appropriate
- Infectious causes and aetiologies such as Clostridium difficile or viral gastroenteritis;
- Antibiotics if appropriate (for example an oral fluroquinolone for 7 days) particularly if the patient is neutropenic ($<1 \times 10^9$/L) or has a fever;
- Discontinuation of loperamide and start of octreotide (Sandostatin);

It may also be appropriate to consider:

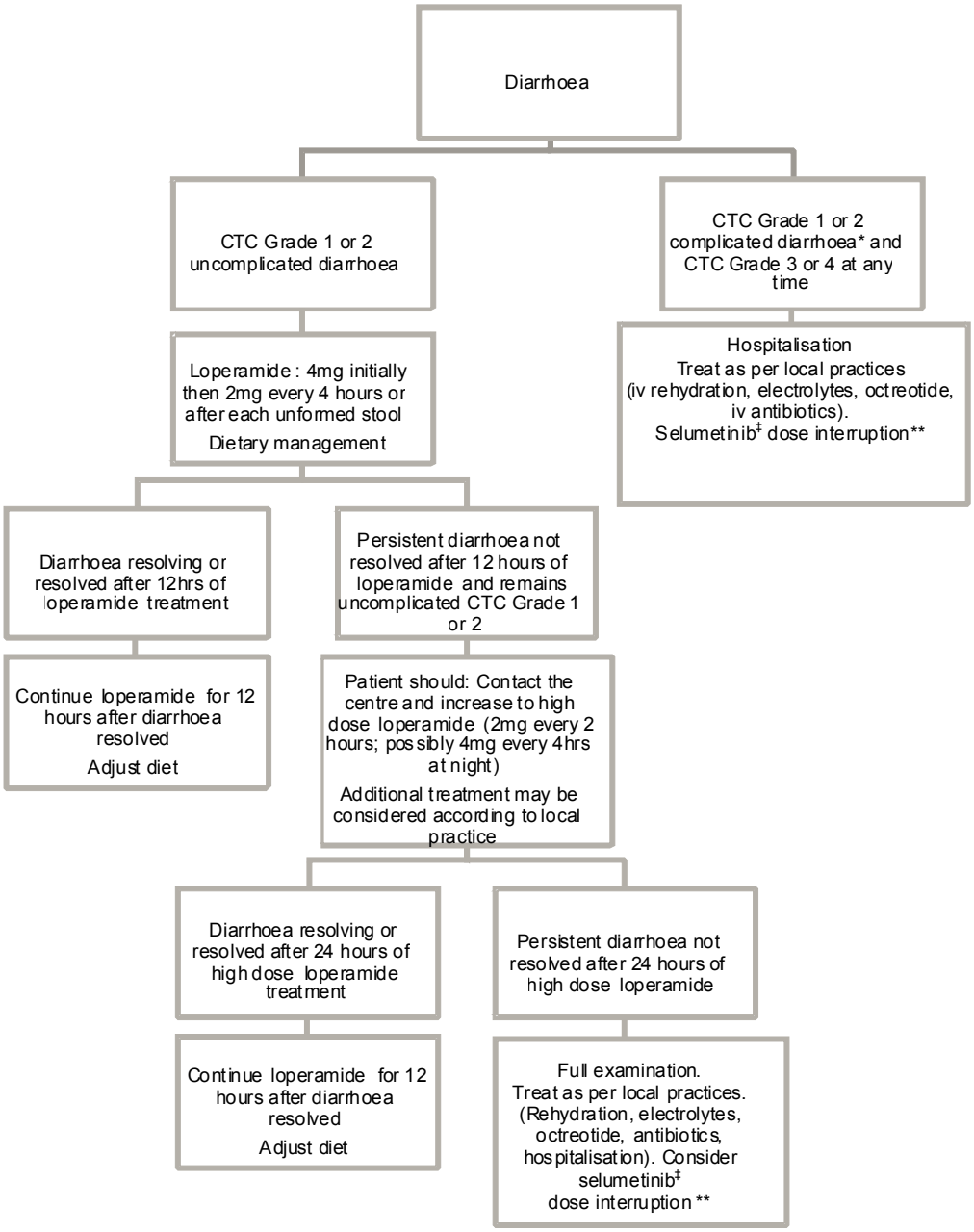
- Addition of other second-line anti-diarrhoeal agents according to local practice
- Selumetinib (or matching placebo) interruption until resolution of the diarrhoea
- Hospitalisation

3.3 Management of any grade uncontrolled or complicated diarrhoea, or Grade 3-4 diarrhoea

- Hospitalisation and full evaluation,

- Intravenous fluids, electrolytes and antibiotics if needed (eg. fluroquinolone)
- Interrupt selumetinib (or matching placebo) until diarrhoea and associated symptoms resolve
- Start octreotide (Sandostatin).
- In studies involving combination of selumetinib (or matching placebo) with other anti-cancer treatment, interruption or delay of the combination agent may be considered according to manufacturer's guidance or local practice.

Figure 1 Guidance for the management of patients with diarrhoea



*Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension
****Consider interruption or delay of combination anticancer agent if applicable**
‡ selumetinib or matching placebo
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4. GUIDANCE FOR MANAGEMENT OF PATIENTS WITH DYSPNOEA