NOVARTIS

Clinical Development & Medical Affairs

SOM230 (Pasireotide) LAR and RAD001 (Everolimus)

Protocol CSOM230DIC03 / NCT01563354

# Multicenter 3-arm trial to evaluate the efficacy and safety of Pasireotide LAR or Everolimus alone or in combination in patients with well differentiated neuroendocrine carcinoma of the lung and thymus - LUNA Trial

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## Protocol Summary

**Study title:**

Multicenter 3-arm trial to evaluate the efficacy and safety of Pasireotide LAR or Everolimus alone or in combination in patients with well differentiated neuroendocrine carcinoma of the lung and thymus - LUNA Trial

**Study phase:**

II

**Study objectives:**

Primary objective

- To evaluate the efficacy of pasireotide LAR and everolimus alone or in combination in progressive patients with a well differentiated neuroendocrine tumor of the lung or thymus. The primary endpoint is defined as the proportion of patients who are progression free (i.e. **disease control rate**) at 9 months, according to RECIST V. 1.1. Disease control rate is defined as the proportion of patients showing a best overall response of complete (CR) or partial (PR) response or stable disease (SD), according to RECIST V. 1.1.

Secondary objectives

- To assess the overall progression-free survival (PFS) throughout the study in patients with a well differentiated neuroendocrine tumor of the lung or thymus. The endpoint **progression-free survival (PFS)** is defined as the time from first study drug administration to objective tumor progression or death from any cause, according to RECIST V. 1.1.
- To assess the disease control rate of pasireotide LAR and everolimus alone or in combination in patients with a well differentiated neuroendocrine tumor of the lung or thymus at 12 months.
- To assess the time to response, duration of response, objective response rate and best overall response of pasireotide LAR and everolimus alone or in combination during 12 months of treatment in patients with a well differentiated neuroendocrine tumor of the lung or thymus.

  The endpoint of "**time to response"** is defined as the time from start of treatment to the first objective tumor response (PR or CR) observed, according to RECIST V. 1.1. The endpoint of "**duration of response"** is defined as the time from onset of the first objective tumor response (CR/PR) to objective tumor progression or death from any cause. The endpoint of "**objective response rate"** is defined as the proportion of patients showing a best overall response of CR or a PR at 9 and 12 months, according to RECIST V. 1.1. criteria.

  The endpoint of "**best overall response"** is defined as the best response recorded from the start of the treatment until disease progression/recurrence, taking as reference for PD the smallest measurements recorded since the treatment started.
- To assess the biochemical response rate (BRR), duration of biochemical response (DBR) and biochemical progression-free survival (BPFS) of pasireotide LAR and everolimus alone or in combination in patients with a well differentiated neuroendocrine tumor of the lung or thymus. The endpoint of "**biochemical response rate (BRR)"** is the percentage of patients showing normalization or a decrease of ≥30% of serum chromogranin A (CgA), compared to baseline.

  The endpoint of **"duration of biochemical response (DBR)"** is defined as the time from the first documentation of biochemical response to the first documentation of biochemical progression* or to death due to any cause, whichever occurs first.

  *Biochemical progression is defined as the increase of serum CgA levels ≥25% *versus* baseline.

[redacted]

The endpoint of **"biochemical progression-free survival (BPFS)"** is the time from the first study drug administration to the first documentation of biochemical progression or to death due to any cause, whichever occurs first.

Additionally, the biochemical response on the basis of urine 5-hydroxyindole acetic acid (5HIAA) will be assessed

- To assess the safety and tolerability of pasireotide LAR and everolimus alone or in combination as measured by rate and severity of adverse events in patients with a well differentiated neuroendocrine tumor of the lung or thymus

  Safety will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Incidence of adverse events (AEs), serious adverse events (SAEs), changes from baseline in vital signs, ECG tracings and laboratory results (hematology, blood chemistry) will be reported.

**Study population:**

The target population is comprised of adult patients with an advanced (unresectable or metastatic) well differentiated neuroendocrine carcinoma (typical and atypical according to the 2004 WHO criteria) of the lung or thymus. Patients must be >18 years old with WHO Performance status $\leq$2 and have adequate hematologic, renal and hepatic function.

**Number of patients:**

It is expected that a total of 120 patients with 40 patients in each arm will be enrolled into this study.

**Overview of study design:**

This is a prospective, multicenter, randomized, open-label, 3-arm, phase II study with a single-stage design in each arm to evaluate the efficacy and safety of pasireotide LAR (SOM230) and everolimus (RAD001) alone or in combination in the treatment of patients with a well differentiated neuroendocrine carcinoma of lung or thymus.

The number of patients enrolled is targeted to be approximately 120 with 40 patients randomized to each arm as follows:

Arm 1: treatment with pasireotide (SOM230) LAR (60 mg/month i.m.),

Arm 2: treatment with everolimus (RAD001) (10 mg/day p.o.),

Arm 3: treatment with pasireotide LAR (60 mg/month i.m.) and everolimus (10 mg/day p.o.).

Patients with disease control (SD or better) in the combination arm or monotherapy with pasireotide LAR and everolimus and who are not experiencing unacceptable toxicity are permitted to continue treatment after the 12-month treatment period, in the extension phase of the study.

**Statistical considerations:**

The primary objective of each single-stage trial arm is to evaluate the efficacy of pasireotide LAR and everolimus alone or in combination in patients with a well differentiated neuroendocrine tumor of the lung or thymus.

The primary variable is defined as the proportion of patients who are progression free at Month 9 based on RECIST V. 1.1.

A Fleming single stage design will be employed for each arm. Let p0 be the highest proportion of patients progression-free at Month 9 which would indicate that the treatment is clearly ineffective, and p1 be the minimum required proportion of patients progression-free. The trial tests the null hypothesis H0 that the observed proportion of patients progression-free, p, is less than or equal to p0 against the alternative hypothesis H1 that p is greater than or equal to p1. It consists of entering a predetermined number of subjects and deciding in favor of p0 or p1 based on the success rate observed by using an

[redacted]

appropriate cut-off between p0 and p1. If the number of responses is greater than or equal to R+1, p0 is rejected. If the number of responses is less than or equal to R, p1 is rejected.

In this trial, p0 and p1 have been set equal to 0.20 and 0.45 respectively. Forty (40) patients are planned to be randomized in each treatment group. If the number of responses is 13 or more, the hypothesis that $p \leq p0 = 20\%$ is rejected with a target alpha error rate of 5% and an actual alpha error rate of 4.3%; if the number of responses is 12 or less, the hypothesis that $p \geq p1 = 45\%$ is rejected with an actual beta error rate of 4%.

The secondary objective of "Progression-free survival (PFS)" is defined as the time from first study drug administration to objective tumor progression or death from any cause. If a patient has not had an event, PFS is censored at the date of the last adequate tumor assessment. PFS will be explored by presenting the Kaplan-Meier curve and estimator.

**Operating characteristics (One-arm, single-stage, Fleming design)**

| p0 | p1 | Target | | Cut-Off R + 1 | N | Actual | |
|---|---|---|---|---|---|---|---|
| | | Alpha | Beta | | | alpha | Beta |
| 20% | 45% | 5% | 10% | 13 | 40 | 4.3% | 4% |

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## Table of contents



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## List of figures



## List of tables



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## List of abbreviations

| | |
|---|---|
| 5-FU | 5-Fluorouracil |
| 5-HIAA | 5-hydroxyindole acetic acid |
| AC | Atypical carcinoid tumor |
| ACE | Angiotensin-converting enzyme |
| ACTH | Adrenocorticotropic hormone |
| ADA | American Diabetes Association |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AKT/PKB | Protein kinase B |
| ALT (GPT) | Alanine aminotransferase (glutamic pyruvic transaminase) |
| ASCO | American Society of Clinical Oncology |
| AST (GOT) | Aspartate aminotransferase (glutamic oxaloacetic transaminase) |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area under the curve |
| b.i.d. | Bis in die/twice a day |
| BAL | Bronchoalveolar lavage |
| beta-HCG | Beta-human chorionic gonadotropin |
| BPFS | Biochemical progression-free survival |
| BRR | Biochemical response rate |
| BSC | Best supportive care |
| BUN | Blood urea nitrogen |
| cAMP | Cyclic adenosine monophosphate |
| CDS | Core data sheet |
| CgA | Chromogranin A |
| CI | Confidence interval |
| Cl | Clearance |
| CPK | Creatine phosphokinase |
| CR | Complete response |
| CRF | Case Report/Record Form |
| CRO | Contract Research Organization |
| CS&E | Clinical Safety and Epidemiology |
| CSR | Clinical Study Report |
| CT | Computed Tomography |
| CTC/CTCAE | Common Toxic Criteria/Common Toxic Criteria for Adverse Events |
| CYP3A4 | Cytochrom P450 3A4 |
| DBL | Database lock |
| DBR | Duration of biochemical response |
| DKA | Diabetic ketoacidosis |
| DLCO | Diffusing capacity of the lung for carbon monoxide |
| DLT | Dose limiting toxicity |
| DM | Diabetes mellitus |
| DMC | Data Monitoring Committee |
| EASD | European Association for the Study of Diabetes |
| EBUS | Endobronchial ultrasound-guided fine needle aspiration |
| EC | Ethics Committee |

[redacted]

| | |
|---|---|
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EOS | End of study |
| FAS | Full Analysis Set |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GEP | Gastroenteropancreatic |
| GERD | Gastroesophageal reflux disease |
| GGT | Gamma-glutamyl transferase |
| GI | Gastrointestinal |
| GIP | Glucose-dependent insulinotropic polypeptide |
| GLP-1 | Glucagon-like peptide-1 |
| HbA1c | Hemoglobin A1c subtype (glycated hemoglobin) |
| HBcAb | Hepatitis B core antibody |
| HBsAb | Hepatitis B surface antibody |
| HBsAg | Hepatitis B surface antigen |
| HBV DNA | Hepatitis B Virus – Deoxyribonucleic acid |
| HCV-RNA PCR | HCV Ribonucleic acid – Polimerase Chain Reaction |
| HDL | High-density lipoprotein |
| HIF | Hypoxia-inducible factor |
| HMG-CoA | 3-hydroxy-3-methyl-glutaryl-CoA |
| HPF | High-power fields |
| HR | Hazard ratio |
| i.m. | Intramuscular(ly) |
| i.v. | Intravenous(ly) |
| IB | Investigator's Brochure |
| $IC_{50}$ | Half maximal inhibitory concentration |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IGF | Insulin-like growth factor |
| IHC | Immunohistochemistry |
| ILD | Interstitial lung disease |
| IN | Investigator Notification |
| INR | Internation Normalized Ratio |
| IRB | Institutional Review Board |
| ITT | Intent-To-Treat population |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LAR | Long-acting release |
| LCC | Large cell carcinoma |
| LDH | Lactate dehydrogenase |
| LFT | Liver function test |
| LH | Luteinizing hormone |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEN-1 | Multiple endocrine neoplasia type 1 |
| MRI | Magnetic Resonance Imaging |

[redacted]

| | |
|---|---|
| MTD | Maximum tolerated dose |
| mTOR | Mammalian target of rapamycin |
| MUGA | Multiple-Gated Acquisition |
| NE | Neuroendocrine |
| NET | Neuroendocrine Tumor |
| NSCLC | Non small cell lung cancer |
| o.d. | Omni die/once a day |
| p.o. | Per os/by mouth/orally |
| ORR | Objective response rate |
| OS | Overall survival |
| PCR | Polymerase Chain Reaction |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PFT | Pulmonary function tests |
| PGP | P-glycoprotein |
| PI3K | Phosphoinositide 3-kinase |
| PJP | *Pneumocystis jirovecii* pneumonia |
| PK | Pharmacokinetics |
| pNET | Pancreatic NET |
| PR | Partial response |
| PRRT | Peptide receptor radionuclide therapy |
| PT | Prothrombin time |
| PTEN | Phosphatase and tensin homolog |
| PTS | Post-text supplements |
| PTT | Partial prothrombin time |
| QD | Quaque die/every day |
| RAD001 | Everolimus |
| RAP | Reporting Analysis Plan |
| RCC | Renal cell carcinoma |
| REB | Research Ethics Board |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| s.c. | Subcutaneous |
| SAE | Serious adverse event |
| SCLC | Small cell lung cancer |
| SD | Stable disease |
| SDev | Standard deviation |
| SEER | Surveillance, Epidemiology and End Results |
| SEGA | Subependymal giant cell astrocytoma |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| SOM230 | Pasireotide |
| SSA | Somatostatin analogue |
| SSC | Small cell carcinoma |
| SC | Steering Committee |
| SSRs | Somatostatin receptors |
| SSTR | Somatostatin receptor subtype |

[redacted]

| | |
|---|---|
| t.i.d. | Ter in die/three times a day |
| TdP | Torsades de Pointes |
| TC | Typical carcinoid tumor |
| $T_{max}$ | Time of occurrence for maximum (peak) drug concentration |
| TSC | Tuberous sclerosis complex |
| TSH | Thyroid stimulating hormone |
| TTP | Time to tumor progression |
| ULN | Upper limit normal |
| VEGF | Vascular endothelial growth factor |
| VP-16 | Etoposide phosphate |
| WBC | White blood cell |
| WHO | World Health Organization |

[redacted]

## Glossary of terms

| | |
|---|---|
| Assessment | A procedure used to generate data required by the study |
| Cycles | Number and timing or recommended repetitions of therapy are usually expressed as number of days (eg: q28 days) |
| Enrollment | Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) |
| Investigational drug | The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug." |
| Investigational treatment | Drug whose properties are being testing in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage |
| Other study treatment | Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment |
| Subject Number (Subject No.) | A unique identifying number assigned to each patient/healthy volunteer who enrolls in the study |
| Period | A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc. |
| Premature patient withdrawal | Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression |
| Randomization number | A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment |
| Stage in cancer | The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body |
| Stop study participation | Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later |
| Study treatment | Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins.<br>In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination. |
| Study treatment discontinuation | Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal |
| Variable | Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints |

[redacted]

## Amendment 5

### Amendment rationale

In total, 124 patients have been randomized in the trial. 43 patient completed the core phase of the study and 41 entered in the extension phase.So far, 30 patients have discontinued the study treatment and 11 patients are still ongoing in the Extension phase.

The primary analysis of the study data was performed on 26th February 2016. For the core phase analysis, the data cutoff that was applied for a patient was either 12 months of study treatment or "End of Core Phase Evaluation" phase.

The primary efficacy endpoint was defined as the proportion of patients who were progression free at Month 9, based on RECIST V1.1. The primary analysis was to check if a sufficient number of patients were progression free at month 9 and the null hypothesis would be either accepted or rejected on the basis of the total number of responders. Accordingly, it would be concluded that the primary objective has been met/not met.

While performing the primary analysis for PFR at month 9, it was observed that enough number of responses was observed in all the treatment arms. In case of Pasireotide-LAR and combination arm, 13 patients had responses out of 41 patients and for Everolimus, 14 patients had responses out of 42 patients. The observed number of responses was enough to claim that the null hypothesis can be rejected. Hence it can be said that the primary objective was met.

The Study Steering Committee assessed the results of the primary endpoint during the Steering Committee Meeting held in May 2016. As patients were receiving a benefit from participation in the study, the study protocol is being amended. This amendment includes details to extend the duration of the study [from 104 weeks (2 years) to as long as all patients continue to demonstrate benefit and do not fulfill any of the study discontinuation criteria]. Only tumor evaluation and safety data will be collected after the 4th Visit in the Extension Phase. In addition to that, some sections of the protocol have been clarified and some inconsistencies corrected."**Other major changes implemented with the current protocol are:**

to delete [redacted], [redacted], [redacted] and [redacted] as protocol author and to add [redacted] as [redacted] and [redacted] as [redacted].

### Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike-through red font for deletions, red font for insertions.

Table of contents and list of tables have been updated according to modifications implemented throughout the protocol. Main changes were made to the following protocol sections:

**Protocol summary**

Summary modified to be in line with changes included in the protocol, and with study Endpoints.

[redacted]

**Section 1**

- Updates to include new information on pasireotide/everolimus marketing approvals, clinical experience, and safety data

**Section 4**

Section 4 and Figure 4-1

- Modification of the duration of extension phase from "until disease progression" to "until they no longer demonstrate benefit or fulfill any of the study discontinuation criteria".
- Modification of end of study definition from "the last visit two years after the start of treatment of the last randomized patient or when all patients have progressed whichever comes first to when all patients have discontinued the study.

**Section 7**

Section 7 and Table 7-1

Specification Patients who discontinue study treatment after 12 months of treatment, without evidence of progression or for reasons other than disease progression will continue to have tumor evaluation assessments "until disease progression or LPLV whichever occurs first".

## IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

## Amendment 4

### Amendment rationale

The amended version 03 (finalized on July 2013) of the study protocol is being amended after the submission to Competent Authorities/Ethics Committee mainly to remove the replacement policy (to avoid the introduction of biases in the study), to change the timepoint at which the primary endpoint will be evaluated (from month 12 to month 9) and to update information on everolimus and pasireotide LAR based on the new versions of the respective Investigator Brochures (ed. 13 dated 12 May 2014 for everolimus; ed. 14 dated 02 June 2014 for pasireotide LAR). In addition to that, some information already present in the protocol have been clarified and some inconsistencies corrected.

In order to avoid biased results, it has been decided to remove the replacement policy for patients discontinuing the trial for reasons other than disease progression and for patients with missing tumor assessment or unknown overall lesion response for the evaluation of the primary endpoint. These cases will be considered as "non-progression free" for the primary endpoint (i.e. rate of progression free, defined also as disease control rate) and will be censored at the time of the last adequate tumor assessment for the time-to-event endpoints (e.g. progression-free survival analysis).

As a consequence of the above decision (i.e. removal of the replacement policy), it has been decided to change the timing of the primary endpoint from Month 12 to Month 9 and to modify the assumptions for sample size estimation and the decision rule based on the primary endpoint, according to the Fleming single-stage design (see Section 10.8).

The reason for this change in the timing of the analysis is to limit the impact of the discontinuations for reasons other than disease progression on the decision rule. The assessment at 9 months is also supported by the disease severity in the study population recruited.

Of all neuroendocrine tumors (NETs), almost 25% are located in the respiratory tract. Typical carcinoids comprise between 1 to 2% and atypical carcinoids 0.1 to 0.2% of all pulmonary neoplasms (Öberg et al. 2012). However, data currently available on the recruitment of LUNA trial diverges from this prevalence, showing a higher proportion of patients with atypical histological classification.

Compared to the subgroup analysis performed in the lung-NET patients from RADIANT-2 (44 patients), patients recruited in the LUNA study present with a higher aggressive tumor biology (Fazio et al. 2013). In the RADIANT-2 subgroup of lung-NET, 75% of patients were classified as well-differentiated (low-grade, mitotic count <2 x 10 HPF) versus the LUNA study where a higher proportion of patients are well differentiated, atypical (intermediate grade, mitotic count of 2-10 x 10 HPF).

According to the evaluation and advice received by the Steering Committee (SC) members, the timepoint of 9 months for the analysis of the primary endpoint is reasonable and meaningful, based on current clinical experience and known biological behavior of lung-NET tumors.

No change in the treatment duration (i.e. 12 months in the core study) has been implemented. The 12-month assessments will remain to provide sufficient data for an accurate overall efficacy assessment of the treatments and to follow the standard evaluation of endpoints such as 12-month progression-free survival (PFS) in similar patient populations.

New information extrapolated from the recent [pasireotide Investigator Brochure] (IB, ed. 14 dated 02 June 2014) which has been reported in the protocol is:

- update on marketing approvals, and new applications for marketing authorization;
- update on safety data, with a special focus on hyperglycemia and QT-prolongation effects, and management recommendations for drug-related adverse events;
- description of the results of clinical studies in patients with NETs;
- update in terms of concomitant medications being allowed or prohibited;
- effects on fertility.

Data being included in the protocol based on the new [everolimus Investigator Brochure] (ed. 13 dated 12-May-2014) are related to:

- update on marketing approvals and new applications for marketing authorization;
- update on the number of patients being exposed to this agent during clinical trials and on cumulative post-marketing exposure in the oncology setting;
- update on safety data, and management recommendations for drug-related adverse events;
- update on the results of the main clinical studies in NET patients;
- update in terms of concomitant medications being allowed or prohibited;
- effects on fertility.

Other major changes implemented with the current protocol are:

- to delete [redacted] as protocol author and to add [redacted] as expert statistician
- to remove the distinction between the key secondary endpoint and the other secondary endpoints;
- to evaluate secondary endpoints both at 9 and 12 months;
- to delete “time to progression (TTP)” from the list of secondary endpoints. In this setting, results on TTP are expected to be equivalent to PFS;
- [redacted]
- [redacted]

[redacted]

- to reword the sentence related to the exclusion criterion #16. The positivity to hepatitis C antibody test (anti-HCV) indicates that a patient has a history of HCV infection (despite a negative viral load at baseline) but it will not exclude the subject from the enrollment into the LUNA study. Patients known to have a history of HCV infection, despite a negative viral load test at baseline (including those that were treated and are considered "cured") should be monitored every 4 weeks (± 1 week) for the risk of hepatitis C reactivation. The monitoring interval for the risk of hepatitis C reactivation has been changed from 4-8 weeks to 4 weeks (± 1 week);
- to specifiy that the monitoring for hepatitis B/C reactivation has to be performed in all patients, irrespective of the treatment arm they have been assigned to, taking into account the results arising from the four hepatitis B tests and the positivity for anti-HCV, respectively. However, in light of evidence that the risk for hepatitis B/C reactivation is related to everolimus, the drug interruption/discontinuation recommendations will apply to everolimus only;
- to specify that, in case of non-infectious pneumonitis, the drug interruption/discontinuation recommendations will apply to everolimus only, in light of evidence that the risk for this event is related to this agent;
- to specify that the monitoring of ECG changes has to be performed in all patients, irrespective of the treatment arm they have been assigned to, taking into account the observed QTcF value. However, in light of evidence that the risk for ECG changes is related to somatostatin analogue (SSA) treatment, the drug interruption/discontinuation strategy will apply to pasireotide LAR only;
- to specify that, for the duration of the trial, pasireotide LAR and everolimus will be supplied by Novartis or by local commercial stock, if available. Therefore, if at any time during the study life pasireotide LAR or everolimus become available in the Countries participating to the study, the local commercial stock should be used;
- to specify that patients could take their daily dose of everolimus as a single 10-mg tablet or as two 5-mg tablets taken together (QD), depending on the tablet strength available in the Country;
- to add a sentence in which it is specified what can occur in case a patient misses the daily dose of everolimus at the scheduled time point. The patient will be given two options: to take the study drug within 8 hours after the normal time of administration, or to skip it until the next day;
- to specify that, after the occurrence of an AE and the consequent reduction of pasireotide LAR dose, the re-escalation from 20 to 40 mg has to be performed within 56 days;
- to include the possibility to use the 2.5 ml syringe, if the 3-ml is not available, to reconstitute pasireotide LAR suspension;
- to clarify that all images for tumor assessment will be saved on a CD-rom and will be locally stored at the site in order to allow any future double check of the tumor assessment, if needed;
- to include a sentence referring to the identification of pathological lymph nodes as target lesions, when measurable (i.e. short axis ≥ 15mm by CT scan), as per RECIST V. 1.1;

[redacted]

- to include the definition of short axis for lymph nodes as the axis perpendicular to longest diameter, which will contribute to the baseline sum, as per RECIST V. 1.1;
- to include the definition of biochemical response for chromogranin A (CgA), the main biochemical marker (Kouvaraki et al. 2004; Yao et al. 2010), and for 5-hydroxyindole acetic acid (5HIAA) [in accordance to the criteria of the Italian Trials in Medical Oncology Group (Bajetta et al. 1993; Bajetta et al. 2006)];
- to specify that the biochemical response rate (BRR) and biochemical progression will be evaluated on the basis of serum CgA levels. Additionally, the biochemical response on the basis of urine 5HIAA will be assessed;
- to include a sentence referring to diet restrictions to apply when patients are asked to collect urine samples for 5HIAA evaluation in view of the fact that some foods contain significant amounts of hydroxyindoles that may influence 5HIAA measurements. Thus, patients will be asked to amend their diet for three days before starting urine collection and during the collection to avoid interference with the test;
- to update and reword sections on prohibited medications and medications that require caution and/or action, in order to be better understandable;
- to correct protocol inconsistencies and typos.

## Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike-through red font for deletions, red font for insertions.

Table of contents and list of tables have been updated according to modifications implemented throughout the protocol. Main changes were made to the following protocol sections:

**Protocol summary**

- Summary modified to be in line with changes included in the protocol, and with study endpoints listed in Table 3-1 and in Section 3.2.

**Section 1**

- Removal of cell size (large) from Table 1-1 when referring to typical and atypical carcinoids because, in the 2004 WHO classification criteria, there is no reference to cell size for typical and atypical carcinoids.
- Harmonization of the 5-year overall survival rates reported in this section, by using the paper from Chong et al. (2006) as a reference. The rates included in Table 1-1 were slightly different from those reported in the text of the section.
- Updates to include new information on pasireotide/everolimus marketing approvals, clinical experience, and safety data, as in the new IBs.

**Section 3**

- Section 3 and Table 3-1 modified to:
  - change the timepoint for the primary endpoint (from 12 to 9 months), as by amendment rationale;

[redacted]

- remove the distinction between the key secondary endpoint and the other secondary endpoints;
- remove the secondary endpoint "time to progression (TTP)", as by amendment rationale;
- include the definitions of "objective response rate", "best overall response", "duration of biochemical response" and "biochemical progression-free-survival".

**Section 4**

- Clarification that tumor measurements will be based on triphasic CT/MRI, as as already reported in Section 7.2.1.1.
- Correction of a mistake in the sentence "Disease control rate is defined as progression-free survival (PFS) according to RECIST V. 1.1" to "Disease control rate and progression-free survival will be evaluated during the extension phase".

**Section 5**

- Specification that patients with a well differentiated tumor will be enrolled in the study, as by study title and study objectives.
- Clarification being added to the inclusion criterion #1 stating that patients with a well differentiated tumor will be enrolled in the study, as by study title and study objectives.
- Clarification being added to the inclusion criterion #3 stating that baseline tumor assessment will be performed by triphasic CT/MRI, as already reported in Section 7.2.1.1.
- Removal of the Hepatitis C antibody test (anti HCV) from the exclusion criterion #16. The positivity to this test does not exclude patients from enrollment into the LUNA study.

**Section 6.1**

- Sections "Management of Infections" and "Management of stomatitis/oral mucositis/mouth ulcers" updated according to the new everolimus IB (ed. 13).
- Section "Management of hyperglycemia" updated according to the new pasireotide IB (ed. 14), with subsection "Monitoring of glucose levels" updated to specify some information that were already included in the patient diary, and subsection "Dose adjustments" reworded to specify that the interruption of treatment due to grade 3 hyperglycemia should not last ≥56 days from last dose, for pasireotide, and should not last ≥28 days from last dose, for everolimus (as already reported in Section 6.3.1.1 and Section 6.3.1.2).
- Section "Management of non-infectious pneumonitis" updated according to information included in the new everolimus IB (ed. 13), with specification that, in case of non-infectious pneumonitis, the dose reduction strategy applies only to everolimus since this AE can be related to the treatment with this agent.
- Section "Monitoring for hepatitis B reactivation" updated, as by amendment rationale, to:
  - correct a mistake in Table 6-3 (distinction of patients with prior or no prior HBV vaccination);
  - specify that patients at risk of hepatitis B reactivation should have HBV DNA monitored every 4 weeks (± 1 week);

[redacted]

  - specify that the monitoring for hepatitis B reactivation has to be performed in all patients, irrespective of the treatment arm they have been assigned to, taking into account the results arising from the four hepatitis B tests.
- Section "Monitoring for hepatitis C" updated, as by amendment rationale, to:
  - clarify that a patient who tests positive for the presence of HCV-RNA PCR will be ineligible for the LUNA study whereas a patient known to have a history of HCV infection (despite a negative viral load at screening) should be monitored every 4 weeks (± 1 week);
  - specify that the monitoring for hepatitis C reactivation has to be performed in all patients with a known history of HCV infection, irrespective of the treatment arm they have been assigned to.
- Section "Management of ECG changes" updated to include new information on the cardiac safety profile of pasireotide, as in the new pasireotide IB (ed. 14), with specification that the monitoring of ECG changes has to be performed in all patients, irrespective of the treatment arm they have been assigned to, taking into account the observed QTcF value.
- Section "Hepatic safety management" reworded to make it clearer, easier to understand, and aligned with that described in Table 6-4.

**Section 6.3**

- Inclusion of a sentence in Table 6-6 to specify that re-escalation of pasireotide LAR from 20 to 40 mg has to be performed within 56 days.
- Inclusion of a sentence to specify that the initial once-daily oral dose of everolimus (10 mg) can be administered either as two 5 mg tablets taken together (QD) or as a single 10 mg tablet, and in case a dose reduction is required due to toxicity, patients initially receiving the 10 mg strength will be provided with the 5 mg strength.
- Table 6-8 updated according to what reported in the new everolimus IB (ed. 13).

**Section 6.4**

- Section modified to include also concomitant therapies, not only concomitant medications (with the possibility of performing palliative radiotherapy or surgery during the study, after discussion with Novartis Clinical Trial Team).
- Overall section reworded to make it clearer and easier to understand, and being aligned with updated information from the new IBs (ed. 13 for everolimus; ed. 14 for pasireotide).
- Introduction of a new sentence stating that the use of the anticoagulant medication warfarin should be avoided. Warfarin should be replaced by selective Factor Xa inhibitors (rivaroxaban, apixaban, dabigatran) which are acceptable from a safety point of view since there have no effect on prothrombin time (PT), and partial thromboplastin time (PTT).
- Inclusion of a sentence stating that "prolonged (>2 weeks in duration) treatment with systemic corticosteroid treatment is not allowed during the study".
- Inclusion of the link to the website listing the drugs prolonging the QT interval. The previous link did not run any more.

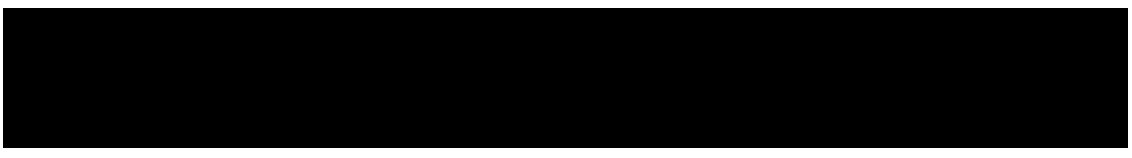
[redacted]

**Section 7.1**

- Section updated to change the order of the following criteria for premature withdrawal: "Pregnancy, patient withdrawing informed consent, new cancer therapy, patient lost to follow-up and death", because they are not "study specific criteria" but common criteria for discontinuation.
- Specification of information regarding QTcF value, according to what reported in Section 6.1.4.9.
- Removal of the replacement policy, as by amendment rationale.

**Section 7.2**

- Change in the timepoint for the primary endpoint (from 12 to 9 months), as by amendment rationale.
- Inclusion of a sentence clarifying that all images will be saved on a CD-rom and will be locally stored at the site in order to allow any future double check of the tumor assessment, if needed.
- Inclusion of new paragraphs referring to the calculation of the baseline sum of the longest diameters for all target lesions; the identification of pathological lymph nodes as target lesions, when measurable; and the definition of short axis for lymph nodes, as per RECIST V. 1.1.
- Inclusion of the subsection "Response assessment" for the primary endpoint which was previously reported for secondary efficacy assessment only. This part was modified by separating response assessment for target lesions from that of non-target lesions, according to RECIST V. 1.1 criteria.
- Inclusion of the definition of biochemical response for CgA, the main biochemical marker (Kouvaraki et al. 2004; Yao et al. 2010), and for 5HIAA [in accordance to the criteria of the Italian Trials in Medical Oncology Group (Bajetta et al. 1993; Bajetta et al. 2006).
- Specification that the biochemical response rate (BRR) and biochemical progression will be evaluated on the basis of serum CgA levels. Additionally, the biochemical response on the basis of urine 5HIAA will be assessed.
- Inclusion of a sentence referring to diet restrictions to apply when patients are asked to collect urine samples for 5HIAA evaluation.
- Inclusion of a sentence stating that total white blood cells (WBC) count will be evaluated as absolute and, only if available, as differential.
- Inclusion of the chance to evaluate urea, instead of BUN, if BUN cannot be directly evaluated.
- Change in the second time point at which female patients of childbearing potential should have a negative serum pregnancy test (not 48 hours prior to treatment start but at visit 2).
- Section "Hepatitis screening" revised to:
    - remove a contradictory statement in terms of screening for hepatitis B. Prior to randomization, all patients (not a selected group of patients at risk) must be tested for Hepatitis B viral load and serologic markers, that is: Hepatitis B VirusDeoxyribonucleic acid (HBV-DNA), Hepatitis B surface antigen (HBsAg), Hepatitis B surface Antibody (HBsAb), and Hepatitis B core Antibody (HBcAb), as



by exclusion criterion #16. If a patient tests positive for the presence of HbsAg and/or HBV-DNA, he/she will be considered ineligible for the study according to Exclusion Criterion #16. In case of eligibility, the results from the other two tests (HBsAb and HBcAb) will detect which patients have to be monitored for the risk of hepatitis B reactivation every 4 weeks during the study, as reported in Section 6.1.4.8;

- remove a contradictory statement in terms of screening for hepatitis C. All patients will be tested for HCV-RNA PCR. If positive, the patient will be considered ineligible for the LUNA study, according to the Exclusion criterion #16. Patients known to have a history of HCV infection (positivity to anti HCV), despite a negative viral load at baseline, will be monitored for the risk of hepatitis reactivation. The monitoring will take place every 4 weeks (± 1 week) (not every 4-8 weeks as previously stated).

**Section 8**

- Correction of the name of the form in which information about deaths will be collected.
- Section being updated according to information on fertility included in the new IBs (ed. 13 for everolimus; ed. 14 for pasireotide).

**Section 10:**

- Change of some part of this section referring to the statistical methods and data analysis, as by amendment rationale.
- Change in the list of major protocol violations, to be in line with changes introduced in the VAP3 (Novartis Validation and Planning 3) module that classify protocol deviations.
- Change in the timepoint at which the primary endpoint will be evaluated (from 12 to 9 months), as by amendment rationale.
- Updated sample size section with new null and alternative hypotheses, as per amendment rationale.
- Removal of the secondary endpoint “TTP”, as by amendment rationale.
- Change in the analysis of infections which will be no more analysed separately from AEs.
- Clarification of the way ECG data will be analysed, from a statistical point of view.
- Change in the way vital signs will be analysed.

[redacted]

## IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

## Amendment 3

### Amendment rationale

The amended version 02 (finalized on December 2012) of the study protocol is being amended after the submission to Competent Authorities/Ethics Committee mainly to implement several requests of modification from Competent Authorities/Ethics Committee, to update information of pasireotide LAR based on the new version of the Investigator Brochure ed. 13 dated 24-May-2013, to correct information based on the RAD001 IB ed 11 erratum document dated 24-May-2013, and to better clarify some information already present in the protocol.

Competent Authorities requests are focused especially on:

- Clarify the target population described in Inclusion criterion #1
- Implement an exclusion criterion for female patients pregnant and breast-feeding
- Implement a more frequent monitoring of the Thyroid Function Tests
- Implement a more detailed guidance for physicians in the response to a QTc prolongation on ECG.

The new information extrapolated from the Pasireotide LAR IB ed. 13 dated 24-May-2013 which will be implemented in the protocol is:

- The description of the results of a phase III study with NET patients treated with Pasireotide LAR.

The data to be modified in the protocol based on the RAD001 IB ed. 11 Erratum dated 24-May-2013 are related to:

- Afinitor dose adjustment and management recommendation for Non-Infectious Pneumonitis
- Effects of everolimus on fertility.

Other changes implemented with the current protocol are:

- To include [redacted] and [redacted] and to delete [redacted] as protocol authors
- To delete the specification in the Amendment 2 Rationale section that there is the possibility to increase the Everolimus dose in case of tolerability issues for patients with non-infectious pneumonitis
- To delete the specification in the Changes to the Protocol section of Amendment 2 that there is the possibility to increase the Everolimus dose in case of tolerability issues for patients with non-infectious pneumonitis
- To update comment in the Changes to the Protocol section of Amendment 2, related to Section 6.1.4.7
- To correct some typos in Amendments 1 and 2 Rationales
- Clarify in the Inclusion Criterion #2 that the administration of the study drugs can be also the first line of treatment
- To enhance clarity of the end of the treatment definition and align sections

[redacted]

- To correct a wrong information in Table 6-9 about the possibility to keep the patient in study even if the re-escalation of the dose of Pasireotide LAR from 20mg to 40mg is not possible
- To reword and reorganize paragraphs of sections of prohibited medications and the medications that require caution and/or action, in order to be better understandable
- To include the possibility to use the Pasireotide LAR 40mg to obtain the dose of 20mg if 20mg strength is not available at the site
- To clarify the IVRS randomization process
- To update Table 7-1 with the new assessments required by the Competent Authorities. (i.e. ECG and Thyroid Function Tests)
- To correct the Table 7-2 to clarify that Pasireotide LAR and/or Everolimus will be provided also at visit 18 for patients that continue treatment at the end of the Core Phase
- To align the description of the assessments in the body of the protocol with Tables 7-1 and 7-2
- To correct some protocol inconsistencies and typing errors.

## Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike-through red font for deletions, red font for insertions.

Table of contents and list of tables have been updated according to modification implemented throughout the protocol. Changes were made to the following protocol sections:

**Section 2.1:**

- Section updated for Pasireotide LAR clinical efficacy in NET.

**Section 4.1.3:**

- Section updated to enhance clarity of the end of the treatment definition.

**Section 4.4:**

- Section updated to clarify which are the Novartis reasons for an Early study discontinuation.

**Section 5.2:**

- Revision of Inclusion Criterion # 1 to add a clear explanation of which patients' population will be included in the study.
- Revision of Inclusion Criterion #2 to add the clarification that there is no limit to the number of previous treatment lines and also naïve patients can be enrolled.

**Section 5.3:**

- Introduction of a new exclusion criterion for female patients pregnant and breast-feeding.
- Revision of the Exclusion criterion # 21 to better clarify the risk factors for Torsades de Pointes.

[redacted]

**Section 6.1.4.7:**

- Table 6-2 was corrected to insert:
  - the right grade of improvement of Non-Infectious Pneumonitis from which the treatment could re-start.
  - the right time within which the treatment should be re-started to avoid patient withdrawal from the study in presence of Non-Infectious Pneumonitis grade 2.
  - the right time within which the treatment should be re-started to avoid patient withdrawal from the study in presence of Non-Infectious Pneumonitis grade 3.

**Section 6.1.4.9:**

- Revision of the section to update the indications for the management of the ECG changes.

**Figure 6-3:**

- Figure updated based on the new indications implemented in the section 6.1.4.9.

**Section 6.1.7:**

- Section updated to align sections related to the end of study definition.

**Section 6.3.2:**

- Table 6-9 has been modified in order to correct a typo; to specify that if the dose re-escalation of Pasireotide LAR to 40mg is not possible the patient cannot be maintained in the study.

**Section 6.4.2:**

- Revision of the section to reword and reorganize the paragraphs of the section of the medications that require caution and/or action, in order to be better understandable.

**Section 6.4.3:**

- Revision of the section to reword and reorganize paragraphs of section of prohibited medications, in order to be better understandable.

**Section 6.5.1:**

- Revision of the section to better clarify the IVRS randomization process.

**Section 6.5.2:**

- Revision of the section to better clarify the IVRS randomization process.

**Section 6.6.1.1:**

- The Table 6-13 has been modified in order to indicate that the 20mg dose could be obtained using also a portion of the volume of the 40mg strength.
- Section updated to add the indication that if the 20mg strength is not available at the site the dose could be obtained from the 40mg strength.

**Section 7.1:**

- The Table 7-1 has been modified in order to:
  - Specify that the assessment performed at the End of Core study also apply for the Early withdrawal.

[redacted]

- Specify that the visit 18 has to be performed at week 52 and not at week 53.
- Specify that the Thyroid function tests will be performed at week 12 (visit 8) and at week 24 (visit 11).
- Specify that ECG will be performed at week 8 (visit 7).
- Specify that Pasireotide LAR injection will be done also at visit 18 for patients that will continue treatment at the end of the Core Phase.
- Specify that Everolimus administration will be done also at visit 18 for patients that will continue treatment at the end of the Core Phase.

- The Table 7-2 has been modified in order to:
  - Specify that Pasireotide LAR injection will be done monthly at visit 18 for patients that will continue treatment at the end of the Core Phase.
  - Specify that Everolimus administration will be done also at visit 18 for patients that will continue treatment at the end of the Core Phase.
  - Specify that patients who discontinue study treatment after 12 months of treatment without evidence of progression or for reasons other than disease progression will continue to have tumor evaluation assessments.

**Section 7.2.2.5.2:**

- Sections changed to add the timelines for the International Normalized Ratio (INR) during the Extension phase.

**Section 7.2.2.5.6:**

- Sections changed to add the timelines for the Lipid profile during the Extension phase.

**Section 7.2.2.5.7:**

- Section changed to specify that the thyroid function tests will be assessed at week 12 (visit 8) and at week 24 (visit 11).

**Sections 7.2.2, 7.2.2.2, 7.2.2.5, 7.2.2.5.1, 7.2.2.5.3, 7.2.2.5.4, 7.2.2.5.4, 7.2.2.5.5, 7.2.2.5.8, 7.2.2.6.4, 7.2.2.7.1:**

- Sections updated with the indication that the timeline of these assessments for the Extension phase are indicated in the Table 7-2.

**Section 8.4:**

- Section changed to update the information about the fertility present in the RAD001 IB ed. 11 Erratum dated 24-May-2013.

**Section 10:**

- Section changed to delete the last paragraph because the assumption described in it is not applicable for the study.

[redacted]

## IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

## Amendment 2

## Amendment rationale

The amended version 01 (finalized on November 29th, 2011) of the study protocol is being amended before submission to Competent Authorities/Ethics Committee mainly to clarify the importance of routine patient glucose self-monitoring, to detect and treat hyperglycemia as early as possible, and to give specific guidance on dose adjustment in the different treatment arms.

The combination of pasireotide LAR, which alters insulin and incretin secretion, and everolimus, which may affect insulin sensitivity, could result in a higher risk for hyperglycemia than each agent alone. Based on the currently available preliminary data, it is hypothesized that one possible reason for the high rate of grade 3 hyperglycemia could be the suboptimal monitoring of blood glucose.

In study CSOM230F2102 (pasireotide LAR 60 mg q28d in combination with everolimus 10 mg qd) three hyperglycemia grade 3 Adverse Events (AEs) were observed, two of them were reported as serious adverse events (SAEs). One patient had a medical history of diabetes mellitus. Concomitant medications included metformin. The patient accidentally received pasireotide at a single dose of 80 mg. The patient had not received everolimus. Fifteen days after commencing pasireotide the patient developed signs of hyperglycemia with symptoms of fatigue and polydipsia. Five days later, the patient was admitted to the hospital for hyperglycemia (self-measured at [redacted] mg/dl and measured in hospital at [redacted] mg/dl). The subject was treated with insulin adjusted to blood glucose levels. Pasireotide dosage was reduced to 40mg. The investigator reported that the study medication along with the insufficient antidiabetic medication had contributed to the hyperglycemia. Due to the tight monitoring in this study, and early intervention for treating hyperglycemia, this patient was well managed and did not develop more severe complications of hyperglycemia. The second patient´s medical history included diabetes mellitus type II. The patient received the first dose of the study medication (everolimus) at a dose of 10 mg. Twelve days after start of study drug the patient was hospitalized to initiate insulin therapy (Insulin Lispro injection) for treatment of diabetes mellitus.

As of July 3, 2012, in study CSOM230I2201 (oral everolimus alone or in combination with pasireotide LAR i.m.) the majority of patients included to date developed various degrees of hyperglycemia irrespective of glucose values at baseline. Pooled analysis of blinded safety data identified eighteen patients with grade ≥3 hyperglycemia so far. Five cases were reported as SAE, two of these comprised a grade 4 hyperglycemia (ketoacidosis). One of theses cases developed metabolic acidosis with fatal outcome. This patient's medical history included left colectomy, intestinal occlusion, hypertension, chronic obstructive bronchopneumonia and dyslipidemia. Concomitant medication included candesartan cilexetil, ezetimibe, omeprazole, and tiotropium bromide. The patient started medication with everolimus and pasireotide LAR and received one dose of pasireotide LAR and the last dose everolimus on study day 27. On day 24, the patient started developing asthenia, deterioration of general condition, vomiting, and diarrhea. Three days later the patient was hospitalized and showed signs of confusion, dehydration, marbled skin under the lower limb: blood culture was positive for E. Coli, and

[redacted]

ketoacidosis was diagnosed. On day 29, the patient died with an acute, severe metabolic acidosis that may have resulted from ketoacidosis, although sepsis was also considered as a contributory factor. In addition to ketoacidosis, inhalation pneumonia, sepsis and acute respiratory distress were also considered as having contributed to the patient's death.

The other patient who had Grade 4 hyperglycemia had a medical history that included hypertension, diabetes mellitus type II, insomnia, and hypercholesterolemia. Concomitant medications included repaglinide, metformin, omeprazole, lisinopril with hydrochlorothiazide, zolpidem, emuliquen and paracetamol. The patient started the study medication everolimus and pasireotide LAR and received one dose of pasireotide, and 20 days of everolimus. On day 21 of cycle 1, the patient presented with a deterioration of [redacted] health status, and suffered from fainting and was hospitalized and diagnosed with diabetic ketoacidosis on the same day. Lab results showed a glucosuria of [redacted] mg/dL, glucose (serum) of [redacted] mg/dL, troponin I [redacted] mg/L, CK (creatinine kinase) [redacted] U/ and hemoculture showed Klebsiella oxycota. Hyperglycemia was controlled with insulin, and the patient was treated with antibiotics. Study treatment was interrupted as a result of the event. The patient was discharged from the hospital 12 days later after hyperglycemia was controlled and treatment with intravenous antibiotics was completed.

In order to prevent and appropriately treat hyperglycemia, specific guidance on dose adjustment in the different treatment arms is provided. Management of hyperglycemia in the combination and pasireotide LAR monotherapy arms was updated and monitoring of glucose levels for patients with normal glucose at baseline in combination and pasireotide LAR monotherapy arms by fingerstick testing was added. The glucose assessments by fingerstick testing for patients with normal glucose metabolism at baseline and allocated in the everolimus monotherapy arm were removed, as the assessments are not considered required for these patients, based on the currently known safety profile. Furthermore, all patients will be required to have local laboratory assessments of glucose level during all study visits. The glucose level will be assessed at day 49 visit in patients of everolimus monotherapy arm only if medically indicated. Other changes implemented with the current amendment are:

- To include [redacted] and to delete [redacted] and [redacted] as protocol authors
- To include updated information on antitumor activities of somatostatin analogues and clinical experience on pasireotide LAR
- To update information on approval status of everolimus worldwide and on clinical experience with everolimus
- To remove the background information on mutational status of genes encoding for drug targets and for proteins involved in drug target pathway
- To include pre-clinical data in study rational and purpose
- To update rational for dose and regimen selection section
- To include the possibility to reduce everolimus by two dose levels to 5 mg every other day in case of tolerability issues
- To include the 20 mg strength of pasireotide LAR that should be used to re-start study drug treatment in case of tolerability issues
- To classify as extension phase (instead of follow-up phase) the treatment period following the core study

[redacted]

- To specify also in the inclusion criteria #3 and #5 that MRI can be used to assess lesions at baseline to maintain consistency throughout the protocol
- To clarify that the use of subcutaneous (s.c.) somatostatin analogs is allowed up to 48 hours prior to starting study treatment (exclusion criterion #3)
- To clarify that the 6 months wash-out period from previous therapy with radioligand therapy is considered prior to starting study treatment. The recovery from the adverse effects of such therapy is requested
- To reduce the wash-out period (from 3 months to 4 weeks or 5 half lives, whichever is longer) from prior chemotherapy and immunotherapy prior to starting study treatment considering appropriate a 4 weeks- or 5 half-lives wash out period (exclusion criterion #7). The recovery from the adverse effects of such therapy is requested
- To exclude from study participation patients with hepatic artery embolization, cryoablation or radiofrequency ablation of hepatic metastasis within the last 3 months prior to starting study treatment. The recovery from the adverse effects of such therapy is requested
- To reduce the wash-out period (from 3 months to 4 weeks or 5 half lives, whichever is longer) from a previous treatment with an investigational drug within a clinical trial prior to starting study treatment , considering appropriate a 4 weeks- or 5 half-lives wash out period (exclusion criterion #8). The recovery from the adverse effects of such therapy is requested
- To reduce the wash-out period (from 3 months to 4 weeks) from previous radiotherapy prior to starting study treatment (exclusion criterion # 14). The recovery from the adverse effects of such therapy is requested
- To exclude from study participation patients with detectable HBV-DNA to be consistent with the exclusion of patients with chronic active hepatitis B at baseline (exclusion criterion #15)
- To exclude from study participation patients with detectable HCV-RNA-PCR test at baseline to be consistent with the exclusion of patients with chronic active hepatitis C (exclusion criterion #15)
- To specify that a wash-out period of 5 half lives from previous treatment with drugs known to prolong QT is needed for inclusion in the clinical trial (exclusion criterion #20)
- To specify that highly effective contraception measures should be followed during clinical trial participation (exclusion criterion #23)
- To change the allowed dose delay from 21 to 28 days to recover from on treatment toxicities considering the 28-day cycle duration
- To specify that the combination treatment of pasireotide LAR and everolimus will be discontinued in case one drug of the combination is discontinued due to an adverse event.
- To specify that, in case of tolerability issues, no dose re-escalation for everolimus will be performed
- To provide recommendation about treatment management in case of tolerability issues

- To clarify that everolimus dose can be reduced up to 5 mg every other day in case the patient requires co-administration of a CYP3A4 and PgP inhibitors to adjust the AUC to the range observed without inhibitors
- To delete the PK samples management for patients receiving an inducer of CYP3A4 in addition to everolimus, since no PK analysis is planned during study conduction
- To specify that strong CYP3A4 and PgP inhibitors are not allowed during study participation
- To update the list of allowed concomitant medications during study participation according to new information available
- To specify that azithromycin co-administration is not allowed while on study treatment being a drug that induces QT prolongation
- To delete the specifications about the needle to be used to withdraw the suspension of pasireotide LAR as needles will be used according to local practice
- To update baseline requirements, target lesion definition and response assessment according to RECIST 1.1
- To define response of CgA or 5HIAA as normalization or a $\geq$ 50% reduction of CgA or 5HIAA levels compared to baseline
- To specify that free thyroid T3 and T4 hormone levels will be collected at screening/baseline and EOS
- To introduce the possibility to perform serum pregnancy test instead of urine pregnancy test at baseline, every months during core phase and every 3 months during extension phase, according to local practice
- [redacted]
- To include some details about the Data Monitoring Committee and the Steering Committee
- To correct some protocol inconsistencies and typing errors.

## Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike-through red font for deletions, red font for insertions.

Table of contents and list of tables have been updated according to modification implemented throughout the protocol.

Changes were made to the following protocol sections:

Section 1.2.3

- Section updated for pasireotide LAR pre-clinical and clinical experience.

Section 1.2.2

- Section updated for everolimus approvals from FDA and EMA.

Section 1.2.2.3

- Section updated for everolimus clinical experience.

[redacted]

Section 1.2.3

- Section modified to remove information on mutational status of genes encoding for drug targets and for proteins involved in drug target pathway.

Section 2.1

- Section modified to include pre-clinical data supporting the use of the combination of pasireotide LAR and everolimus.

Section 2.3

- Section updated for previous clinical data details.

Section 4.1.2

- Section revised to better clarify that everolimus and pasireotide LAR dose can be adjusted in case of toxicity issues.

Section 4.1.3

- Section title changed according to re-classification of follow-up phase to extension phase.

Figure 4.1

- Follow up phase changed to extension phase.

Section 5.2

- Revision of inclusion criteria #3 and #5 to add the possibility to assess lesions using MRI at baseline.

Section 5.3

- Revision of the following exclusion criteria:
  - Exclusion criterion #3: to specify that s.c. somatostatin analogs are allowed up to 48 h prior to start of study treatment.
  - Exclusion criterion #6: to specify that patients who received radioligand therapy within 6 months prior to starting study treatment are excuded. The recovery from the adverse effects of such therapy is requested for study participation.
  - Exclusion criterion #7: to reduce wash-out period from previous chemotherapy or immunotherapy prior to starting study treatment. The recovery from the adverse effects of such therapy is requested.
  - Introduction of a new exclusion criterion for patients who received cryoablation or radiofrequency ablation with hepatic artery embolization, of hepatic metastasis within the last 3 months prior to starting study treatment. The recovery from the adverse effects of such therapy is requested.
  - Exclusion criterion #8: to reduce the wash-out period from previous treatment with an investigational drug within a clinical trial prior to starting study treatment. The recovery from the adverse effects of such therapy is requested.
  - Exclusion criterion #13: to reduce the interval between previous radiotherapy and the start of study treatment administration. The recovery from the adverse effects of such therapy is requested.

[redacted]

- Exclusion criterion #14: to correct the value for $O_2$ saturation at rest on room air from 80 to 88%.
- Exclusion criterion #15: to specify that patients with detectable HBV-DNA and HCV-RNA-PCR at baseline are not eligible.
- Exclusion criterion #21: to specify that drugs known to prolong QT are allowed as far as not administered within 5 half lives prior to start of study treatment.
- Exclusion criterion #23 and addition of a new exclusion criterion: to update the definition of highly effective contraception.

Section 6.1.4.5

- Modification of the section to implement appropriate hyperglycemia screening, monitoring and management. Table 6-1 added to summarize hyperglycemia management.

Section 6.1.4.7

- Table 6-2 was modified to specify everolimus dose adjustment in case of grade 2 non-infectious pneumonitis.

Section 6.1.4.8

- Revision of the section to remove references to prophylactic treatment for patients with detectable HBV-DNA at baseline and patients with detectable HCV RNA at baseline.

Section 6.1.4.9

- Figure 6-3 modified to remove text boxes referring to PK samples.

Section 6.1.5

- Figure 6-4 modified to specify that no PK sample will be collected.

Section 6.3.1.1

- Revision of the section to specify that pasireotide LAR dose reduction up to 20 mg is allowed and change the allowed dose delay from 21 to 28 days to recover from toxicities.

Section 6.3.1.2

- Revision of the section to specify that everolimus dose reduction to 5 mg every other day is allowed, to clarify that after the recovery form tolerability issues no dose-re-escalation of everolimus will be performed and to change the allowed dose delay to recover from toxicities.

Section 6.3.2

- Recommendations for treatment management in case of tolerability issues have been provided. Table 6-9 has been introduced.

[redacted]

Section 6.4.1

- Tables updated with inducers, moderate and strong inhibitors.

Section 6.4.2

- Revision of the section to:
  - Add an explanation about the use with caution of PgP and CYP3A4 inducers and inhibitors during the study
  - Change the everolimus dose to be used in case of concomitant use CYP3A4 or PgP inhibitors.
  - Update the list of PgP and CYP3A4 inducers and inhibitors.

Section 6.4.3

- Revision of the section to specify that strong CYP3A4 and PgP inhibitors are not allowed during study participation and that everolimus blood level will not be assessed for patients receiving CYP3A4 inducer. The co-administration with azithromycin was deleted as it induces QT prolongation.

Section 6.6.1

- Pasireotide 20 mg strength introduced in Table 6-11.

Section 6.6.1.1

- Revision of the section to delete the specifications of the needle to be used for pasireotide LAR preparation and administration. Furthermore, details of pasireotide LAR 20 mg strength are provided.

Section 6.6.3.1

- Pasireotide LAR 20 mg strength has been introduced.

Section 7.1

- The Table 7-1 has been modified in order:
  - To specify that concomitant medication and adverse events will be evaluate also on day 49. To provide indications about the glucose level assessment in the different treatment arms.
  - To include a safety follow up visit to be performed 56 days after treatment discontinuation for patients with disease progression at week 53 or who prematurely discontinued study treatment.
  - To specify that PTT will be performed at screening/baseline
- The Table 7-2 has been modified:
  - To change follow up phase into extension phase
  - To include a safety follow up visit to be performed 56 days after treatment discontinuation.
  - To provide indications about the glucose level assessment in the different treatment arms.

[redacted]

Section 7.1.4.1

- Section modified to specify that patients with blood glucose values consistently in excess of 250 mg/dL persisting after interruption of study drug in spite of continuous, appropriate therapeutic intervention(s) will be discontinued.

Section 7.1.5

- Section title was modified from Follow up period to Extension period.

Section 7.2.1.1

- Revision of the section to introduce the possibility to assess lesions using MRI at baseline, to re-classify follow up phase as extension phase and to better specify baseline requirements and target lesion definition according to RECIST v1.1.

Section 7.2.1.2

- Revision of the section to re-classify follow up phase as extension phase and to better clarify the response assessment according to RECIST v 1.1 and to define response of CgA or 5HIAA as normalization or a $\geq$50% reduction of CgA or 5HIAA levels compared to baseline.

Section 7.2.2.5.3

- Section modified according to modification of section 7.2.2.5.4.

Section 7.2.2.5.4

- Section added to provide details about the assessment of glucose, insulin, and glycated hemoglobin during study participation.

Section 7.2.2.5.7

- Section changed to specify that free T3 and T4 hormones are included in thyroid function assessments.

Section 7.2.2.5.9

- Definition of effective contraception has been updated. Name of follow up phase has been changed to extension phase. The possibility to perform serum pregnancy test instead of urine pregnancy test has been introduced.

Section 7.2.2.5.10

- The referenced number of exclusion criterion for hepatitis C and B has been corrected from 21 to 16.

[redacted]

Section 7.2.4.2

- In Table 7-5 the visit number was corrected from visit 6 and 7 to visit 7 and 8.

Section 8.4

- Section revised to include highly effective contraception requirements.

[redacted]

Section 8.6

- Section modified to provide further details on Independent Data Monitoring Committee.

Section 8.7

- Section modified to specify that a Steering Committee charter will be provided.

Section 10.4.1

- Section modified to add MRI.

[redacted]

Section 13

- Reference section has been updated.

### IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

## Amendment 1

## Amendment rationale

The original version (version 00, finalized on October 6th, 2011) of the study protocol is being amended before submission to Competent Authorities/Ethics Committee to increase the hepatic-related safety measures for patients treated with pasireotide LAR.

During an internal medical review of liver related laboratory values, 3 healthy volunteers treated with pasireotide (SOM230) were identified with elevations in liver function tests. Two subjects met the criteria for Hy's Law (i.e. ALT > 3 x ULN with concurrent total bilirubin >2 x ULN, without increases in alkaline phosphatase and no other cause(s) identified for the abnormal findings). One subject received pasireotide 600 μg bid s.c. for 7 days, while the second subject received pasireotide 1950 μg bid s.c. for 5 days. The third subject (pasireotide 600 μg bid s.c. for 7 days) had ALT and total bilirubin increases that met the criteria for Hy's Law but the alkaline phosphatase was not assessed and the subject received a potentially confounding concomitant medication. ALT values for all 3 subjects were greater than 3 x ULN but < 4 x ULN and total bilirubin values were ≤ 4 x ULN. All 3 cases were asymptomatic, presented within 10 days after initial pasireotide s.c. administration, and were reversible with discontinuation of pasireotide. None of the cases were reported as adverse events and the subjects completed the respective studies per protocol.

An assessment of liver enzyme categorical outliers has been completed across the pasireotide s.c. development program (up to October 2011). The 3 healthy volunteers that met the biochemical criteria of Hy's Law (including the subject without the ALP value) are included amongst the 654 healthy volunteers as presented below. None of the other patients (i.e. Cushing's disease, carcinoid syndrome or acromegaly) in the development program met the criteria for Hy's Law.

- 654 healthy volunteers have been exposed to pasireotide s.c.:
  - 3 out of 654 (0.5%) met the biochemical criteria of Hy's Law
  - 16 out of 654 (2.4%) subjects had an ALT or AST > 3x ULN
  - 3 of the healthy volunteers had an ALT or AST > 5xULN
  - 17 out of 654 (2.6%) subjects had a total bilirubin of 2xULN (including 7 patients with pre-existing liver disease and elevations of total bilirubin)
- 156 patients in phase 1 and phase 2 trials have been exposed to pasireotide s.c.:
  - None of the patients met the biochemical criteria of Hy's Law
  - 6 out of 156 (3.8%) patients had an ALT or AST > 3xULN
  - 4 out of 156 (2.6%) patients had an ALT or AST > 5xULN
  - 2 out of 156 (1.3%) patients had a total bilirubin of ≥ 2xULN;
- 162 patients with Cushing's disease in phase 3 trials have been exposed to pasireotide (s.c.):
  - None of the patients met the biochemical criteria of Hy's Law
  - 8 out of 162 (4.9%) patients had an ALT or AST > 3x ULN

[redacted]

- 1 out of 162 (0.6%) patients had an ALT or AST > 5x ULN
- None of the patients out of 162 with Cushing's disease had a total bilirubin of ≥ 2xULN.

The pasireotide Compassionate Use Program (approximately 200 patients as of October 2011) was also reviewed. A single Cushing's disease patient [redacted] who was previously presented in an Investigator Notification in September 2010 was the only patient identified meeting the biochemical criteria Hy's Law.

A review of the unblinded data from the clinical program with the pasireotide long acting release (LAR) formulation did not reveal cases meeting the biochemical criteria Hy's Law .

As a consequence of these observations, enhanced hepatic-related safety measures will be taken to ensure patient safety.

Other minor changes implemented with the following amendment are:

- To change the Statistician. The responsibility passed from [redacted] to [redacted] ad interim
- To include [redacted] as author of the clinical trial protocol.
- To align inclusion and exclusion criteria
- To specify that one single vial of 60 mg pasireotide LAR will be reconstituted with the vehicle instead of one 20 mg vial plus one 40 mg vial. The 40 mg vial will be supplied to sites to be used in case pasireotide LAR dose is reduced for suspected pasireotide LAR-related toxicities.
- To specify that gallbladder evaluation will be performed together with the radiological tumor evaluation as safety assessment at baseline for all patients, on treatment only for patients treated with pasireotide LAR.

## Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike-through red font for deletions, red font for insertions.

Changes were made to the following protocol sections:

- Section 5.2 Inclusion criteria
- Section 5.3 Exclusion criteria
- Section 6.1.5 Hepatic Safety Management NEW
- Section 6.3.2.1 Hepatic-related discontinuation criteria
- Section 6.6.1.1 Preparation procedure for pasireotide LAR
- Section 6.6.3.1 Pasireotide LAR
- Section 7.1 Study flow and visit schedule
- Section 7.1.4.1 Criteria for premature patient withdrawal
- Section 7.2.1.1 Primary efficacy assessment
- Section 7.2.2 Safety and tolerability assessments
- Section 7.2.2.5.2 Coagulation
- Section 7.2.2.5.3 Biochemistry

[redacted]

- Section 7.2.2.5.4 Liver Function Tests
- Section 7.2.2.5.9 Hepatitis screening
- Section 7.2.2.6.4 Gallbladder Assessment

## IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

# 1 Background

## 1.1 Overview of neuroendocrine tumors of the lung and thymus

### 1.1.1 Lung neuroendocrine carcinoma

Lung cancer is the third most frequent cancer type of men and women worldwide. The main types of lung cancer are non small cell lung cancer (NSCLC; 70%-80%) and small cell lung cancer (SCLC, ~25%). Lung "carcinoid" tumors are well differentiated neuroendocrine carcinomas (lung-NETs) of the lung and account for 1%–2% of all pulmonary neoplasms and for ~25% of all carcinoid tumors. Approximately 10%–20% of pulmonary carcinoids are atypical carcinoids, and the remaining 80%–90% are typical carcinoids. Patients with carcinoid tumors are younger than those with common primary lung cancer. Unlike typical carcinoids, atypical carcinoids are associated with a history of cigarette smoking (83%–94% of cases) and occur more often in men (2:1) (Schreurs et al. 1992). Most typical carcinoids (80%–90%) are stage I, whereas approximately 50% of atypical carcinoids are stage I cancers. The standard treatment with curative intent for carcinoid tumors is surgery to completely remove the tumors. The 5-year overall survival rates for typical carcinoids and atypical carcinoids are 87% and 56%, respectively, and the survival rate for atypical carcinoid is significantly poorer than that for typical carcinoid (Chong et al. 2006).

Lung-NETs share most morphological and clinical features observed in gastrointestinal NETs. Similarly, pure NETs and mixed forms can be distinguished pathologically. Clinical presentation of NETs range from benign typical carcinoid tumors (TCs) to atypical carcinoid tumors (ACs) having a low-grade behavior, to the highly aggressive poorly differentiated carcinomas of the small and large cell neuroendocrine types, which share the same poor prognosis (Righi et al. 2007).

As per 2004 WHO classification of NETs of the lung, architectural and other parameters, together with the mitotic index and the presence of necrosis as the two most relevant characteristics, lead to the current classification into the four different categories proposed in the spectrum of NETs of the lung (Travis et al. 2004).

**Table 1-1 Differential pathological findings in NE lung tumors (2004 WHO classification) (Travis et al. 2004; *Chong et al. 2006)**

| | Typical carcinoid (TC) | Atypical carcinoid (AC) | Large cell NE carcinoma | Small cellcarcinoma |
|---|---|---|---|---|
| Organoid pattern | Characteristic | Characteristic | Present, less extensive | Absent |
| Cells size | | | Large | Small |
| Cytoplasm | Abundant | Abundant | Abundant | Scanty |
| Nuclear pleomorphism | Usually absent | Occasionally present | Present | Present |
| Prominent nucleoli | No | No | Yes | No |
| Mitoses (x10 HPF) | <2 | 2-10 | >10 (mean 70) | mean 70 |
| Necrosis | Absent | Usually focal | Extensive | Extensive |
| 5-year overall survival* | 87%* | 56%* | 21%* | <10% |

[redacted]

In lack of knowledge about precise functional classification of these tumors in terms of hormonal production, only common NE markers are of diagnostic significance in the definition of identification of pulmonary NETs. Among such markers, chromogranins/ secretogranins are of major interest; chromogranin A (CgA) is stored in high amounts in well differentiated NETs and to a variable extent in poorly differentiated NE carcinomas.

The current therapeutic approach and only curative treatment of pulmonary NETs is surgical resection based on the principle of complete resection with preservation of as much normal lung tissue as possible. Pulmonary NETs always require major surgical procedures with systematic nodal dissection, and a careful search for multifocal lesions should always be performed (Ferolla et al. 2009).

Afinitor has been approved in 2016 by FDA and the European Commission as first systemic treatment for patients with advanced, progressive, non-functional lung NET, based on the results from RADIANT-4 trial. Before this approval certain treatment approaches by use of chemotherapy as single-agent treatment or in combination had shown anti-tumoral activity in neuroendocrine tumors. Under these, in the recent past, temozolomide showed good results in advanced NETs. In a retrospective analysis in which the efficacy of temozolomide was evaluated in 36 patients with advanced stages of neuroendocrine tumors (gastric, thymic, pulmonary, pancreatic origin), an overall objective radiologic response rate of 14%, and stable disease of 53% was observed. In particular, patients with bronchial and thymic carcinoids had disease control rate (response or stabilization) in 62% and 71% of cases, respectively (Ekeblad et al. 2007). Other chemotherapy regimens (e.g. streptozotocin + 5-FU, cisplatinum + etoposide) in the treatment of patients with metastatic pulmonary carcinoid tumors showed a low effect on tumor growth (Granberg et al. 2001).

Even though, up to now only Afinitor is approved to be used in the treatment of lung- NETs. Till today, the clinical management of bronchial neuroendocrine tumors is not standardized and clear therapeutic guidelines are still missing.

### 1.1.2 Thymus Neuroendocrine Carcinoma

The thymic neuroendocrine tumours are epithelial tumours of the thymus gland that are predominantly or exclusively composed of neuroendocrine cells which can be demonstrated on immunohistochemistry.

The neuroendocrine tumours of the thymus comprise of typical carcinoid (TC) and atypical carcinoid (AC), as well as large cell carcinoma (LCC) and small cell carcinoma (SCC).

The prevalence of thymic carcinoid is approximately 0.3% of total carcinoids of all sites. These tumours are uncommon and occur in all age groups with male predominance.

In 1972, Rosai and Higa reported that thymic carcinoids may occur in association with multiple endocrine neoplasia type 1 (MEN-1), a genetic disorder that predisposes to the development of multiple endocrine and non-endocrine proliferations (Rosai et al. 1972).

A large number of cases of NETs arising in the thymus are associated with paraneoplastic syndromes. Among these, Cushing's syndrome is the most frequent given that an increased secretion of ACTH has been reported in one-third of sporadic thymic NETs.

[redacted]

An aggressive surgical approach in the management of thymic neuroendocrine tumour offers the best possible treatment. The role of chemotherapy and radiotherapy (RT) in the postoperative management of thymic neuroendocrine tumour continues to be debated.

Single agents or combination drug therapies with 5-fluorouracil, streptozotocin, carmustine, etoposide phosphate (VP-16), and cisplatin have been used previously without any significant impact on the recurrence rate or overall survival. Thymic carcinoid tumours express somatostatin receptors (SSRs) and there are successful interventions with long acting octreotide in primary and metastatic tumours (Dutta et al. 2010; Ferolla et al. 2007).

## 1.2 Introduction to investigational treatment(s) and other study treatment(s)

### 1.2.1 Overview of Pasireotide (SOM230) LAR

Pasireotide is an injectable somatostatin analogue. The formulation of pasireotide used in this trial is the long-acting depot formulation (long-acting release, LAR).

It is a novel cyclohexapeptide with the following chemical name: (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11- (4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19- hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2-aminosuccinic acid] salt. Inactive ingredients of pasireotide LAR include: mannitol, carmellose sodium (carboxymethylcellulose sodium), poloxamer 188 and water for injection.

Pasireotide has been approved in Europe and in the US as a subcutaneous (s.c.) formulation under the trade name Signifor® for the treatment of patients with Cushing's disease for whom medical therapy is appropriate. Pasireotide, as the long-acting depot formulation, is also being developed for the treatment of acromegaly. Data from two Phase III studies in acromegaly which both met their primary endpoint became available in 2012, and marketing authorization for pasireotide LAR in the treatment of acromegalyhas been granted both by FDA and the European Commission in 2015. Pasireotide LAR is also being studied for the treatment of Cushing's disease, neuroendocrine tumors, and dumping syndrome.

#### 1.2.1.1 Mechanism of Action

Like natural somatostatin and other somatostatin analogues, pasireotide exerts its pharmacological activity via binding to somatostatin receptors. There are five known somatostatin receptor subtypes (SSTR): SSTR 1, 2, 3, 4 and 5. Somatostatin receptors are expressed in different tissues under normal physiological conditions. Somatostatin analogues activate these receptors with different potencies (Schmid and Schoeffter 2004) and this activation results in a reduced cellular activity and inhibition of hormone secretion. Somatostatin receptors are strongly expressed in many solid tumors, especially in neuroendocrine tumors where hormones are excessively secreted e.g. acromegaly (Freda 2002), gastroenteropancreatic (GEP)-NET (Oberg et al. 2004) and Cushing's disease (Van der Hoek et al. 2005).

First-generation somatostatin analogues (octreotide and lanreotide) have a high affinity to SSTR subtype 2 (SSTR2), with moderate or no affinity to the remaining subtypes. Pasireotide

[redacted]

is a novel cyclohexapeptide somatostatin analogue that exhibits a unique binding profile, binding with high affinity to four of the five known human somatostatin receptors (Table 1-2). Compared to Sandostatin® (octreotide acetate), pasireotide exhibits a binding affinity which is 30-40 times higher for human SSTR1 and SSTR5, 5 times higher for human SSTR3, and similar to the affinity for SSTR2 receptors. A detailed summary of available preclinical data is provided in the [pasireotide LAR Investigator's Brochure].

**Table 1-2 Binding profile for octreotide and pasireotide at SSTR 1-5 (IC50, M)**

| Compound | SSTR1 | SSTR2 | SSTR3 | SSTR4 | SSTR5 |
|---|---|---|---|---|---|
| Octreotide acetate (SMS) | $2.8\times10^{-7}$ | $3.8\times10^{-10}$ | $7.1\times10^{-9}$ | $>10^{-6}$ | $6.3\times10^{-9}$ |
| Pasireotide (SOM230) | $9.3\times10^{-9}$ | $1.0\times10^{-9}$ | $1.5\times10^{-9}$ | $>10^{-6}$ | $1.6\times10^{-10}$ |
| Ratio of $IC_{50}$: octreotide/ Pasireotide | 30 | 0.4 | 5 | -- | 40 |

### 1.2.1.2 Antitumor actions of somatostatin analogs

Somatostatin analogs show antineoplastic activity in a variety of experimental models *in vivo* and *in vitro* (Pollak and Schally 1998, Schally 1988, Weckbecker et al. 1993). They inhibit the growth of various cancer cell lines, such as those of gastric, lung, colorectal, prostatic, ovarian, kidney, brain, or thyroid origin (Froidevaux and Eberle 2002, Keri et al. 1996, Schally et al. 2004, Weckbecker et al. 1993).

Pasireotide has shown anti-tumor effects *in vitro* and *in vivo*. Pasireotide LAR (8 and 80 mg/kg s.c.) dose-dependently decreased tumor volume to 66% and 21% of control in a human prostate tumor model (DU-145) (Schmid et al. 2010). Furthermore, pasireotide inhibited proliferation in primary NET cell lines (KRJ-I and P-STS) ( Kidd et al. 2011).

A recent analysis of the Surveillance, Epidemiology and End Results (SEER) database found a significant increase in survival from 1988 to 2004 compared with 1973 to 1987, coinciding with the introduction of octreotide in 1988 (Yao et al. 2008a). More recently, the PROMID study has shown that octreotide LAR was able to increase time to tumor progression (TTP) when compared to placebo from 6 months to 14.3 months in patients with advanced NET of the midgut or unknown primary tumor location (Rinke et al. 2009). The effect of higher doses of octreotide on tumor growth has also been evaluated using a non-marketed formulation of the compound. In one study, 12 patients with advanced, progressive midgut NETs received octreotide pamoate 160 mg every second week for 2 months followed by monthly injections for 12 months. Stable disease was achieved by 75% of patients for a median duration of 12 months (range 6 to 24 months).

### 1.2.1.3 Clinical Experience

Overall, clinical experience with pasireotide in humans shows an adverse event (AE) profile similar to that of octreotide, with the exception of an increased frequency of hyperglycemia.

Preliminary data from a healthy volunteer study [CSOM230C2101] which assessed single i.m. doses of pasireotide LAR up to 60 mg (N=5 per cohort) show that pasireotide LAR was well tolerated, and that the adverse events observed are comparable with those observed with

[redacted]

octreotide LAR. Diarrhea was the most common adverse event which was sometimes associated with abdominal pain and/or flatulence. The gastrointestinal events were mild or moderate in severity. About half of the subjects reported transient mild injection site pain. Preliminary safety data are available from 20 carcinoid patients inadequately controlled by somatostatin analogues treated with pasireotide LAR study [CSOM230C2110] (Table 1-3). These patients were under treatment with pasireotide LAR i.m. depot injections at doses of 20 mg, 40 mg or 60 mg for up to six weeks at the time of the safety summary. Pasireotide LAR was generally well tolerated. The mean change in average number of bowel movements from baseline (mean of the seven days prior to the first pasireotide LAR injection compared to the mean of the last 7 days of months 3) was +12.4 (SDev 47.2) in the 20 mg group, -7.2 (SDev 32.0) in the 40 mg group and -11.3 (SDev 36.5) in the 60 mg group. The most commonly reported AEs were gastrointestinal; however, most of these events were considered unrelated to study drug. PK Interim analysis has shown that a steady state appeared to be achieved following three monthly i.m. injections of 20 mg (N=12), 40 mg (N=14) or 60 mg (N=16) pasireotide LAR in carcinoid patients.

**Table 1-3 Most frequent AEs associated with Pasireotide LAR treatment**

| Adverse Event (Preferred term) | Pasireotide LAR 20 mg (N=5) n (CTC= grade 3) | Pasireotide LAR 40 mg (N=7) n (CTC= grade 3) | Pasireotide LAR 60 mg (N=8) n (CTC= grade 3) | Pasireotide LAR Any dose (N=20) n (%) (n=CTC grade 3) |
|---|---|---|---|---|
| Diarrhea | 1 | 2 | 2 | 5 (25.0%) |
| Fatigue | 1 | 2 (1) | 1 | 4(20.0%) (1) |
| Dyspnea | 1 | 2 (1) | 1 | 4 (20.0%) (1) |
| Flushing | 1 | 1 (1) | 1(1) | 3 (15.0%) (2) |
| Back Pain | 1 | 1 | 1 | 3 (15.0%) |
| Nausea | 1 | 1 | 0 | 2 (10.0%) |
| Palpitations | 0 | 2 | 0 | 2 (10.0%) |
| Abdominal Pain | 1 | 1 | 0 | 2 (10.0%) |
| Steatorrhea | 1 | 1 | 0 | 2 (10.0%) |
| Asthenia | 1 | 1 | 0 | 2 (10.0%) |
| Headache | 0 | 1 | 1 | 2 (10.0%) |
| Anorexia | 0 | 1 | 1 | 2 (10.0%) |
| Hyperglycemia | 0 | 1 (1) | 1 | 2 (10.0%) (1) |
| Odema Peripheral | 0 | 1 | 0 | 1 (5.0%) |
| Erythema | 1 | 0 | 0 | 1 (5.0%) |

Number (%) of patients with most frequent AEs (>5% for any dose group) regardless of relationship to study drug (preliminary data from study [CSOM230C2110])
Source: [CSOM230C2110]

Similar results were obtained in other Phase I, Phase II and III studies, with the most frequently reported AEs being of gastrointestinal origin, predominantly diarrhea, nausea, and abdominal pain. Generally, these events were mild, transient, and only occasionally caused patients to discontinue treatment.

Specifically, single doses of pasireotide s.c. up to 1500 µg QD and multiple s.c. doses up to 1500 µg QD, 750 µg b.i.d., and 2100 µg b.i.d., and continuous (7-day) s.c. infusion by a pump, have been well tolerated by healthy volunteers and patients with acromegaly, metastatic

[redacted]

carcinoid tumor, or Cushing's disease. The most common AEs of gastrointestinal origin were seen at all doses, but occurred more frequently at higher doses in all studies. The frequency of gastrointestinal events appeared to decrease with time in multiple-dose studies. A number of subjects also reported mild-to-moderate headaches. Generally, events were mild, transient, and only occasionally caused patients to discontinue treatment.

The overall conclusion arising from cumulative review of Signifor® post-marketing data (cumulative patient exposure since the first launch of pasireotide being estimated of approximately 98 patient-years) is that the safety profile seen from the post-marketing experience so far is consistent with the known labeled core safety information in the Core Data Sheet (CDS).

Further details on the safety of pasireotide LAR can be found in [pasireotide LAR Investigator's Brochure]. In addition, the Section 6.1.4 of the protocol ("Handling of specific toxicities") describes in details some specific AEs associated with pasireotide treatment, with a special focus on hyperglycemia, and QT interval prolongation.

#### 1.2.1.3.1 Pasireotide clinical studies in NETs

In a Phase I study of pasireotide LAR in patients with metastatic carcinoid tumors [CSOM230C2110], clinical response of symptom improvement over a 3-month period was seen most often at the highest dose (60 mg every 28 days).

In a Phase II study of pasireotide s.c. in patients with metastatic carcinoid tumours [CSOM230B2202], clinical response of symptom improvement was observed at doses of 600 µg s.c. b.i.d. and above. For those patients who achieved complete or partial treatment success, the disease stabilized. Overall, tumor response assessment indicated there was no evidence of tumor shrinkage. Given the results of this study, doses above 600 µg s.c. b.i.d. were considered for future clinical trials to maximize the clinical benefit of pasireotide in patients with metastatic carcinoid tumors.

In another phase II, in patients with advanced NETs of the digestive system whose symptoms of carcinoid syndrome (diarrhea/flushing) were inadequately controlled by octreotide LAR, pasireotide 600–900 mg s.c. bid was effective and generally well tolerated in controlling the symptoms of diarrhea and flushing in 27% of patients. Evaluation of tumor response in 23 patients showed 13 patients with stable disease and ten with progressive disease at study end (Kvols et al. 2012).

A Phase III study ([CSOM230C2303]) comparing pasireotide LAR 60 mg versus octreotide LAR 40 mg in patients with metastatic carcinoid tumors (at the time of the snapshot on 17 Nov-2011 when 88 patients have been treated) was terminated early as futility was demonstrated based on the proportion of patients achieving symptom response at Month 6. The overall proportion of patients who achieved symptom response at Month 6 was 9/43 patients (20.9%) in the pasireotide group and 12/45 patients (26.7%) in the octreotide group. The odds ratio of achieving symptom response at Month 6 among patients receiving pasireotide versus octreotide was 0.731 (95% confidence interval: 0.271, 1.974). The proportion of patients who achieved stable disease at Month 6 was higher in the pasireotide group (60.8% *vs*. 42.3%), while overall response rate (CR+PR) at Month 6 was comparable between the two treatment groups (2.0% in the pasireotide group *vs*. 3.8% in the octreotide

[redacted]

group). Disease control rate was 62.7% with pasireotide LAR and 46.2% with octreotide LAR (odds ratio: 1.96; 95%IC: 0.89-4.32, p=0.93). An unplanned, exploratory analysis based on investigator's assessment presented at the 2013 ASCO annual meeting showed that pasireotide LAR significantly extended the median time without tumor growth by five months and reduced the risk of cancer progression by 54% compared to octreotide LAR. The median investigator-assessed PFS was 11.8 months in the pasireotide LAR arm and 6.8 months in the octreotide LAR arm, which was statistically significant (HR=0.46; P=0.045).

### 1.2.2 Overview of Everolimus (RAD001)

Everolimus is a derivative of rapamycin with the following chemical name: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4azatricyclo[30.3.1.04,9] hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone.

Inactive ingredients of immediate release tablets are: butylhyroxytoluene/butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose/hydroxypropyl methylcellulose, crospovidone, lactose anhydrous.

Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus was approved in Europe (July 2013) and other global markets (trade name: Certican®) for renal and cardiac transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation who are at low-to-moderate immunologic risk. It is also indicated for the prophylaxis of allograft rejection in adult patients receiving a liver transplant.

Everolimus has also undergone extensive development in oncology as Afinitor® since 2002 for patients with various hematologic and non-hematologic malignancies as a single agent or in combination with other antitumor agents. Afinitor® was approved for advanced renal cell carcinoma (RCC) in 2009 in various countries, including Europe and the US. In 2010, Afinitor® received accelerated USA approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. Everolimus is also available as Votubia® in the EU (conditional approval in 2011) for patients aged ≥3 years with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery. In light of the results from the Core Phase of study [M2301] (EXIST-1), the approved indication was subsequentely updated on 29 August 2012 by FDA who granted accelerated approval for the following expanded indication "pediatric and adult patients with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected". The European Commission granted approval for the expanded indication on 15 November 2013. In addition, Afinitor® received accelerated approval from FDA in 2012 for the treatment of adult patients with renal angiomyolipoma and TSC, not requiring immediate surgery. The effectiveness of Afinitor® in the treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 48.1 weeks (study [M2302], EXIST-2) (Bissler et al. 2013). Further follow-up of patients is required to determine long-term outcomes. On 31 October 2013, the EC granted Votubia® for the following indication: "treatment of adult patients with renal angiomyolipoma associated with

[redacted]

TSC who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors) but who do not require immediate surgery".

Afinitor® was also approved for treating "progressive pancreatic NET (pNET) in patients with unresectable, locally advanced, or metastatic disease" in 2011 in various countries, including the USA and Europe. A broader regulatory approval of Afinitor® for the treatment of advanced NETs was granted in some countries based on the results of Phase III study [C2325] of everolimus in combination with octreotide LAR (Sandostatin LAR®) *versus* Sandostatin LAR® and placebo in patients with advanced NETs with a history of carcinoid syndrome.

As of 14 Sep 2016, Afinitor® has been approved in 113 countries worldwide for patients with pNET/neuroendocrine tumors.In 2012, Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced $HR^+/HER2^-$ breast cancer) in combination with exemestane in a number of countries worldwide, including the US, where it is approved after failure of treatment with letrozole or anastrozole in the USA, and in the EU, following a non-steroidal aromatase inhibitor.

Most recently, approvals were granted to Afinitor by the European Commission, FDA and several other Health Authorities for the treatment of advanced progressive non-functional neuroendocrine tumors of gastrointestinal and lung origin based on the results of the RADIANT-4 study [T2302].

Everolimus is being investigated as an anticancer agent based on its potential to act:

- directly on the tumour cells by inhibiting tumour cell growth and proliferation and/or
- indirectly by inhibiting angiogenesis leading to reduced tumour vascularity, via potent inhibition of tumour cell vascular endothelial growth factor (VEGF) production and VEGF-induced proliferation of endothelial cells.

#### 1.2.2.1 mTOR pathway and cancer

At the cellular and molecular level, everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the PI3 kinase pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3 kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumour development (Cohen and McGovern 2005, Bjornsti and Houghton 2004).

#### 1.2.2.2 Preclinical studies

Everolimus inhibits the proliferation of a range of human tumour cell lines *in vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an anti-angiogenic agent.

[redacted]

In preclinical models, the administration of everolimus was associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated (p)-S6 (p-S6) and p-4E-BP1, and occasionally with an increase in phosphorylated AKT, a protein upstream of mTOR signaling pathway.

#### 1.2.2.3 Clinical experience

The pharmacokinetic characteristics of everolimus have been extensively investigated in the context of the drug's development as an immunosuppressant in solid organ transplantation where everolimus was administered twice daily as a part of an immunosuppressant, multi-drug regimen consistently including cyclosporin A and glucocorticoids. Recent Phase I studies provide steady-state pharmacokinetics for both the weekly and daily schedules at varying dose levels in patients with advanced cancers (O'Donnell et al. 2008; Tabernero et al. 2008).

Everolimus is rapidly absorbed after oral administration, with a median time to peak blood levels ($t_{max}$) of 1-2 hours post dose. Everolimus is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Everolimus is also a substrate of P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systematically absorbed everolimus may be influenced by medicinal products that interact with CYP3A4 and/or P-glycoprotein. Caution should be exercised when co-administering everolimus with CYP3A4 inhibitors or inducers. A detailed summary of available PK data is provided in the [Investigator's Brochure].

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In addition, healthy volunteer subjects and non-oncology hepatically impaired subjects have participated in clinical pharmacology studies.

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose schedules. Its safety profile is characterized by manageable AEs, mostly of grade 1 and 2 in severity. These AEs are generally reversible and non-cumulative.

On the basis of a pooled safety data in oncology patients receiving everolimus (N=2,470) in clinical studies (including randomized, double-blind, placebo- or active comparator-controlled phase-III trials and phase II studies related to the approved indications in oncology), the most common adverse drug reactions (ADRs) [incidence ≥1/10 and suspected to be related to treatment by the Investigator] were (in decreasing order): stomatitis, rash, fatigue, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, hyperglycemia, weight decreased, pruritus, asthenia, peripheral edema, hypercholesterolemia, epistaxis, and headache. The most common grade 3 or 4 ADRs (incidence ≥1/100 to <1/10 and suspected to be related to treatment by the investigator) were stomatitis, anemia, hyperglycemia, fatigue, infections, pneumonitis, diarrhea, asthenia, thrombocytopenia, neutropenia, dyspnea, lymphopenia, proteinuria, hemorrhage, hypophosphatemia, rash, hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and pneumonia.

In the pooled safety database, the following new or worsening clinically relevant laboratory abnormalities were reported with an incidence of ≥1/10 (very common, listed in decreasing frequency):

[redacted]

- *hematology*: hemoglobin decreased, lymphocytes decreased, white blood cells decreased, platelets decreased, and neutrophils decreased (or collectively as pancytopenia);
- *clinical chemistry*: glucose (fasting) increased, cholesterol increased, triglycerides increased, AST increased, phosphate decreased, ALT increased, creatinine increased, and potassium decreased.
- Most of the observed abnormalities were mild (grade 1) or moderate (grade 2). Grade 3/4 hematology and chemistry abnormalities include:
- *hematology*: lymphocytes decreased, hemoglobin decreased (very common), neutrophils decreased, platelet count decreased, white blood cells decreased (all common).
- *clinical chemistry*: glucose (fasting) increased (very common), phosphate decreased, potassium decreased, AST increased, ALT increased, creatinine increased, cholesterol (total) increased, triglycerides increased, albumin decreased (all common)

Non-infectious pneumonitis, which is a known risk for all mTOR inhibitors, was identified early in the program and management guidelines were implemented. Infections (including fungal) were observed more commonly with everolimus.

Finally, in clinical trials and post-marketing spontaneous reports, everolimus has been associated with serious cases of:

- hepatitis B reactivation, including fatal outcome (with reactivation of infections being an expected event during periods of immunosuppression);
- renal failure events (including acute renal failure), some with fatal outcome, and proteinuria (thus, renal function of patients should be monitored particularly in situations where patients have additional risk factors that may further impair renal function);
- amenorrhea (including secondary amenorrhea);
- *pneumocystis jirovecii* pneumonia (PJP), some with fatal outcome;
- angioedema (reported with and without concomitant use of everolimus and ACE inhibitors).

#### 1.2.2.3.1 Everolimus Phase II/III studies in NETs

In pancreatic NET cells, mTOR is activated in response to signalling by insulin-like growth factor 1 (IGF-1) (Van Gompel 2004, von Wichert et al. 2000). Interruption of this signalling pathway through treatment with everolimus in combination with a somatostatin analogue was the goal of a recent phase 2 clinical trial conducted by J. Yao at the MD Anderson Cancer Center (Yao et al. 2010). The clinical data on efficacy and safety of everolimus plus depot octreotide 30 mg IM every 28 days in patients with metastatic or unresectable, well-differentiated, neuroendocrine carcinoma have recently been updated (Yao et al. 2007 and 2008b). A total of 60 evaluable patients have been treated in two cohorts; the two cohorts of patients received everolimus at 5 mg/day and 10 mg/day. Out of the sixty treated diseases, 30 were carcinoids, and 30 islet cell tumours. Sixty-five percent of the patients were in progression at the time of study entry. Overall, 13 (22%) patients were reported to have partial

[redacted]

response (5 carcinoids and 8 islet cell tumours, respectively), 42 (70%) with stable disease (24 in carcinoids and 18 in islet cell, respectively) and 5 (8%) with progressive disease (1 in carcinoid and 4 in islet cell, respectively) per RECIST. Overall, median PFS was 60 weeks (63 in carcinoids and 50 in islet cell, respectively). Median overall survival (OS) has not been reached yet, with a 2-yr survival rate of 81%. The combination of everolimus and Sandostatin LAR 30 mg appears to have been well tolerated. The most common toxicity reported was mucositis. CTC grade 3/4 toxicities reported included: anemia, thrombocytopenia, aphthous ulcer, diarrhea, edema, fatigue, hyperglycemia, nausea, pain, and rash.

RADIANT-1 [CRAD001C2239] is a phase II open label, parallel group study in pNET in which patients were allowed to receive either everolimus 10 mg daily as monotherapy (stratum 1) or everolimus 10 mg daily in combination with Sandostatin LAR 30 mg (stratum 2). A total of 160 evaluable patients have been assigned in the 2 strata: 115 patients in stratum 1 and 45 in stratum 2. 11 out of the 115 patients (9.6%) who received everolimus alone had a partial response vs. 2 (4.4%) in the second stratum (octreotide combined with everolimus). A stable disease was achieved in 67.8% (78 patients) of the patients in the stratum 1, and 80% of the patients (36 patients) in the stratum 2. Median PFS was 9.7 months in the stratum 1 and 16.7 months in the stratum 2. The median OS was 24.9 months in stratum 1 but it was not reached for stratum 2 at the time of data cut-off (Yao et al. 2010). New data arising from this study are consistent with previous observations, by showing a median OS of 28.8 months in stratum 1 *vs* 38.8 months in stratum 2 [RAD001 Investigator brochure].

RADIANT-3 [CRAD001C2324] is a phase III double-blind trial in which 410 patients with advanced pancreatic neuroendocrine tumours were randomised 1:1 to everolimus 10 mg/day + best supportive care (BSC) or placebo + BSC. Results from this study demonstrated a statistically significant clinical benefit of everolimus over placebo by a 2.4-fold prolongation of median PFS as per local investigator assessment (11.04 vs 4.6 months; hazard ratio [HR] = 0.35; 95% confidence interval [CI] 0.27–0.45; $p < 0.0001$), resulting in a 65% reduction in the estimated risk of progression (HR 0.35; $p<0.0001$). Similar results were obtained by central review (Yao et al. 2011). The estimated rate of patients who were alive and progression-free at 18 months was 34.2% with everolimus as compared with 8.9% with placebo, indicating that a sizable proportion of patients achieved a prolonged benefit with everolimus. The overall survival results (cut-off date: 28 February 2010) are not yet mature and no statistically significant difference in OS was noted (HR=0.99; 95% CI: 0.68-1.43). Crossover of 72.9% of patients from placebo to open-label everolimus following disease progression likely confounded the detection of any treatment-related difference in OS.

Overall, safety findings from the longer-term follow-up of studies [C2324] (RADIANT-3) and [C2239] (RADIANT-1) did not alter the established safety profile of everolimus. The overall clinical benefits support the treatment of patients with advanced pNETs; the safety profile was manageable and consistent with previous experience in this setting. No new safety concerns emerged. Most adverse events (AEs) were of grade 1-2 intensity and were transient.

RADIANT-2 [CRAD001C2325] is a phase III double-blind trial in which 429 patients with advanced neuroendocrine tumours and a history of carcinoid syndrome symptoms were randomised 1:1 to everolimus + octreotide LAR or placebo + octreotide LAR. Median PFS by investigator review (284 events) was significantly better with everolimus and octreotide (12.0 vs 8.6 months; HR = 0.78; 95% CI 0.62–0.98; $p = 0.018$), but by central review (223 events),

the difference was not significant (16.4 vs 11.3 months; HR = 0.77; 95% CI 0.59–1.00; p = 0.026) (Pavel et al. 2010, Pavel et al. 2011).
An exploratory subanalysis from the RADIANT-2 study evaluated the efficacy and safety of everolimus + octreotide LAR in a cohort of patients with low-to-intermediate grade advanced lung NETs (n=44) (Fazio et al. 2013). 33 patients were on treatment with everolimus + octreotide LAR, and 11 patients were on placebo + octreotide LAR. Median PFS was 13.63 months in the everolimus + octreotide LAR arm *vs* 5.59 months in the placebo + octreotide LAR arm (relative risk for progression: HR, 0.72; 95% CI, 0.31–1.68; P=0.228). More patients receiving everolimus + octreotide LAR experienced minor tumor shrinkage (not partial response as per RECIST) than those receiving placebo plus octreotide LAR (67% *vs* 27%). Overall, this exploratory subanalysis of the RADIANT-2 trial indicates that in patients with advanced lung NET, the addition of everolimus to octreotide LAR improves median PFS by 2.4-fold compared with placebo + octreotide LAR. These clinically significant observations support the continued evaluation of everolimus treatment regimens in this patient population.

All these results indicating that everolimus is effective in p-NETs (RADIANT-3) and in NETs associated with carcinoid syndrome (RADIANT-2) are supported by recent evidence from RAMSETE, a phase II single-arm study in 73 patients with advanced, progressive, nonsyndromic, nonpancreatic NETs who received everolimus (10 mg/day) monotherapy (Pavel et al. 2012). In this study, everolimus was associated with a high proportion of stable disease (55%), the best response, along with a favorable PFS (median: 185 days; 95% CI: 158-255). Efficacy analysis by tumor origin reveals stable disease in 63.2% of patients with primary tumor origin in the lung, thymus, bronchus, or mediastinum *vs* 42.9% of patients with primary tumor origin other than the lung, bronchus or mediastinum.

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[redacted]

# 2 Rationale

## 2.1 Study rationale and purpose

Rapamycin analogs have significant antiproliferative action in a variety of tumors, including pNETs. Sensitivity to rapamycin is reduced by a negative feedback loop via Akt inhibition of mTOR that decrease S6K and abolish this inhibitory feedback loop to IRS-1, resulting in increased Akt phosphorylation (O'Reilly et al. 2006). SSAs can inhibit the PI3K pathway by inhibiting p85 tyrosine phosphorylation and decreasing Akt phosphorylation, sensitize cells to mTOR-inhibition and increase the antiproliferative effects of rapamycin (Cerovac et al. 2010, Grozinsky-Glasberg et al 2008). This hypothesis has been verified in a rat xenograft model using the human prostate tumor model (DU-145). Here, single injections of pasireotide LAR resulted in significant dose-dependent reduction of tumors (Schmid et al. 2010) ). Treatment with everolimus resulted in a dose-dependent increase of pAKT in tumor tissue. This increase in pAKT was strongly reduced when everolimus and pasireotide LAR were co-administered, both *in vitro* and *in vivo* (Schmid et al. 2010), (Javle, personal communication). In the rat, pasireotide inhibits IGF-1 plasma levels much more effectively than octreotide at comparable concentrations and has a longer-lasting inhibitory effect. In contrast to octreotide, pasireotide shows no signs of escape over time up to 126 days. The superior IGF-1 lowering property of pasireotide was also observed in Beagle dogs; pasireotide is at least 3 times more potent than octreotide in reducing IGF-1 levels in this species. In Rhesus monkeys, 3 consecutive injections of pasireotide markedly decreased IGF-1 plasma levels from 24 hours onwards while octreotide was only marginally active. In Cynomolgus monkeys, chronic infusion of pasireotide leads to a dose-dependent decrease in IGF-1 levels. [Pasireotide s.c. and Pasireotide LAR Investigator's Brochure] As pasireotide inhibits IGF-1 release more potently than octreotide (Weckbecker et al. 2002), the above data suggest that everolimus and pasireotide have a role in inhibiting cell growth and tumor proliferation by interrupting the IGF-1/PI3K/mTOR signaling cascade, and that everolimus in combination with pasireotide may arrest growth and tumor proliferation to a greater extent than either agent alone and than the combination of everolimus and octreotide.

Somatostatin analogs are the current gold standard medical therapy for the treatment of the disease-related symptoms of functioning NETs (also known as carcinoid syndrome) and functioning pNETs (Oberg et al. 2009). These peptides are effective in reducing symptoms of carcinoid syndrome, specifically diarrhea and flushing, where SSAs provide symptomatic improvement in approximately 58% to 76% of patients with carcinoid syndrome (Oberg et al. 2004). Octreotide (Sandostatin®) and lanreotide (Somatuline®) are the only compounds approved for clinical use that exert their activity primarily via binding to receptor SSTR2 (Schmid and Schoeffter 2004). Although many patients initially respond to treatment with these agents, adequate symptom control can no longer be achieved in approximately 50% of them as early as 12 to 18 months after initiation of therapy. There has been accumulating evidence that octreotide does not only control symptoms in patients with functioning NETs,

[redacted]

but also exerts antiproliferative effects (Appetecchia and Baldelli 2010). This antiproliferative effect of octreotide has been proven in the PROMID trial, a randomized, double-blind, placebo-controlled, multicenter trial in patients with well differentiated inoperable or metastatic midgut NETs. This study reported a significant delay in time to progression (TTP) in patients treated with Sandostatin® LAR 30 mg compared to placebo (Rinke et al. 2009). There is evidence that many tumor cells become resistant to these agents by either downregulation of SSTR2 or over expression of other SSTRs (Cescato et al. 2006, Tulipano et al. 2004). If this is true, then pasireotide may have a beneficial effect in patients who have become resistant to these agents via its enhanced binding to other receptor subtypes.

RADIANT-1 study [CRAD001C2239] suggested that the combination of everolimus with octreotide could further improve PFS in patients with NETs (Yao et al. 2010). This has been tested in a large multinational randomized, double-blind, placebo-controlled, phase III trial comparing octreotide plus placebo with octreotide plus everolimus in patients with functioning NETs: the RADIANT-2 trial [CRAD001C2325]. Although the study narrowly failed to meet its primary PFS endpoint, results provide evidence for the clinical benefit of everolimus, in combination with octreotide LAR, in this patient population (as per the adjudicated central radiology review). A 23% reduction in the hazard rate of progression in favor of the combination arm was observed. 47.2% of patients receiving the combination treatment were estimated to be progression free at 18 months compared with 37.4% in the monotherapy group, indicating that a larger proportion of patients derived longer benefit in the combination with octreotide [CRAD001C2325 CSR], thus lending further evidence of the benefit of the combination of everolimus and a SSA. In addition, an exploratory subanalysis from the RADIANT-2 in a cohort of patients with low-to-intermediate grade advanced lung-NETs (n=44) (Fazio et al. 2013), the addition of everolimus to octreotide LAR improved median PFS by 2.4-fold compared with placebo + octreotide LAR (13.63 months *vs* 5.59 months; relative risk for progression: HR, 0.72; 95% CI, 0.31–1.68; P=0.228). Such evidence supports the continued evaluation of everolimus treatment regimens in this patient population.

A Phase III study [CSOM230C2303] comparing 60 mg of pasireotide LAR *vs.* 40 mg of octreotide LAR in patients with metastatic carcinoid tumors was terminated early as futility was demonstrated based on the proportion of patients achieving symptom response at Month 6. The overall proportion of patients who achieved symptom response at Month 6 was 9/43 patients (20.9%) in the pasireotide group and 12/45 patients (26.7%) in the octreotide group. The odds ratio of achieving symptom response at Month 6 among patients receiving pasireotide vs. octreotide, was 0.731 with 95% confidence interval (0.271, 1.974).The proportion of patients who achieved stable disease at Month 6 was higher in the pasireotide group (60.8% vs. 42.3%) while overall response rate (CR+PR) at Month 6 was comparable between the treatment groups (2.0% in the pasireotide group vs. 3.8% in the octreotide group). Pasireotide LAR significantly extended the median time without tumor growth by five months and reduced the risk of cancer progression by 54% compared to octreotide LAR. The median investigator-assessed PFS was 11.8 months in the pasireotide LAR arm and 6.8 months in the octreotide LAR arm, which was statistically significant (HR=0.46; P=0.045) [CSOM230C2303].

Thus, the rationale for this study is based on both preclinical and clinical considerations:

[redacted]

- combined inhibition of IGF-1-, PI3K- and mTOR-pathways by pasireotide and everolimus may control tumor growth more effectively than either compound alone;
- combination of everolimus with sandostatin LAR seems to improve progression-free survival in NET patients. Thus, the combination of everolimus with pasireotide LAR might result in even better tumor control.

The purpose of this study is to assess efficacy and safety of pasireotide LAR and everolimus alone or in combination.

## 2.2 Rationale for the study design

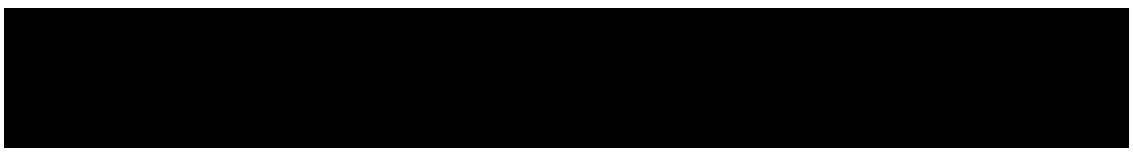
This is a 3-arm, open-label trial evaluating the efficacy and safety of pasireotide LAR or everolimus alone or in combination in patients with a well differentiated neuroendocrine carcinoma of the lung or thymus.

## 2.3 Rationale for dose and regimen selection

The proposed dose of pasireotide LAR is 60 mg once every 28 days (q28d). As of 31 July 2012, following monthly (q28d) injections of 20 mg, 40 mg or 60 mg pasireotide LAR in carcinoid patients [CSOM230C2110], results showed approximately linear dose-exposure proportionality and a steady state achieved following three injections. The release patterns of pasireotide from the first injection of 40 and 60 mg LAR in acromegaly patients and carcinoid patients were similar to those from a single dose of 40 and 60 mg LAR in healthy volunteers. Thus, pasireotide LAR at 60 mg was chosen as standard dose for further development in patients with neuroendocrine tumors. In an ongoing study [CSOM230C2110], pasireotide LAR 60 mg q28d was shown to be safe in NET patients.

The proposed everolimus dosage regimen is 10 mg/day in both monotherapy and combination therapy settings. This is the registered dose for everolimus (Afinitor®) as antiproliferative agent. This regimen is based both on Novartis Phase I/II/III studies and on results from an investigator-sponsored study in NET. Pharmacodynamic modeling indicates that downstream effectors of mTOR are completely suppressed by everolimus at the 10 mg/day dose. In an investigator-sponsored study of everolimus in combination with octreotide in NETs, toxicity observed with everolimus 10 mg/day was similar to that observed for everolimus 5 mg/day (Yao et al. 2007, Yao et al. 2008b). Combination of everolimus 10 mg/day with octreotide LAR 30 mg q28d in another phase II study in patients with pNET [CRAD001C2239] was safe and effective (Yao et al. 2010). Therefore, a dose of everolimus 10 mg/day will be evaluated in this study.

In a phase I dose-escalation study to determine the safety of pasireotide LAR and everolimus [CSOM230F2102], the dose level of 10 mg everolimus and 60 mg pasireotide LAR was declared to be safe (Chan et al. 2010). Preliminary data from this study were presented at ASCO GI 2010. Patients were treated with pasireotide at each dose level, beginning with pasireotide s.c. for 4 weeks in combination with daily everolimus, followed by monthly pasireotide LAR injections in combination with daily everolimus. To achieve steady state, pasireotide s.c. was continued for 2 weeks following the first injection of pasireotide LAR. The first dose level of pasireotide LAR 40 mg and everolimus 5 mg recruited 3 patients without reaching dose-limiting toxicity (DLT). One patient developed grade 3 hyperglycemia



and was started on insulin therapy. The second dose level of pasireotide LAR 40 mg and everolimus 10 mg recruited three patients. One patient developed grade 3 hyperglycemia and was started on insulin therapy. The third dose level of pasireotide LAR 60 mg and everolimus 10 mg was expanded to recruit six patients. One patient developed grade 3 rash and grade 4 hyperglycemia with need for insulin therapy. This was declared maximum tolerated dose (MTD), and it was planned to expand this cohort to 12 patients. All patients in this study showed disease stabilization ([redacted], personal communication). Therefore, a dose of everolimus 10 mg/day in combination with pasireotide LAR 60 mg q28d will be used in this trial.

## 2.4 Rationale for choice of combination drugs

Inhibition of mTOR by everolimus induces growth inhibition, cell cycle arrest and decreased signaling by mTOR and ERK1/2 in the tested cell lines. Everolimus may have a role in inhibiting cell growth, and tumor proliferation by interrupting the IGF-1/PI3K/mTOR signaling cascade. Moreover, everolimus inhibits angiogenesis also in an indirect way, via potent inhibition of tumor cell HIF-1 activity and VEGF production and VEGF-induced proliferation of endothelial cells, leading to reduced tumor vascularity. These observations suggest the hypothesis that everolimus may arrest growth and tumor proliferation activity through the dual inhibition of mTOR and an anti-angiogenic effect.

Pasireotide LAR inhibits IGF-1 and the GH/IGF-1 axis more efficiently than octreotide.

Everolimus is a strong inhibitor of mTOR. Therefore, it is reasonable to expect that pasireotide LAR in combination with everolimus will be more effective in inhibiting IGF-1 and mTOR, thus having additional clinical benefits in NET patients than either agent alone.

## 2.5 Rationale for choice of comparators drugs

Not applicable.

# 3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

**Table 3-1 Objectives and related endpoints**

| Objective | Endpoint | Analysis |
|---|---|---|
| **Primary** | | Refer to Section 10.4 |
| To evaluate the efficacy of pasireotide LAR and everolimus alone or in combination in progressive patients with a well differentiated neuroendocrine tumor of the lung or thymus | Primary endpoint is defined as the proportion of patients who are progression free (i.e. "*disease control rate*"*) at 9 months, according to RECIST V. 1.1<br>*"*Disease control rate*" is defined as the proportion of patients showing a best overall response of complete (CR) or partial (PR) response or stable disease (SD), according to RECIST V. 1.1. | |
| **Secondary** | | Refer to Section 10.5.1 |
| To assess overall progression-free survival (PFS) throughout the study in patients with a well differentiated neuroendocrine tumor of the lung or thymus. | *"Progression-free survival (PFS)"* is defined as the time from first study drug administration to objective tumor progression or death from any cause, according to RECIST V. 1.1 | Refer to Section 10.5.2 and Section 10.5.3 |
| To assess the disease control rate of pasireotide LAR and everolimus alone or in combination, at 12 months, in patients with a well differentiated neuroendocrine tumor of the lung or thymus. | *"Disease control rate"* at 12 months, according to RECIST V. 1.1. | |
| To assess the time to response, duration of response , objective response rate and best overall response of pasireotide LAR and everolimus alone or in combination during 12 months of treatment in patients with a well differentiated neuroendocrine tumor of the lunf or thymus. | The endpoint "*time to response"* is defined as the time from start of treatment to the first objective tumor response (PR or CR) observed, according to RECIST V. 1.1.<br>The endpoint *"duration of response"* is defined as the time from onset of the first objective tumor response (CR/PR) to objective tumor progression or death from any cause.<br><br>The endpoint *"objective response rate"* is defined as the proportion of patients showing a best overall response of CR or PR at 9 and 12 months, according to RECIST V. 1.1. criteria.<br>The endpoint *"best overall response"* is defined as the the best response recorded from the start of the treatment until disease progression/recurrence, taking as reference for PD the smallest measurements recorded since the treatment started. | |
| To assess the biochemical response rate (BRR), duration of biochemical response (DBR) and biochemical progression-free survival (BPFS) of pasireotide LAR and everolimus alone or in combination in patients with a well differentiated neuroendocrine tumor of the lung or thymus | The endpoint "*biochemical response rate* (BRR)" is the percentage of patients showing normalization or a decrease of ≥ 30% of serum CgA compared to baseline.<br>The endpoint *"duration of biochemical response (DBR)"* is defined as | |

[redacted]

| Objective | Endpoint | Analysis |
|---|---|---|
| | the time from the first documentation of biochemical response to the first documentation of biochemical progression or to death due to any cause, whichever occurs first.<br>Biochemical progression is defined as an increase of serum CgA levels ≥25% versus baseline.<br>The *endpoint "biochemical progression-free survival (BPFS)*" is defined as the time from the first study drug administration to the first documentation of biochemical progression or to death due to any cause, whichever occurs first.<br>Additionally, the biochemical response on the basis of urine 5-hydroxyindole acetic acid (5HIAA) will be assessed. | |
| To assess the safety and tolerability of pasireotide LAR and everolimus alone or in combination as measured by rate and severity of adverse events in patients with a well differentiated neuroendocrine tumor of the lung or thymus. | Safety will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Incidence of adverse events (AEs), serious adverse events (SAEs), changes from baseline in vital signs, ECG tracings and laboratory results (hematology, blood chemistry) will be reported. | |

[redacted]

[redacted]

## 3.1 Primary objective

To evaluate the efficacy of pasireotide LAR and everolimus alone or in combination in progressive patients with a well differentiated neuroendocrine tumor of the lung or thymus. The primary endpoint is defined as the proportion of patients who are progression free (i.e. disease control rate) at 9 months, according to RECIST V. 1.1.

Disease control rate is defined as the proportion of patients showing a best overall response of complete (CR) or partial (PR) response or stable disease (SD) according to RECIST V. 1.1

## 3.2 Secondary objectives

- To assess overall progression-free survival (PFS) throughout the study in patients with a well differentiated neuroendocrine tumor of the lung or thymus.
  The endpoint **"progression-free survival (PFS)"** is defined as the time from first study drug administration to objective tumor progression or death from any cause, according to RECIST V. 1.1.
- To assess the disease control rate of pasireotide LAR and everolimus alone or in combination, at 12 months, in patients with a well differentiated neuroendocrine tumor of the lung or thymus.
- To assess the time to response, duration of response, objective response rate and best overall response of pasireotide LAR and everolimus alone or in combination during 12 months of treatment in patients with a well differentiated neuroendocrine tumor of the lung or thymus.

  The endpoint **"time to response"** is defined as the time from start of treatment to the first objective tumor response (PR or CR) observed, according to RECIST V. 1.1.
  The endpoint **"duration of response"** is defined as the time from onset of the first objective tumor response (CR/PR) to objective tumor progression or death from any cause.
  The endpoint **"objective response rate"** is defined as the proportion of patients showing a best overall response of CR or a PR at 9 and 12 months, according to RECIST V. 1.1. criteria.

  The endpoint **"best overall response"** is defined as the best response the best response recorded from the start of the treatment until disease progression/recurrence, taking as reference for PD the smallest measurements recorded since the treatment started.
- To assess the biochemical response rate (BRR), duration of biochemical response (DBR) and biochemical progression-free survival (BPFS) of pasireotide LAR and everolimus alone or in combination in patients with well differentiated neuroendocrine tumor of the lung and thymus.

  The endpoint **"biochemical response rate (BRR)"** is the percentage of patients showing normalization or a decrease of ≥ 30% from baseline of serum CgA compared to baseline.

  The endpoint **"duration of biochemical response (DBR)"** is defined as the time from the first documentation of biochemical response to the first documentation of biochemical progression* or to death due to any cause, whichever occurs first.

  * Biochemical progression is defined as an increase of serum CgA levels ≥25% *versus* baseline.

[redacted]

The endpoint "**biochemical progression free survival (BPFS)"** is the time from the first study drug administration to the first documentation of biochemical progression or to death due to any cause, whichever occurs first.

Additionally, the biochemical response on the basis of urine 5-hydroxyindole acetic acid (5HIAA) will be assessed

- To assess the safety and tolerability of pasireotide LAR and everolimus alone or in combination as measured by rate and severity of adverse events in patients with a well differentiated neuroendocrine tumor of the lung or thymus. Safety will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Incidence of adverse events (AEs), serious adverse events (SAEs), changes from baseline in vital signs, ECG tracings and laboratory results (hematology, blood chemistry) will be reported.

[redacted]

# 4 Study design

## 4.1 Description of study design

This is a prospective, multicenter, randomized, open-label, 3-arm, phase II study with a single-stage design in each arm to evaluate the efficacy and safety of pasireotide LAR and everolimus alone or in combination in the treatment of patients with a well differentiated neuroendocrine carcinoma of the lung or thymus.

The number of patients enrolled is targeted to be 120 with 40 patients randomized to each arm as follows:

- Arm 1: treatment with pasireotide LAR (SOM230) (60 mg/month i.m.),
- Arm 2: treatment with everolimus (RAD001) (10 mg/day p.o.), and
- Arm 3: treatment with pasireotide LAR (60 mg/month i.m.) and everolimus (10 mg/day p.o.).

### 4.1.1 Screening/Baseline phase

At screening visit (Visit 1) the investigator or his/her designee will assign a unique number to patients being considered for the study. The patient must provide a signed informed consent form (ICF) prior to any study related procedure. This study will use an Interactive voice response system (IVRS) for randomization to one of the three treatment arms. Once the

[redacted]

patient provides a signed ICF and eligibility is confirmed (all inclusion/exclusion criteria have been verified), the investigator and/or his designee can register the patient using the IVRS. A screening period of 28 days is allowed to assess eligibility.

Baseline tumor measurements will be based on screening triphasic CT/MRI tumor assessment, according to RECIST Version 1.1 (assessment completed within 4 weeks prior to randomization can be used for baseline measurement). Non-tumor related assessments are also to be performed at screening.

### 4.1.2 Treatment phase

Upon completion of all screening tests and confirmation of eligibility, patients will be randomly assigned on a 1:1:1 basis to receive treatment with either pasireotide LAR or everolimus alone or a combined treatment with pasireotide LAR and everolimus.

Patients will receive treatment with study drug(s) for a period of 12 months or until radiologically documented disease progression, start of new cancer therapy, intolerable toxicity, withdrawal of consent or discontinuation due to any other reason.

Patients will be considered to have completed the core study after the 12-month evaluation has been performed.

During the study treatment, radiological and biochemical response assessments will be performed every 3 months.

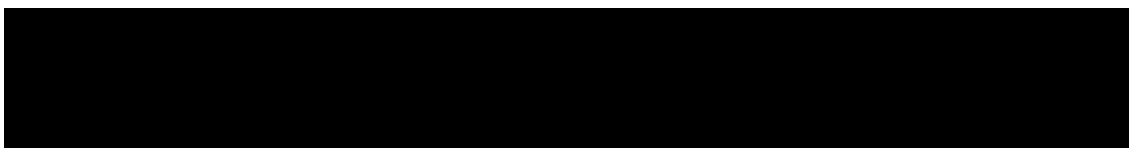
Patients assigned to the pasireotide LAR treatment arm will be given a 60 mg i. m. depot injection every 28 days for 12 months. A dose decrease is permitted if tolerability issues arise (see Section 6.3.1.1).

Patients assigned to the everolimus treatment will receive a dose of 10 mg/day p.o. for 12 months. A dose decrease is allowed if tolerability issues arise (see Section 6.3.1.2).

Patients assigned to receive a combined treatment with pasireotide LAR and everolimus will be treated with both regimens and dose modifications are applicable as in the monotherapy arms. It is the investigator's decision to decrease one or both drugs depending on the profile of the adverse effects. If, however, condition for dose reduction in this arm is not clear (e.g. tolerability issue is not clearly attributable to one of the medications), the Novartis clinical team should be contacted.

### 4.1.3 Extension phase

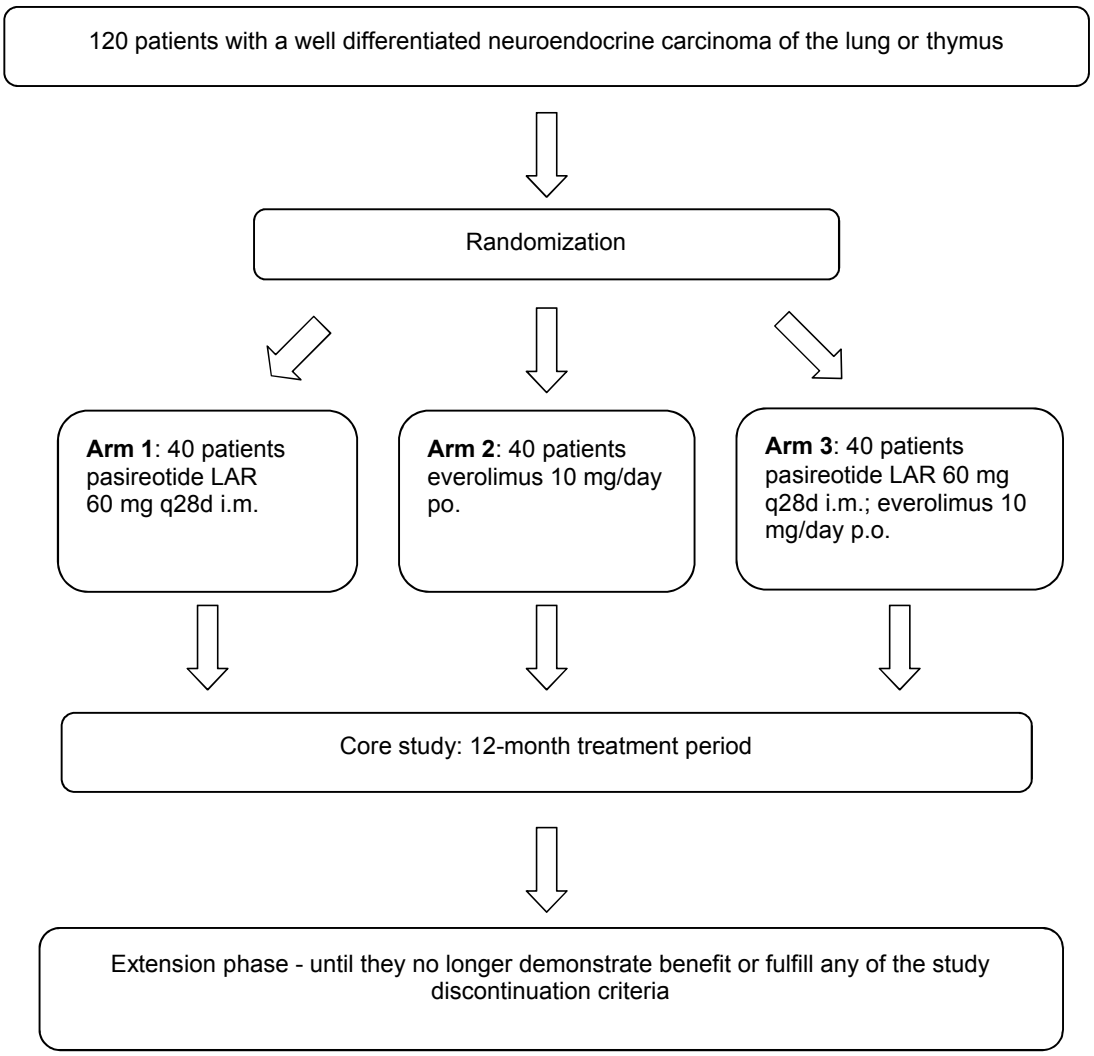
Patients who are receiving clinical benefit from the treatment with the combination or the monotherapy with pasireotide LAR or everolimus and who are not experiencing unacceptable toxicity are permitted to continue treatment after the 12-month treatment period until they no longer demonstrate benefit or fulfill any of the study discontinuation criteria Disease control rate as well as progression-free survival (PFS) according to RECIST V. 1.1 will be evaluated during the extension phase All assessments which are required in the extension phase are listed in Table 7-2. Patients will have the option to receive therapy as long as they continue to demonstrate benefit and do not fulfill any of the study discontinuation criteria (see Section 7.1.4.1 criteria for premature patient withdrawal) or as soon as the Clinical Trial ceases to be in the interests of the health of the Clinical Trial Subjects, based on the Data Monitoring



Committee (DMC) recommendations (see Section 8.6), or until the pasireotide and/or everolimus development programs is discontinued, whichever comes first (see reference to Section 4.4 early study termination).

All patients will have a safety follow-up visit at the end of the extension phase scheduled 56 days after the last dose of the study treatment to follow up for AEs and SAEs that may have occurred after discontinuation from the study treatment.

**Figure 4-1 Study design**



## 4.2 Timing of interim analyses and design adaptations

Not applicable.

## 4.3 Definition of end of the study

The end of the study is defined as when all patients have discontinued the study.

## 4.4 Early study termination

Patients will have the option to receive therapy as long as they continue to demonstrate benefit and do not fulfill any of the study discontinuation criteria (see Section 7.1.4.1: Criteria for premature patient withdrawal) or until the Clinical Trial ceases to be in the interests of the health of the Clinical Trial Subjects, based on DMC recommendations (see Section 8.6), or until the pasireotide and/or everolimus development programs are discontinued (whichever comes first). Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.4 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

# 5 Population

## 5.1 Patient population

The target population is comprised of adult patients with an advanced (unresectable or metastatic) well differentiated neuroendocrine carcinoma (typical and atypical) of the lung or thymus. It is expected that 120 patients (40 in each arm) will be enrolled into this study.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrollment in the study.

## 5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Histological confirmed advanced (unresectable or metastatic) well differentiated typical and atypical carcinoid tumors of lung or thymus. (Cytology by endobronchial ultrasound-guided fine needle aspiration (EBUS) alone is not enough. Histopathology is required).
2. Patients of all treatment lines, including treatment naïve patients, can be enrolled.
3. At least one measurable lesion of disease on triphasic computed tomography (CT) scan or Magnetic Resonance Imaging (MRI) as defined by RECIST V. 1.1 criteria.
4. WHO Performance Status of 0, 1 or 2.
5. Radiological documentation of disease progression within 12 months prior to randomization. The triphasic CT or MRI confirming the progression according to RECIST V. 1.1 should not be older than 4 weeks to be used as baseline CT or MRI. CT scans and MRIs older than 4 weeks have to be repeated.

[redacted]

6. Patients must have adequate liver, renal and bone marrow function:
   - Adequate bone marrow function:
     - ANC $\geq 1.5 \times 10^9$/L,
     - Platelets $\geq 100 \times 10^9$/L,
     - Hemoglobin > 9 g/dL.
   - Adequate liver function:
     - Total serum bilirubin $\leq 1.5 \times$ ULN,
     - INR < 1.3,
     - ALT and AST $\leq 3 \times$ ULN
   - Adequate renal function: serum creatinine $\leq 1.5 \times$ ULN.
7. Adult patients (male or female) >18 years old.
8. Patients must give a written informed consent prior to any trial-related procedures.

## 5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Poorly differentiated neuroendocrine carcinoma.
2. Non-neuroendocrine thymoma.
3. Prior treatment with any long-acting somatostatin analog within one month prior to randomization. Treatment with s.c. form of somatostatin analogs as "rescue" medication is allowed only until 48 hours prior to starting study treatment (continuation of "rescue" medication during the study is not allowed).
4. Patients with severe functional disease who require symptomatic treatment with somatostatin analogs can not be included in the protocol.
5. Prior therapy with mTOR inhibitors (e.g. sirolimus, temsirolimus, everolimus).
6. Prior therapy with radioligand therapy (peptide receptor radionuclide therapy, PRRT) within 6 months prior to starting study treatment or not recovered from the adverse effects of such therapy.
7. Prior cytotoxic chemotherapy or immunotherapy within 4 weeks or 5 half lives, whichever is longer, prior to starting study treatment or not recovered from the adverse effects of such therapy.
8. Patients with hepatic artery embolization, cryoablation or radiofrequency ablation of hepatic metastasis within the last 3 months prior to starting study treatment or not recovered from the adverse effects of such therapy.
9. Participation in a clinical trial to test an investigational drug within 4 weeks or 5 half lives whichever is longer prior to starting study treatment or not recovered from the adverse effects of such therapy.
10. Sign of recurrence of prior or concomitant malignancies (within the last 3 years or requiring active treatment) other than NET with the exception of previous basal cell skin cancer, previous cervical carcinoma in situ.
11. Mixed tumours are excluded.

[redacted]

12. Known intolerance or hypersensitivity to pasireotide, octreotide, or other somatostatin analogs and everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus).
13. Patients who have undergone major surgery/surgical therapy for any cause within 1 month or surgical therapy of loco-regional metastases within the last 3 months before recording baseline symptoms. Patients should have recovered from the treatment and have a good clinical condition before entering this study.
14. Patients who have received radiotherapy within the last 4 weeks prior to starting study treatment or not recovered from the adverse effects of such therapy.
15. Any of the following severe and/or uncontrolled medical conditions:
    - Severely impaired lung function (spirometry and DLCO ≤50% of normal and $O_2$ saturation ≤88% at rest on room air)
    - Active bleeding diathesis
    - Cushing's syndrome requiring medical treatment within 3 months.
16. Hepatic-related exclusion criteria
    - History of liver disease (such as cirrhosis) or chronic active hepatitis B and C.
    - Presence of Hepatitis B surface antigen (HbsAg) and/or of Hepatitis B Virus – Deoxyribonucleic acid (HBV-DNA)
    - Presence of Hepatitis C virus-Ribonucleic acid-Polimerase Chain Reaction (HCV-RNA-PCR)
    - History of or current alcohol misuse/abuse within the past 12 months
    - Known gallbladder or bile duct disease, acute or chronic pancreatitis.
17. Uncontrolled diabetes mellitus as defined by HbA1c ≥8% despite adequate therapy.
18. Patients unwilling or unable to comply with the requisites of the protocol.
19. Patients with symptomatic cholelithiasis.
20. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, advanced heart block or a history of acute myocardial infarction within the 24 weeks preceding randomization.
21. QT-related exclusion criteria:
    - Patients with a baseline QTcF >470 msec
    - History of syncope or family history of idiopathic sudden death
    - Long QT syndrome
    - Sustained or clinically significant cardiac arrhythmias
    - Risk factors for Torsades de Pointes such as hypokalemia, hypocalcemia, hypomagnesemia (unless corrected prior to and during study), cardiac failure, clinically significant/symptomatic bradycardia, or high-grade AV block
    - Concomitant medications known to prolong the QT interval. A wash-out of 5 half lives from previous treatment with drugs known to induce QT prolongation is needed prior to starting study treatmentConcomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes mellitus or Parkinson's disease), HIV, liver cirrhosis, uncontrolled hypothyroidism or cardiac failure.

22. Patients with the presence of active or suspected acute or chronic uncontrolled infection or with a history of immunocompromise, including a positive HIV test result (ELISA and Western blot).
23. Patients who have any current or prior medical condition that may interfere with the conduct of the study or the evaluation of its results in the opinion of the Investigator or the Sponsor's Medical Monitor.
24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
25. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 8 weeks after stopping of study medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization: have had surgical bilateral oophorectomy with or without hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization with appropriate post-vasectomy documentation of the absence of spermatozoa in the ejaculate (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
    - Combination of any two of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

    In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
26. Sexually active males must use a condom during intercourse while taking the treatment and for 2 months after the last dose of study treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Female partners of male patients must be also advised to use one of the following contraception methods:
    - Use of oral, injected or implanted hormonal methods of contraception or other approved hormonal methods of contraception
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    - Total abstinence or patient sterilization (male or female).

[redacted]

# 6 Treatment

## 6.1 Investigational treatment, other study treatment, supportive treatment

The investigational study drugs used in the course of this trial are pasireotide (SOM230) LAR and everolimus (RAD001). For the duration of the trial, pasireotide LAR and everolimus will be supplied by Novartis, or by local commercial stock, once available.

Therefore, if at any time during the study life pasireotide LAR and/or everolimus become commercially available in the Countries participating to the study the local commercial stock should be used.

**Definition of terms:**

- Study drug = pasireotide (SOM230) LAR or everolimus (RAD001)
- Study treatment = pasireotide (SOM230) LAR or everolimus (RAD001) alone or a combination of pasireotide LAR and everolimus.

### 6.1.1 Dosing regimen

Patients will be randomized centrally on a 1:1:1 basis to receive treatment with either pasireotide LAR (arm 1) or everolimus (arm 2) or a combination of either regimen (arm 3).

A treatment cycle is defined as 28 days.

#### 6.1.1.1 Pasireotide LAR administration

Pasireotide LAR 60 mg will be administered as an i.m. depot injection once every 28 days (+/- 3 days) starting at Day 1 (visit 2).

#### 6.1.1.2 Everolimus administration

Everolimus will be dispensed by the study center personnel on an outpatient basis. Patients will be provided with an adequate supply of everolimus for self-administration at home.

Everolimus will be dosed starting on Day 1 (Visit 2). Patients will be instructed to take one 10 mg tablet or, alternatively two 5 mg tablets taken together (QD), depending on the available strength of the commercial stock used. Everolimus tablets have to be taken orally with a glass of water, once daily at the same time each day either consistently with food or consistently without food. Any dietary habits around the time of everolimus intake should be as consistent as possible throughout the study. The tablet/tablets should be swallowed as a whole and not be chewed or crushed. In cases where the tablet/tablets cannot be swallowed, it/they should be disintegrated in water just prior being taken. Approximately 30 mL of water should be put into a glass. The tablet/tablets should then be added and the contents stirred gently (for a maximum of 7 minutes) until the tablet/tablets are disintegrated. The contents should then be drunk. Afterwards, the glass should be rinsed with an additional 30 mL of liquid and drunk.

If vomiting occurs, no attempt should be made to replace the vomited dose unless two everolimus tablets (or one 10 mg tablet) are clearly visible. If two everolimus tablets (or one 10 mg tablet) are clearly visible, then the patient should replace the everolimus dose. Patients

[redacted]

should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

If the patient misses a dose at the scheduled time, the administration of the study drug can:

- occurr within 8 hours after the normal time of administration, and the new time of administration can be considered as a reference for the next administration (eg. if the normal time of administration is 8 am, the 8 am missing dose could be administered by 4 pm of the same day)
- or be skipped until the next day.

#### 6.1.1.3 Combination of pasireotide LAR and everolimus

Patients randomized to the arm 3 will be given a combination therapy based on pasireotide LAR 60 mg i.m. every 28 days and everolimus 10 mg p.o. daily.

### 6.1.2 Ancillary treatments

Not applicable.

### 6.1.3 Rescue medication

See Section 6.1.4.

### 6.1.4 Handling of Specific Toxicities

#### 6.1.4.1 Management of Infections

Everolimus has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis, candidiasis or *pneumocystis jirovecii* pneumonia (PJP) have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to sepsis, respiratory failure) and occasionally have had a fatal outcome. Physicians and patients must be aware of the increased risk of infections with everolimus, be vigilant for symptoms and signs of infection and, in case a diagnosis of infection is made, initiate appropriate treatment promptly and consider interruption or discontinuation of everolimus.

Treat pre-existing fungal infections prior to starting treatment with everolimus.

If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

Cases of PJP, some with fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

#### 6.1.4.2 Management of skin toxicity

Skin toxicity has been reported for patients receiving everolimus treatment.

[redacted]

For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course) or pimecrolimus.

#### 6.1.4.3 Management of stomatitis / oral mucositis / mouth ulcers

Stomatitis, oral mucositis and mouth ulcers have been reported for patients receiving everolimus treatment.

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa -e.g. gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis- must be monitored more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to everolimus should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. The paradigm for treatment of stomatitis/oral mucositis/mouth ulcers, below reported, should be followed:

1. For mild toxicity (grade 1: minimal symtoms, normal diet), no dose adjustments are reguired. Use conservative measures such as **non-alcoholic mouth wash or salt water (0.9%) mouth wash** several times a day until resolution.
2. For moderate toxicity (grade 2: patients have pain but are able to maintain adequate oral alimentation), a temporary dose interruption until recovery to grade ≤1 is recommended. Everolimus can be reinitiated at the same dose. If stomatitis recurs at grade 2, it is recommended to interrupt treatment untile recovery to grade ≤1, and reinitiate treatment at a lower dose. The suggested treatments are **topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol)** with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. For severe toxicity (grade 3: patients are symptomatic and cannot maintain adequate oral alimentation), a temporary dose interruption until recovery to grade ≤1 is recommended. Everolimus can be reinitiated at a lower dose. Manage with **topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol)** with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
4. For more severe toxicity (grade 4: symptoms associated with life-threating consequences), discontinue everolimus and treat with appropriate medical therapy.
5. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
6. Antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.)

[redacted]

should be avoided in all patients due to their strong inhibition of everolimus metabolism, therefore leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

#### 6.1.4.4 Management of hyperlipidemia

Hyperlipidemia has been reported for patients receiving everolimus treatment.

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>2.5 × upper normal limit) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g. atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

#### 6.1.4.5 Management of hyperglycemia

Hyperglycemia has been frequently reported in patients receiving everolimus and pasireotide therapy.

Clinical studies of pasireotide in healthy volunteers and in patients with Cushing's disease, acromegaly or NET with carcinoid syndrome have reported transient, asymptomatic increases in fasting and postprandial glucose levels. Although hyperglycemia was observed in healthy volunteers and across all disease populations receiving pasireotide, this AE was most prominent in patients with Cushing's disease, a setting in which glucose metabolism is inherently dysregulated. The majority of hyperglycemia events were grade 1 and 2. Some patients developed grade 3 or 4 events, and SAEs related to hyperglycemia have been reported including diabetic ketoacidosis (DKA). Hyperglycemia appears to be reversible upon pasireotide discontinuation.

In a phase III study [CSOM230B2305] assessing the safety and efficacy of pasireotide LAR s.c. over 6 months in patients with *de novo* or persistent/recurrent Cushing's disease, two hyperglycemia-related emergencies occurred: one case of DKA, and one case of diabetic hyperglycemic coma. The former patient discontinued from the study and the latter continued treatment with study drug while taking insulin to treat hyperglycemia. Both events were reported after pasireotide LAR dose was increased from 40 to 60 mg. However, it is important to highlight that in the patient with the SAE of DKA, pasireotide LAR was initiated when her underlying diabetes was poorly controlled (HbA1c 8.7% prior to first dose of pasireotide LAR and after cross-over from octreotide) while receiving no anti-diabetic therapy which in part could have contributed to the exacerbation of hyperglycemia resulting in DKA and hospitalization.

[redacted]

Two clinical studies have been conducted ([CSOM230B2216] and [CSOM230B2124]) in healthy volunteers to further understand the mechanism of pasireotide-induced hyperglycemia and to evaluate the potential clinical utility of antidiabetic agents in the management of pasireotide-induced hyperglycemia. Data from [CSOM230B2216] study indicate that pasireotide decreases insulin secretion, particularly in the postprandial period, as well as the glucagon-like peptide-1 (GLP-1)/glucose-dependent insulinotropic polypeptide (GIP) secretion. Results from [CSOM230B2124] study suggest that the incretin-based therapies (GLP-1 analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors) may have the best potential to manage the hyperglycemia associated with pasireotide. Some patients in [CSOM230B2305] required insulin to treat their hyperglycemia. The mTOR pathway is related to the insulin signaling pathway, and it is likely that everolimus decreases insulin sensitivity whereas pasireotide-induced hyperglycemia is secondary to a decrease in insulin and incretin (such as GLP-1 and GIP) secretion. The combination of the two drugs (pasireotide LAR, which may alter insulin and glucagon secretion, and everolimus which may affect insulin sensitivity) may therefore result in a higher risk for hyperglycemia than each agent alone. Based on the currently available preliminary data regarding [CSOM230F2102] and [CSOM230I2201] studies, it is hypothesized that one possible reason for the high rate of grade 3 hyperglycemia could be due to suboptimal monitoring of blood glucose.

It is important that optimal glycaemic control is achieved before starting a patient on study treatment, and that glucose levels are monitored during the trial.

The principal investigator is to educate the patient on the signs and symptoms of hyperglycemia. The principal investigator is to evaluate the risks for hyperglycemia in all patients. It is recommended to follow established guidelines by expert international diabetes associations such as the American Diabetes Association (ADA 2011) and European Association for the Study of Diabetes (EASD) (Nathan 2006, Nathan 2008, ADA 2011).

#### 6.1.4.5.1 Monitoring of glucose levels

**For patients in the pasireotide LAR monotherapy arm and in the pasireotide LAR and everolimus combination arm**

All patients in the combination arm and in pasireotide LAR monotherapy arm must self-monitor glucose levels.

Patients with normal glucose metabolism at baseline should self-monitor their fasting blood glucose level once daily by fingerstick for the first 2 months, then twice a week for the next 2 months and once a week thereafter throughout the study.

Patients with a prior history or newly observed fasting hyperglycemia, impaired glucose tolerance or diabetes mellitus, or at risk of developing these conditions should self monitor their blood glucose by fingerstick twice daily (once fasting and once 2-hours post-prandial). The site should call the patient after approximately 10 days after day 1 and day 29 visits (i.e. for the first 2 cycles) and should ask for the blood glucose results.

All patients should contact the site (or medical care, if the site is unavailable) if the fasting blood glucose level is >130 mg/dL (7.2 mmol/L) on any two separate occasions and come for an additional visit as soon as possible to confirm the values and to ensure early intervention.

[redacted]

Any patient should contact the site (or medical care, if the site is unavailable) immediately if the fasting blood glucose value is ≥200 mg/dL (11.1 mmol/L) at any time. At this visit, fasting plasma glucose levels will be measured at local lab. Patients with confirmed fasting hyperglycemia should start self-monitoring of their blood glucose by fingerstick twice daily (once fasting and once 2-hours post-prandial), if not already done. They may be also be referred to a specialist for appropriate management of hyperglycemia. In order to ensure early intervention, if needed, glucose levels will be tested at the local lab at all visits.

All patients will keep a diary for appropriate detection and management of hyperglycemia throughout the trial and present the collected data to their physician/diabetes specialist for evaluation. The sponsor will provide the patient diaries but this data will not be collected by the sponsor.

**For patients in the everolimus monotherapy arm**

All patients in the everolimus monotherapy arm showing ≥ grade 3 hyperglycemia (>250mg/dL; >13.9 mmol/L) at any point visit throughout the study, should start monitoring their blood glucose by fingerstick twice daily (once fasting and once 2 hours post-prandial).

All patients should contact the site (or medical care, if the site is unavailable) if their fasting glucose value (during self monitoring) is >130 mg/dL (7.2 mmol/L) on any two separate occasions and come for an additional visit as soon as possible to confirm the values and to ensure early intervention. Any patient should contact the site (or medical care, if the site is unavailable) immediately if the fasting blood glucose value (during self monitoring) is ≥200 mg/dL (11.1 mmol/L) at any time. At this visit, fasting plasma glucose levels will be measured at local lab. Patients may be referred to a specialist for appropriate management of hyperglycemia.

These patients should be encouraged to keep a diary for their blood glucose throughout the trial and present the collected data to their physician/diabetes specialist for evaluation. The sponsor will provide the patient diaries but this data will not be collected by the sponsor.

In order to ensure early intervention, if needed, fasting glucose levels will be tested at the local laboratory at all visits, excluding visit 6 when glucose will not be assessed unless it is medically indicated.

**For all patients**

Any patient showing a fasting plasma glucose >130 mg/dL (7.2 mmol/L), or 2-hour post-prandial capillary glucose (PPG) ≥180 mg/dL (10 mmol/L) on two separate occasions, and/or HbA1c >7% should be evaluated by a diabetes specialist for appropriate treatment (Position statement ADA 2011). In addition, these patients should be given information regarding diabetes disease management. Initiation or adjustment of antidiabetic treatment should be considered as early as possible. In addition, these patients should begin monitoring their blood glucose by fingerstick twice daily (fasting and 2 hours post-prandial) if not already done.

Appropriate management for the hyperglycemia includes:

- The use of anti-diabetic agents for mild to moderate hyperglycemia such as incretin enhancers (e.g. GLP-1 analogues or DPP4 inhibitors or insulin secretagogues).

[redacted]

- Insulin should be used for moderate to severe hyperglycemia.
- Drugs like metformin may be used if the patient has history suggestive of insulin resistance or metabolic syndrome, who are taking everolimus and have/or have had fasting hyperglycemia. These agents may not be efficacious in patients with isolated post-prandial hyperglycemia as observed with pasireotide given its mechanism of action, but may be useful in patients with everolimus-induced hyperglycemia.

#### 6.1.4.5.2 Dose adjustments

**For patients on pasireotide LAR monotherapy**

For patients showing ≥ grade 3 hyperglycemia (>250 mg/dL; >13.9 mmol/L) at any point throughout the study, pasireotide LAR treatment should be interrupted.

- If hyperglycemia recovers to grade ≤ 1, pasireotide LAR can be reinitiated at the lowest dose level (20 mg). If hyperglycemia is well controlled, the dose of pasireotide LAR can be escalated in steps to the original dose with the appropriate monitoring of blood glucose levels. These patients should also begin monitoring their blood glucose by fingerstick twice daily (once fasting and once 2 hours post-prandial), if not already done;
- If grade 3 hyperglycemia (>250 mg/dL; >13.9 mmol/L) persists despite interruption of pasireotide LAR treatment (≥ 56 days from last injection) and despite optimal antidiabetic treatment, the patient should be discontinued from the study.

**For patients in the everolimus monotherapy arm**

In addition to optimizing antidiabetic therapy, in patients showing ≥ grade 3 hyperglycemia (>250 mg/dL; >13.9 mmol/L) at any point throughout the study, the dose of everolimus should be interrupted until recovery to grade ≤ 1. Then, everolimus should be reintroduced at one dose level lower. These patients should monitor their blood glucose by fingerstick twice daily (one fasting and one 2 hours post-prandial).

If grade 3 hyperglycemia (>250 mg/dL; >13.9 mmol/L) persists despite interruption of everolimus treatment (≥28 days from last dose) and in spite of optimal antidiabetic treatment, the patient should be discontinued from the study (Table 6-1).

**For patients in the pasireotide LAR and everolimus combination arm**

For patients showing ≥ grade 3 hyperglycemia (>250 mg/dL; >13.9 mmol/L) at any point throughout the study, pasireotide LAR treatment should be interrupted.

- If hyperglycemia recovers to grade ≤ 1, pasireotide LAR can be reinitiated at the lowest dose level (20 mg). If hyperglycemia is well controlled, the dose of pasireotide LAR can be escalated in steps to the original dose with the appropriate monitoring of blood glucose levels. These patients should also begin monitoring their blood glucose by fingerstick twice daily (once fasting and once 2 hours post-prandial), if not already done.
- If grade 3 hyperglycemia (>250 mg/dL; >13.9 mmol/L) persists despite interruption of pasireotide LAR treatment (≥ 56 days from last injection) and despite optimal antidiabetic treatment, the dose of everolimus should also be interrupted, i.e. this patient should be discontinued from the study (Table 6-1).

[redacted]

**Table 6-1 Dosing modification for hyperglycemia**

| CTCAE grade | Pasireotide LAR monotherapy arm | Everolimus monotherapy arm | Everolimus and pasireotide LAR combination arm |
|---|---|---|---|
| Grade ≤ 2 (≤250 mg/dL; ≤13.9 mmol/L) | No dose adjustment necessary.<br><br>Consider start or adjustment of antidiabetic therapy. | No dose adjustment necessary.<br><br>Consider start or adjustment of antidiabetic therapy. | No dose adjustment necessary.<br><br>Consider start or adjustment of antidiabetic therapy. |
| Grade ≥ 3 (>250 mg/dL; >13.9 mmol/L) | Interrupt pasireotide LAR until recovery to grade ≤ 1<br><br>Optimize antidiabetic therapy.<br>- If hyperglycemia recovers to grade ≤ 1, reinitiate pasireotide LAR at the lowest dose level (20 mg). If hyperglycemia is well controlled, the dose of pasireotide LAR can be escalated in steps to the original dose with the appropriate monitoring of blood glucose levels.<br><br>- If grade ≥3 hyperglycemia (>250 mg/dL; >13.9 mmol/L) persists despite interruption of pasireotide LAR treatment (≥56 days from last injection) and despite optimal antidiabetic treatment, the patient should be discontinued from the study | Interrupt everolimus until recoveryto grade ≤ 1<br><br>Optimize antidiabetic therapy.<br>- If hyperglycemia recovers to grade ≤ 1, reintroduce everolimus at one dose level lower.<br>- If grade 3 hyperglycemia (>250 mg/dL; >13.9 mmol/L) persists despite interruption of everolimus treatment (≥28 days from last dose) and in spite of optimal antidiabetic treatment, the patient should be discontinued from the study | Interrupt pasireotide LAR until recovery to grade ≤ 1<br><br>Optimize antidiabetic therapy.<br>- If hyperglycemia recovers to grade ≤ 1 reinitiate pasireotide LAR at the lowest dose level (20 mg). If hyperglycemia is well controlled, the dose of pasireotide LAR can be escalated in steps to the original dose with the appropriate monitoring of blood glucose levels.<br><br>- If grade ≥3 hyperglycemia (>250 mg/dL; >13.9 mmol/L) persists despite interruption of pasireotide LAR treatment (≥56 days from last injection) and despite optimal antidiabetic treatment, interrupt everolimus and discontinue the patient from the study. |

### 6.1.4.6 Management of diarrhea

Diarrhea has been reported for patients receiving everolimus and pasireotide treatment.

Appearance of diarrhea attributed to everolimus toxicity may be treated with loperamide. Other medications for diarrhea may be used as needed such as cholestyramine for the management of diarrhea due to short gut syndrome.

The investigator must report dose administered and frequency appropriately on the CRF.

### 6.1.4.7 Management of non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Both asymptomatic radiological changes (grade 1: radiological lung changes only) and symptomatic non-infectious pneumonitis (grade 2: not interfering with activities of daily living or grade 3: interfering with activities of daily living and oxygen indicated) have been reported in patients receiving everolimus therapy.

[redacted]

- Patients with non-symptomatic radiological changes suggestive of non-infectious pneumonitis and few or no symptoms can generally continue everolimus therapy without dose alteration.
- Clinically significant toxicity associated with the use of mTOR inhibitors is typically associated with pulmonary symptoms including dyspnea, nonproductive cough, fatigue, and fever. Patients with moderate symptoms may require interruption of therapy until symptoms improve, followed by re-introduction of everolimus at a lower dose (grade 2). The use of corticosteroids may be indicated. Patients with severe symptoms (grade $\geq$3) require permanent discontinuation of everolimus. Corticosteroids may speed recovery in this group.

Individuals participating in this trial will be assessed for any signs of interstitial lung disease (ILD) indicative of pneumonitis at baseline and routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. In addition, chest radiological imaging and pulmonary function tests (PFTs) will be conducted in the discretion of the investigator, if clinically indicated. If non-infectious pneumonitis develops during the study, the guidelines in Table 6-2 should be followed and consultation with a pulmonologist is recommended.

Overall, in light of evidence that the risk for non-infectious pneumonitis is related to everolimus, the drug interruption/discontinuation strategy will apply to everolimus only (see Table 6-2).

**Table 6-2 Guidelines for management of non-infectious pneumonitis**

| Worst Grade Pneumonitis | Required Investigations | Management of Pneumonitis | RAD001 Dose Adjustment |
|---|---|---|---|
| Grade 1 (asymptomatic, radiographic findings only) | CT scans with lung windows. Repeat at least every three cycles until return to normal limits. | No specific therapy is required. | Administer 100% of everolimus dose. |
| Grade 2 (symptomatic, not interfering with activities of daily living) | CT scan with lung windows. Consider pulmonary function testing including spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every three cycles until return to normal limits. Consider a bronchoscopy with biopsy and/or BAL. | Symptomatic only. Prescribe corticosteroids if symptoms are troublesome. | Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to grade < 1. Re-initiate everolimus at a lower dose. Discontinue treatment if failure to recover within 4 wks. |
| Grade 3 (symptomatic, interfering with activities of daily living; O2 indicated) | CT scan with lung windows and pulmonary function testing including spirometry, DLCO, and room air O2 saturation at rest.; Repeat at least every two cycles until return to normal limits. Bronchoscopy with biopsy and/or BAL is recommended. | Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated. | Interrupt treatment until symptoms resolve to grade ≤ 1. May restart treatment at a reduced dose (by one level), if evidence of clinical benefit. Discontinue treatment, if failure to recover within 4 wks. If toxicity recurs at grade 3, consider discontinuation. |

[redacted]

| Worst Grade Pneumonitis | Required Investigations | Management of Pneumonitis | RAD001 Dose Adjustment |
|---|---|---|---|
| Grade 4 (life-threatening, ventilatory support indicated) | CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every two cycles until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended if possible. | Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated. | Discontinue treatment. |

### 6.1.4.8 Management of hepatitis reactivation

#### 6.1.4.8.1 Monitoring for hepatitis B reactivation

Hepatitis B reactivation has been observed in patients receiving everolimus treatment.

Table 6-3 provides details of monitoring according to screening/baseline results of viral load and serologic markers testing.

**Table 6-3 Monitoring for positive baseline hepatitis B results**

| Test | Result | Result | Result | Result | Result |
|---|---|---|---|---|---|
| HBV-DNA | Positive | Positive or negative | Negative | Negative | Negative |
| HBsAg | Positive or negative | Positive | Negative | Negative | Negative |
| HBsAb | Positive or negative | Positive or negative | Positive and no prior HBV vaccination | Positive or negative | Negative or positive with prior HBV vaccination |
| HBcAb | Positive or negative | Positive or negative | Positive or negative | Positive | Negative |
| Recommendation | Patient does not qualify for the study. | | No prophylaxis.<br>Monitor HBV-DNA every 4 weeks (± 1 week)* | | No specific action |
| * The monitoring for hepatitis B reactivation has to be performed in all patients, irrespective of the treatment arm they have been assigned to (thus, not only in patients taking everolimus alone or in combination, but also in patients on pasireotide alone), taking into account the results arising from the four hepatitis B tests. However, in light of evidence that the risk for hepatitis B reactivation is related to everolimus, the drug interruption/discontinuation strategy (see Table 6-4) will apply to everolimus only. | | | | | |

For hepatitis B reactivation, definition and management guidelines see Table 6-4.

**Table 6-4 Guidelines for management of hepatitis B**

| HBV reactivation (with or without clinical signs and symptoms)* | Actions |
|---|---|
| For patients with baseline results:<br>Negative HBV-DNA and HBs-Ag<br>AND<br>Positive HBs-Ab (with no prior history of vaccination against HBV), OR positive HBc-Ab<br>----------<br>**Reactivation is defined as:** | Treat: Start first antiviral medication<br>AND<br>Interrupt everolimus administration until resolution:<br>≤baseline HBV-DNA levels<br>**If resolution occurs within <28 days,** the study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should |

[redacted]

| HBV reactivation (with or without clinical signs and symptoms)* | Actions |
|---|---|
| New appearance of measurable HBV-DNA | continue at least 4 weeks after last dose of study drug.<br>**If resolution occurs after ≥28 days,** patients should discontinue study treatment but continue antiviral therapy for at least 4 weeks after last dose of study drug. |

*All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in this case, they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which both DNA and ALT criteria were met (e.g. for a patient who was HBV-DNA positive on 01-JAN-10 and whose ALT reached ≥ 5 × ULN on 01-APR-10, the date of viral reactivation is 01-APR-10).

#### 6.1.4.8.2 Monitoring for hepatitis C

At screening, all patients will be tested for the presence of HCV Ribonucleic acid-Polimerase Chain Reaction (HCV-RNA-PCR). If a patient tests positive for the presence of HCV-RNA-PCR, he/she will be considered ineligible for the study according to Exclusion Criterion #16.

Patients known to have a history of HCV infection, despite a negative viral load test at baseline (including those that were treated and are considered "cured") should be monitored every 4 weeks (± 1 week) for the risk of hepatitis C reactivation.

The monitoring for hepatitis C reactivation has to be performed in all patients with a known history of HCV infection, irrespective of the treatment arm they have been assigned to (thus, not only in patients taking everolimus alone or in combination, but also in patients on pasireotide alone). However, in light of evidence that the risk for hepatitis C reactivation is related to everolimus, the drug interruption/discontinuation strategy (see Table 6-5) will apply to everolimus only.

For definition of hepatitis C reactivation and the management guidelines, see Table 6-5.

**Table 6-5 Guidelines for management of hepatitis C**

| HCV reactivation* | Actions |
|---|---|
| **For patients with baseline results**: Knowledge of past hepatitis C infection with no detectable HCV-RNA at screening.<br>**Reactivation is defined as**: New appearance of detectable HCV-RNA. | Discontinue study treatment. |

*All reactivations of hepatitis C are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in this case, they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation).

### 6.1.4.9 Management of ECG changes

SSAs have shown an influence on cardiac signal transduction.

Pasireotide administered subcutaneously has been shown to prolong the QT interval in healthy subjects based on two Phase I studies [CSOM230B2113] and [CSOM230B2125]. Additional analysis of thorough QT study data [CSOM230B2125], including quantitative ECG beat to beat restitution analysis, showed that pasireotide does not alter cardiac repolarization in the same manner as drugs known to prolong QT that are associated with pro-arrhythmia.

[redacted]

In clinical studies in Cushing's disease patients, QTcF of >500 msec was observed in two out of 201 patients. These episodes were sporadic and of single occurrence with no clinical consequence observed.

Episodes of torsade de pointes were not observed in any clinical study with pasireotide.

If at any visit a QTcF > 500 msec is observed, triplicate ECGs, each 2-3 minutes apart, need to be taken approximately 1 hour after the initial ECG. The mean QTcF from the triplicate ECGs will be determined. If the mean QTcF is > 500msec, the patient will need to be closely monitored at the hospital and will have to postpone pasireotide LAR treatment until a cardiologist has re-evaluated the ECG (this can be done by the central cardiologist if the trial has one). If the cardiologist confirms a mean QTcF >500 msec, the patient has to discontinue. Otherwise and if the cardiologist confirms that at least one ECG shows a QTcF > 470msec, the cardiac assessments described for a confirmed QTcF > 470msec need to be followed (see Figure 6-1).

If at any visit a 470 msec < QTcF/mean QTcF ≤ 500msec is observed, the following steps need to be taken (refer to Figure 6-1):

- postpone pasireotide LAR administration;
- a cardiology consultation must be sought as soon as practical but within 7 days of the initial abnormal ECG and the cardiologist must re-evaluate the ECG (this can be done by the central cardiologist if the trial has one).
    - If a QTcF > 470msec is NOT confirmed, no further action needs to be taken, and pasireotide LAR can be restarted.
    - If a QTcF > 470msec is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination, including at least a cardiac auscultation) to assess the patient for cardiovascular risk factors.
        - If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient needs to be discontinued immediately (discontinuation criteria to be followed).
        - If following the examination by the cardiologist, the investigator considers that there is not an acute cardiovascular safety risk and that the patient could restart to receive study medication, a Holter ECG (24hr or 48hr depending on the study) must be recorded soon as practical but within 7 days after the initial abnormal ECG / at the next pasireotide LAR injection. The Holter-ECG must be started 30min prior to an injection of study medication.

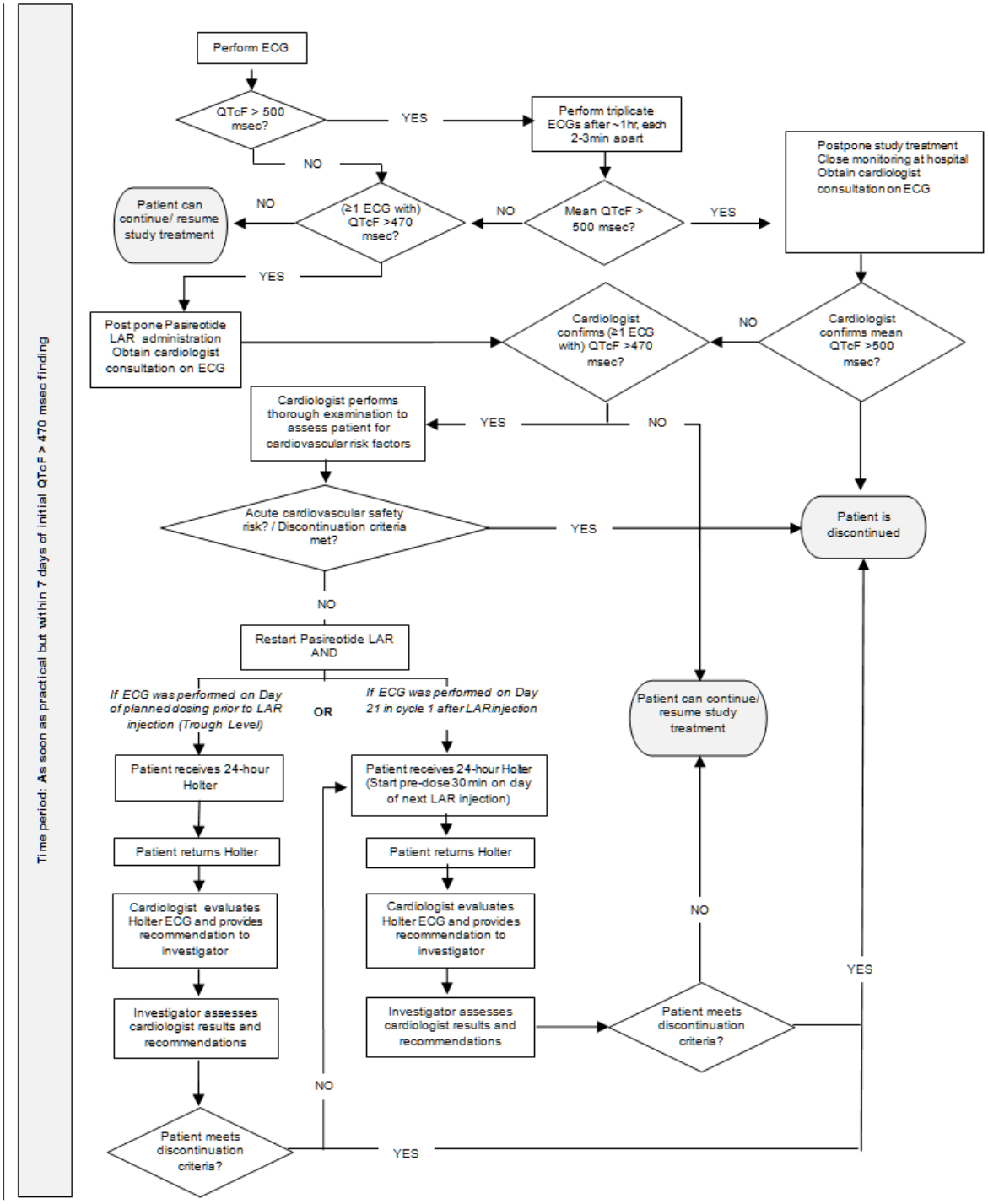
The results of the ECGs, cardiac examination, Holter-ECGs and the recommendation by the cardiologist must be evaluated by the investigator to determine whether the patient should continue the trial or not (discontinuation criteria to be followed).

Overall, the monitoring of ECG changes has to be performed in all patients, irrespective of the treatment arm they have been assigned to (thus, not only in patients taking everolimus alone or in combination, but also in patients on pasireotide alone), taking into account the observed QTcF value. However, in light of evidence that the risk for ECG changes is related to SSA

[redacted]

treatment, the drug interruption/discontinuation strategy (see Figure 6-1) will apply to pasireotide LAR only.

**Figure 6-1 Procedure for QTcF prolongations**




[redacted]

#### 6.1.4.10 Hepatic Safety Management

If any of the criteria below are observed at any scheduled or unscheduled visit the sponsor should be notified immediately upon awareness.

- ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN;
- ALT or AST > 5 x ULN and ≤ 8 x ULN;
- ALT or AST > 8 x ULN.

**ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN**

If this criterion is met with the presence of alkaline phosphatase < 2 X ULN, the patient has to discontinue the study and continue the safety evaluations.

If this criterion is met without the presence of alkaline phosphatase < 2 X ULN, the patient has to perform a **safety follow-up procedure withing 72 hours** of awareness of the abnormality (see Figure 6-2). According to the safety follow-up procedure, the investigator has to perform:

- liver-directed medical history and physical examination (i.e. assess occupational hazards, concomitant medications including OTC medications, inter-current illness, etc);
- liver function tests (LFT): ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is > 2.0 x ULN), Alb, PT (INR), ALP, and GGT;
- hepatitis screening: anti-HAV, IgM (to confirm acute Hepatitis A), HbsAg, anti-HBc, anti-HCV (if positive, PCR viral load should be assessed), anti-HEV, ANA antibodies, anti-smooth muscle anti-bodies, CMV and EBV;
- abdominal ultrasound (liver and biliary tree).

In addition, liver function tests have to be monitored **every 3-4 days** until resolution or return to baseline values.

- If ALT or AST return to less than 5 x ULN study drug can be resumed at the original dose level and the patient can continue the study.
- If ALT or AST rises above 5 x ULN at any time after study drug is resumed, then, the study drug should be discontinued immediately.
- If resolution or return to baseline does not occur after 2 weeks, the patient should be discontinued.

Overall, patients may need to be discontinued if the abnormal liver function criteria are met upon LFT retesting (See Section 6.3.2.1). Progress reports of the event should be maintained until resolution or stabilization (i.e. no further elevation after 2 consecutive assessments).

If any of these criteria are met and deemed an AE by the investigator, the event must be recorded on the AE CRF page; if the event is deemed serious by the investigator, then proceed with completing the SAE form. In addition, any significant findings from the physical examination should be recorded on the AE CRF page.

[redacted]

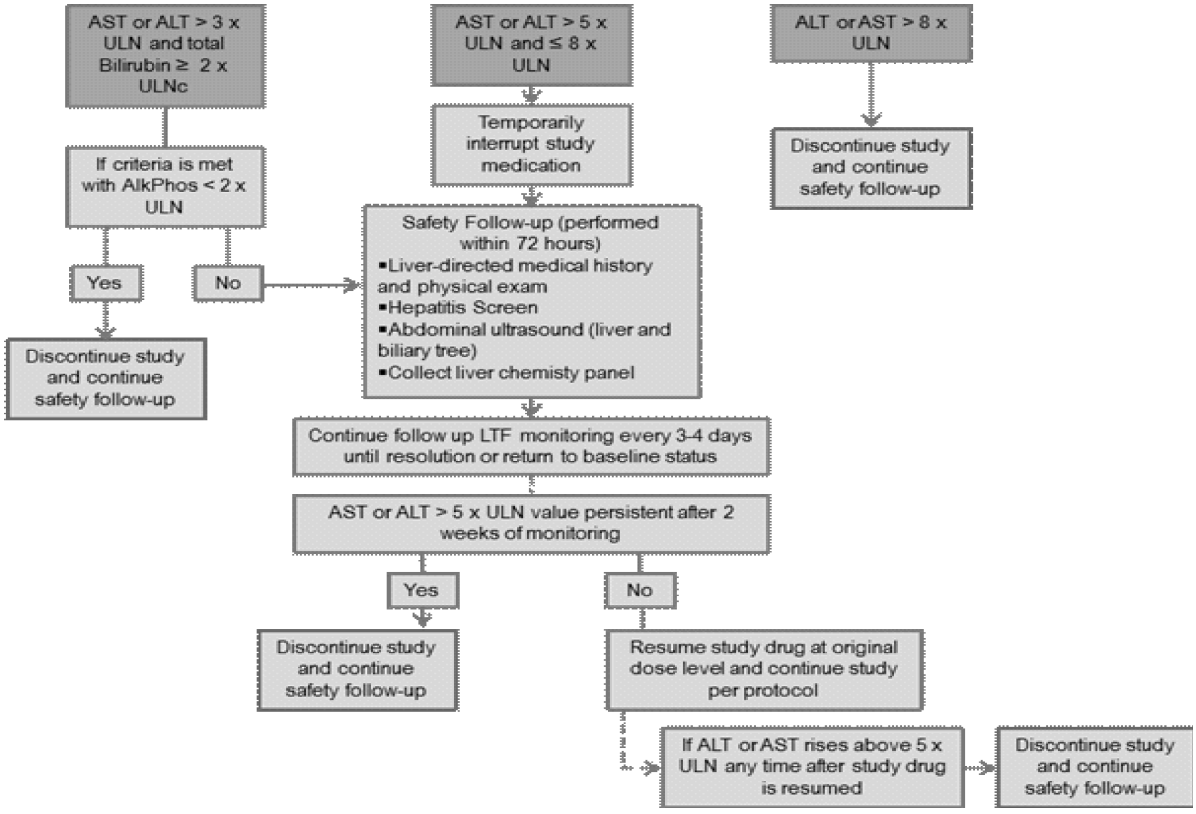
### ALT or AST > 5 x ULN and < 8 x ULN

If this criterion is met, the study treatment has to be temporarily interrupted, and the patient has to perform **a safety follow-up procedure withing 72 hours** of awareness of the abnormality, as above reported (see Figure 6-2).

### ALT or AST > 8 x ULN

If this criterion is met, the study treatment has to be discontinued (see Figure 6-2).

**Figure 6-2 LFT Management Algorithm**




## 6.1.5 Guidelines for continuation of treatment

See Section 6.3.

## 6.1.6 Treatment duration

Patients will be treated with the assigned study treatment for 12 months or until radiologically documented disease progression, intolerable toxicity, start of new cancer therapy, withdrawal of consent or discontinuation due to any other reason.

Patients who are presenting clinical benefit from the treatment with combination or monotherapy and who are not experiencing unacceptable toxicity are permitted to continue treatment after the 12-month treatment period. These patients will be followed until

radiologically documented disease progression, intolerable toxicity, start of new cancer therapy, withdrawal of consent or discontinuation due to any other reason.

The definition of end of the study is reported in Section 4.3.

## 6.2 Dose escalation guidelines (Phase 1 studies only)

Not applicable.

## 6.3 Dose modifications

### 6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment.

#### 6.3.1.1 Dose modifications for pasireotide LAR

Patients who do not tolerate the pasireotide LAR 60 mg i.m. dose are permitted to reduce the dose to 40 mg or to 20 mg. Patients requiring a dose reduction are to return to the higher dose once the tolerability issue is resolved.

All dose changes must be recorded on the CRF.

**Table 6-6 Dosing modification criteria for suspected pasireotide LAR-related toxicities**

| Adverse Event | Action |
|---|---|
| CTCAE grade ≤ 2 | No drug adjustments |
| CTCAE grade ≥ 3 and assessed as drug related<br><br>(except blood glucose changes see Section 6.1.4.5, LFT changes see Section 6.1.5, QTc changes see Section 6.1.4.9 | Reduce dose to 40 mg.<br>If the AE improves to grade ≤ 2 before the next administration, increase dose to 60 mg.<br>If the dose is increased and the AE recurs at CTC grade ≥ 3 the dose will be reduced back to the lower dose and shall not be increased again during the study period.<br><br>If the AE does not improve to grade ≤ 2 on the lower dose before the next administration, reduce the dose to 20 mg. If re-escalation of pasireotide LAR to 40 mg is not possible*, the patient will be discontinued from the study and will be followed for safety.<br><br>If the AE does not improve to grade ≤ 2 on the lowest dose before the next administration, the patient will discontinue the study drug and be followed for safety. |
| * Re-escalation of pasireotide LAR from 20 to 40 mg has to be performed within 56 days. | |

The above guidance should be used for all AEs judged to be related to pasireotide LAR except for changes in blood glucose which should be followed-up as described in Section 6.1.4.5, for changes in LFTs which should be managed according to Section 6.1.5, and for changes in QTc which should be followed-up as described in Section 6.1.4.9.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least weekly until resolution or stabilization of the event, whichever comes first. Patients must be discontinued from the study if they

[redacted]

require a dose delay of ≥56 days. All patients will be followed for adverse events and serious adverse events for 56 days following the last dose of pasireotide LAR.

#### 6.3.1.2 Dose modifications for everolimus

Dose adjustments are permitted for any adverse event suspected to be related to everolimus in those patients unable to tolerate the once-daily oral dose of 10 mg. If the administration of everolimus must be interrupted because of unacceptable toxicity, study drug dosing will be interrupted or modified according to the guidelines in Table 6-7. If the toxicity is intolerable to the patient at the original 10 mg daily dose, interrupt everolimus until recovery to grade ≤1; then, reintroduce everolimus at the initial dose or lower dose level depending on toxicity type and grade (Table 6-8).

If a patient has already decreased 2 dose level (i.e., to 5 mg every other day), no further dose reduction is permitted. Patients who need an additional dose reduction will be required to discontinue the study drug.

The lower dose level introduced after tolerability issues will be maintained throughout the study.

The initial once-daily oral dose of everolimus (10 mg) can be administered at two different strengths: either as two 5 mg tablets, taken together QD, or as a single 10 mg tablet. In case a dose reduction is required due to toxicity, patients initially receiving the 10 mg strength will be provided with the 5 mg strength. Thus, they will be able to take the reduced 5 mg dose as a single 5-mg tablet.

**Table 6-7 Everolimus dose level modification guidelines**

| Dose level | Dose and schedule |
|---|---|
| 0 (starting dose) | 10 mg daily |
| Decrease 1 dose level | 5 mg daily |
| Decrease 2 dose levels | 5 mg every other day |

**Table 6-8 Dosing modification criteria for suspected everolimus-related toxicity**

| Toxicity | Action |
|---|---|
| **Non-hematological toxicity** | |
| Grade 2<br>(except pneumonitis – refer to Table 6-2)<br>(except blood glucose changes – refer to Table 6-1)<br>(except Hepatitis B and C management – refer to Table 6-4 and Table 6-5)<br>(except hepatic toxicity – refer to Figure 6-2) | If the toxicity is tolerable to the patient, maintain the same dose. Initiate appropriate medical therapy and monitor.<br>If the toxicity becomes intolerable to patient, interrupt everolimus until recovery to grade ≤1. Then, reintroduce everolimus at the initial dose.<br>If the toxicity recurs at grade 2, interrupt everolimus until recovery to grade ≤1. Then, reintroduce everolimus at the lower dose level. |
| Grade 3<br>(except hyperlipidemia*)<br>(except blood glucose changes – refer to Table 6-1)<br>(except Hepatitis B and C management – refer to Table 6-4 and Table 6-5)<br>(except hepatic toxicity – refer to Figure 6-2) | Interrupt everolimus until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Then reintroduce everolimus at the lower dose level. For pneumonitis consider the use of a short course of corticosteroids.<br>If the toxicity recurs at grade 3, consider discontinuation. |

[redacted]

| Toxicity | Action |
|---|---|
| Grade 4<br>(except Hepatitis B and C management – refer to Table 6-4 and Table 6-5) | Discontinue everolimus, and treat with appropriate medical therapy. |
| **Hematological toxicity** | |
| Grade 2 Thrombocytopenia (platelets <75, ≥50×$10^9$/L) | Interrupt everolimus until recovery to grade ≤1 (>75×$10^9$/L). Then, reintroduce everolimus at the initial dose.<br>If thrombocytopenia again returns to grade < 2, interrupt everolimus until recovery to grade ≤1. Then, reintroduce everolimus at the lower dose level. |
| Grade 3 Thrombocytopenia (platelets <50, ≥25×$10^9$/L) | Interrupt everolimus until recovery to grade ≤1 (platelets ≥ 75×$10^9$/L). Then, resume everolimus at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue everolimus. |
| Grade 4 Thrombocytopenia (platelets <25×$10^9$/L) | Discontinue everolimus. |
| Grade 3 Neutropenia (neutrophils <1, ≥0.5×$10^9$/L) | Interrupt everolimus until recovery to grade ≤1 (neutrophils ≥1.5×$10^9$/L). Then, resume everolimus at the initial dose. If ANC again returns to Grade 3, hold everolimus until the ANC ≥1.5×$10^9$/L. Then, resume everolimus dosing at the lower dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia. |
| Grade 4 Neutropenia (neutrophils < 0.5×$10^9$/L) | Interrupt everolimus until recovery to grade ≤1 (neutrophils ≥1.5×$10^9$/L). Then, resume everolimus at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue everolimus. |
| Grade 3 febrile neutropenia (not life-threatening) | Interrupt everolimus until resolution of fever and neutropenia to grade ≤1. Hold further everolimus until the ANC ≥1,500/$mm^3$ and fever has resolved. Then, resume everolimus at the lower dose level. If febrile neutropenia recurs, discontinue everolimus. |
| Grade 4 febrile neutropenia (life-threatening) | Discontinue everolimus. |
| Any hematological or non-hematological toxicity requiring interruption for ≥4 weeks (28 days) | Discontinue everolimus. |
| *Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies | |

Investigator should manage anemia as medically indicated per local standards.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least weekly until resolution or stabilization of the event, whichever comes first. The patients must be discontinued from the study if they require a dose delay of ≥28 days. All patients will be followed for adverse events and serious adverse events for 56 days following the last dose of everolimus. All interruptions or dose modifications must be recorded on the relevant section of the CRF.

### 6.3.2 Treatment interruption and treatment discontinuation

Patients experiencing unacceptable toxicity (AE of grade 3 or higher, including laboratory value changes of grade 3 or higher) that the investigator considers directly attributable to the study drugs should have their dose reduced or be withdrawn from the study. Section 6.3.1.1 and Section 6.3.1.2 should be regarded as a guideline for the treatment of patients

[redacted]

experiencing adverse events which are judged to be drug-related. Any deviation from these guidelines should be discussed and approved by the sponsor.

For patients treated in the pasireotide LAR monotherapy arm or in the combination arm, in case the re-escalation from 20 to 40 mg of pasireotide LAR is not possible due to toxicity issues, the patient will be discontinued (Table 6-9). For patients treated in the combination arm, the patient will be maintained on study treatment unless the 20 mg pasireotide LAR dose cannot be re-escalated (Table 6-9). If one drug of the combination is discontinued, the combination treatment will be discontinued.

**Table 6-9 Recommendations for patient discontinuation following study drug adjustment**

| Dose levels reached after tolerability issues | Action |
|---|---|
| Pasireotide LAR 20 mg | If re-escalation to 40 mg* is not possible, the patient will be discontinued and followed for safety |
| Pasireotide LAR 40 mg | Patient can be maintained on study treatment |
| Pasireotide LAR 20 mg and everolimus 5 mg e.o.d. | If re-escalation of pasireotide LAR to 40 mg* is not possible, the patient will be discontinued and followed for safety |
| Pasireotide LAR 40 mg and everolimus 5 mg e.o.d. | Patient can be maintained on study treatment |
| Pasireotide LAR 60 mg and everolimus 5 mg e.o.d | Patient can be maintained on study treatment |
| Pasireotide LAR 20 mg and everolimus 5 mg daily | If re-escalation of pasireotide LAR to 40 mg* is not possible, the patient will be discontinued and followed for safety |
| Pasireotide LAR 40 mg and everolimus 5 mg daily | Patient can be maintained on study treatment |
| Pasireotide LAR 60 mg and everolimus 5 mg daily | Patient can be maintained on study treatment |
| Pasireotide LAR 20 mg and everolimus 10 mg daily | If re-escalation of pasireotide LAR to 40 mg is not possible, the patient can not be maintained on study treatment |
| Pasireotide LAR 40 mg and everolimus 10 mg daily | Patient can be maintained on study treatment |
| * Re-escalation of pasireotide LAR from 20 to 40 mg has to be performed within 56 days. | |

All patients must have evaluations for 56 days after the last dose of study treatment. Patients lost to follow up should be recorded as such on the CRF. Patients who discontinue study drug before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final study visit will be performed. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 56 days following the last dose of study drug.

Patients who discontinue study drug should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

#### 6.3.2.1 Hepatic-related discontinuation criteria

If any of the discontinuation criteria below are met, study medication should be discontinued immediately. In addition, proper safety follow-up management should be performed as outlined in Section 6.1.5. Re-challenge of study medication is prohibited once discontinuation criteria are met.

[redacted]

- ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN and ALP < 2 x ULN;
- ALT or AST > 5 x ULN and ≤ 8 x ULN persistent for more than 2 weeks;
- ALT or AST > 8 x ULN.

## 6.4 Concomitant medications/therapies

As underscored in Section 1.2.2.3, everolimus is a substrate of CYP3A4, being metabolized by this enzyme in the liver and, to some extent, in the intestinal wall. In addition, it is a substrate and moderate inhibitor of the multidrug efflux pump P-glycoprotein (PgP). Therefore, extent of absorption and subsequent elimination of systemically absorbed everolimus may be influenced by agents that are substrates, inhibitors, or inducers of CYP3A4 and/or PgP. For example, inhibitors of PgP may decrease the efflux of everolimus from brain or tumor and therefore increase everolimus concentrations in these tissues.

Table 6-10 reports a comprehensive list of relevant inducers and inhibitors of CYP3A. A strong inhibitor may cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates (including everolimus) whereas a moderate inhibitor may cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates. Distinction is not always categorical as the interaction can vary according to certain conditions.

**Table 6-10 Clinically relevant drug interaction: inducers & inhibitors of isoenzyme CYP3A4**

| **Inducers** |
|---|
| **Strong inducers:**<br>avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)<br>**Moderate inducers:**<br>bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir<br>**Weak inducers:**<br>amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea, garlic (allium sativum), gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, [troglitazone], vinblastine |
| **Inhibitors** |
| **Strong inhibitors:**<br>boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole (Krishna, et al 2009), ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandamycin, voriconazole.<br><br>**Moderate inhibitors:**<br>amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus paraside fruit juice), imatinib, schisandra sphenanthera, tofisopam, verapamil. |
| A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/. This website is continually revised (Version 5.0 released on January 12, 2009) and should be checked frequently for updates. |

The list of relevant substrates, inhibitors or inducers of PgP and PgP/CYP3A dual inhibitors is included in Table 6-11.

[redacted]

**Table 6-11 Clinically relevant drug interactions: substrates, inducers, and inhibitors of PgP and PgP/CYP3A dual inhibitors**

| PgP Substrates | PgP Inhibitors and PgP/CYP3A dual inhibitors | PgP Inducers |
|---|---|---|
| colchicine, digoxin, fexofenadine, indinavir, paclitaxel, talinolol, topotecan, vincristine, everolimus | amiodarone, azirhromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, fluvoxamine, ginko (ginko biloba) indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinensis, St John's wort (Hypericum perforatum), talinolol, telaprevir, telmisartan, ticagrerol, tipranavir, tolvaptan, valspodar, verapamil, | rifampin, St John's wort |
| Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 29, 2012, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table. | | |

In addition, *in vitro* studies showed that everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6, potentially increasing the concentrations of products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index.

In contrast, pasireotide has little or no capacity to inhibit the major P450 enzymes as a direct acting (metabolism independent) reversible inhibitor, or as an irreversible metabolism dependent inhibitor. Pasireotide was found to be a weak *in vitro* inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2E1 and CYP3A4/5 with $IC_{50}$ values ranging from 10 to >100 μM. However, based on the low therapeutic levels, no drug-drug interaction between pasireotide and comedications (as CYP450 substrates) is expected.

Pasireotide was also shown to be able to inhibit PgP ($IC_{50}$ = 0.85 μM) *in vitro* in the inside-out membrane vesicle system, at concentrations of up to 10 μM. However, with the low therapeutic levels (plasma $C_{max.ss}$ <0.1) and no inhibition in cell system, as well as the permeability-limited drug concentrations at the PgP active site, a drug-drug interaction between pasireotide and PGP substrates is not expected *in vivo*.

### 6.4.1 Permitted concomitant therapy

The patients must be instructed not to take any additional medications (over-the-counter products) during the course of the study without prior consultation with the investigator.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. At each visit, the patient must be asked about any new medications he/she is or has taken.

All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be reported in the CRF.

All medications taken ≤30 days prior to study entry should be reported on the relevant section of the CRF. The investigator or his/her designee will continue collecting information on the initiation of additional anticancer therapies up to 56 days after the last dose of study treatment.

[redacted]

Women of childbearing potential will be allowed to use hormonal contraception, as indicated in exclusion criterion #25.

Palliative radiotherapy or surgery may be allowed during the study but they should be discussed with Novartis Clinical Team prior to administration.

### 6.4.2 Permitted concomitant therapy requiring caution and/or action

The following medications should be used with caution during the study:

- Concomitant treatment with moderate inhibitors of CYP3A4 (including but not limited to amprenavir, fosamprenavir, cyclosporine, aprepitant, erythromycin, fluconazole, verapamil or diltiazem) or moderate PgP inhibitors requires caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, **reduce the dose of everolimus to 5 mg**. If well tolerated for two weeks, the everolimus dose can be increased to 10 mg/day. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, consider a washout period of at least 2-3 days (average for most commonly used moderate inihibitors) beforeeverolimus dose is increased to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.
- Concomitant treatment with strong CYP3A4/PgP inducers should be avoided. If patients require co-administration of a strong CYP3A4/PgP inducer (like rifampicin and rifabutin), an everolimus dose increase from 10 mg daily up to 20 mg daily should be considered (based on pharmacokinetic data), using 5 mg increments. Enzyme induction usually occurs within 7-10 days; therefore, study drug dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen with the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily dose used prior to the initiation of the strong CYP3A4 inducer. This dose of everolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3-5 days (reasonable time for significant enzyme de-induction) beforeeverolimus dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer.
- Concomitant treatment with a substrate of CYP3A4 doesn't require dose modification; however, patients should be closely monitored for toxicity (Only patients receiving everolimus).

### 6.4.3 Prohibited concomitant therapy

The following concomitant treatments are not allowed during the study:

- Other investigational drug or therapy.
- Medication known to affect GH or IGF-1 levels.
- Medications that might lead to QT prolongation (the discontinuation of the patient is required prior to starting the respective QT prolonging medication).

  A comprehensive list of drugs that prolong the QT interval and/or induce Torsades de Pointes can be found at: http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=All

[redacted]

- Investigational or commercial anticancer agents other than pasireotide LAR and everolimus (including chemotherapy, hormone therapy, targeted therapy, targeted or biological agents). If such agents are required for a patient, the patient must first be withdrawan from the study. The initiation of any non-protocol specific anti-tumor treatment or surgery is considered an indication of disease progression and should be recorded appropriately.
- Use of prescription medication for diarrhea. Exceptions may be made if the medication is to treat an adverse event.
- Use of dexamethasone therapy administered for nausea and/or vomiting, is prohibited during the study.
- Use of the anticoagulant medication warfarin should be avoided. Warfarin should be replaced by the use of selective Factor Xa inhibitors (rivaroxaban, apixaban, dabigatran) which are acceptable from a safety point of view since they have no effect on prothrombin time (PT), and partial thromboplastin time (PTT)
- The following drugs should also be avoided from 5 days before through to the end of the 5-HIAA collection, given their potential to affect 5-HIAA: chlorpromazine, imipramine, isoniazid, levodopa, monoamine oxidase inhibitors, methenamine, methyldopa, phenothiazines, promethazine, and tricyclic antidepressants, acetanilid, phenacetin, glyceryl guaiacolate (component of many cough syrups), methocarbamol, and reserpine.
- Leukocyte growth factors (e.g. G-CSF and GM-CSF) are not permitted prophylactically but may be prescribed by the investigator for severe neutropenia if deemed appropriate.
- Prolonged (>2 weeks in duration) treatment with systemic corticosteroids.
- Strong CYP3A4 inhibitors and strong PgP inhibitors are not allowed (see Table 6-10).

In addition, patients should refrain from **grapefruit juice, Seville oranges, and star fruit** as well as **the juice of these fruits** which are potent CYP3A4-inhibitor and also affect PgP activity.

Everolimus may affect patient response to vaccinations making the vaccination less effective. As everolimus is an immunosuppressant, live vaccines should be avoided while a patient is treated with everolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a thypoid vaccines.

## 6.5 Patient numbering, treatment assignment and randomization

### 6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the 4-digit Center Number (Center No.) (as assigned by Novartis to the investigational site) with a 5-digit sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database.

[redacted]

Upon signing the ICF, the patient number is assigned by the investigator. At each site, the first patient is assigned patient number 00001, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 00002, the third patient is assigned patient number 00003).

Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened.

### 6.5.2 Treatment assignment and randomization

Patients will be assigned to one of the 3 treatment arms (Section 4.1 and Section 6.1) in a ratio of 1:1:1.

**Stratification:** Randomization will be stratified by typical carcinoid tumor (TC) vs. atypical carcinoid tumor (AC) according to WHO classification and line of study treatment (1st line vs. others). In case of naïve patients, the study treatment will be considered as 1st line. The randomization scheme will be reviewed by a Biostatistics Quality Assurance Group.

**Randomization:** The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

The patient number will be entered into the IVRS system by the site, the randomization number and treatment arm linked to this patient number will be allocated by the system; IVRS will communicate to the site personnel only the treatment arm assigned while the randomization number linked to this will not be communicated. The randomization number will be stored in the IVRS databases and only provided to authorised trial personnel on request. Prior to dosing and at the end of the screening period, all patients who fulfill all inclusion/exclusion criteria will be randomized via IVRS/IWRS to one of the treatment arms. The investigator or his/her delegate will call or log on to the IVRS/IWRS and confirm that the patient fulfils all the inclusion/exclusion criteria. The IVRS will assign the patient one of the treatment arm.

### 6.5.3 Treatment blinding

Not applicable.

## 6.6 Study drug supply

### 6.6.1 Study drug preparation and dispensation

Study medication will be dispensed by an authorized person at the investigator's site. Patients will receive either pasireotide LAR alone and everolimus alone or a combination of pasireotide LAR and everolimus depending on the treatment arm they were randomized to.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the CRF.

[redacted]

**Table 6-12 Preparation and dispensing**

| Study drugs | Dispensing | Preparation |
|---|---|---|
| Pasireotide LAR | i.m. injection performed by study nurse or study physician every 28 days (+/- 3 days) on an outpatient basis | See below |
| Everolimus | Tablets including instructions for administration are dispensed by study personnel on an outpatient basis.<br>Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit. | Not applicable |

#### 6.6.1.1 Preparation procedure for pasireotide LAR

The reconstitution of pasireotide LAR has to be performed just prior to administration. The i.m. injection must be given immediately after the withdrawal of the reconstituted suspension from the vial in the syringe.

**Table 6-13 Handling and preparation of pasireotide LAR dose**

| Dose (mg) | Volume to be injected |
|---|---|
| 20 | 1 x 20 mg vial + 2 mL vehicle: whole volume to be injected |
| 20 | 1 × 40 mg vial + 2 mL vehicle: 0.9 mL of volume to be injected |
| 40 | 1 × 40 mg vial + 2 mL vehicle: whole volume to be injected |
| 60 | 1 × 60 mg vial + 2 mL vehicle: whole volume to be injected |

**60 mg dosage strength (60 mg per vial)**

- Take one (1) pasireotide LAR 60 mg vial.
- Remove the transparent flip-off cap from the vial.
- Take one vehicle ampoule and break off the upper part.
- Withdraw the content of the vehicle ampoule with a needle and the 3 mL syringe (or 2.5 mL syringe, in case the 3mL syringe is not available).
- Remove air bubbles by pushing the piston and wipe the needle with a sterile pad and adjust the volume to 2 mL.
- Inject 2 mL of vehicle into the vial containing the powder (60 mg)
- Shake the vial up and down for at least 30 seconds in order to get a homogenous suspension.
- Withdraw the whole volume of suspension from the vial with a needle and the 3 mL (or 2.5 ml) syringe.
- Reverse the syringe and aspirate in the suspension contained in the needle to the syringe.
- Change the needle with a standard i.m. injection needle.
- Remove air bubbles by pushing the piston and wipe the needle with a sterile pad.
- Immediately, inject the whole volume of suspension intra-muscularly to the patient.

**40 mg dosage strength (40 mg per vial)**

- Take one (1) pasireotide LAR 40 mg vial.
- Remove the transparent flip-off cap from the vial.

[redacted]

- Take one vehicle ampoule and break off the upper part.
- Withdraw the content of the vehicle ampoule with a needle and the 3 mL syringe (or 2.5 mL syringe, in case the 3 mL syringe is not available).
- Remove air bubbles by pushing the piston and wipe the needle with a sterile pad and adjust the volume to 2 mL.
- Inject 2 mL of vehicle into the vial containing the powder (40 mg).
- Shake the vial up and down for at least 30 seconds in order to get a homogenous suspension.
- Withdraw the whole volume of suspension from the vial with a needle and the 3 mL (or 2.5 mL) syringe.
- Reverse the syringe and aspirate in the suspension contained in the needle to the syringe.
- Change the needle with a standard i.m. injection needle.
- Remove air bubbles by pushing the piston and wipe the needle with a sterile pad.
- Immediately inject the whole volume of suspension intra-muscularly to the patient.

### 20 mg dosage strength (20 mg per vial)

- Take one (1) pasireotide LAR 20 mg vial.
- Remove the transparent flip-off cap from the vial.
- Take one vehicle ampoule and break off the upper part.
- Withdraw the content of the vehicle ampoule with a needle and the 3 mL syringe (or 2.5 mL, in case the 3 mL syringe is not available).
- Remove air bubbles by pushing the piston and wipe the needle with a sterile pad and adjust the volume to 2 mL.
- Inject 2 mL of vehicle into the vial containing the powder (20 mg)
- Shake the vial up and down for at least 30 seconds in order to get a homogenous suspension.
- Withdraw the whole volume of suspension from the vial with a needle and the 3 mL (or 2.5 mL) syringe.
- Reverse the syringe and aspirate in the suspension contained in the needle to the syringe.
- Change the needle with a standard i.m. injection needle.
- Remove air bubbles by pushing the piston and wipe the needle with a sterile pad.
- Immediately, inject the whole volume of suspension intra-muscularly to the patient.

### 20 mg dosage strength (40 mg per vial)

- Take one (1) pasireotide LAR 40 mg vial.
- Remove the transparent flip-off cap from the vial.
- Take one vehicle ampoule and break off the upper part.
- Withdraw the content of the vehicle ampoule with a needle and the 3 mL syringe (or 2.5 ml, in case 3ml syringe is not available).

[redacted]

- Remove air bubbles by pushing the piston and wipe the needle with a sterile pad and adjust the volume to 2 mL.
- Inject 2 mL of vehicle into the vial containing the powder (40 mg).
- Shake the vial up and down for at least 30 seconds in order to get a homogenous suspension.
- Withdraw the whole volume of suspension from the vial with a needle and the 3 mL (or 2.5 mL) syringe.
- Reverse the syringe and aspirate in the suspension contained in the needle to the syringe.
- Adjust the volume in the syringe to 0.9 mL.
- Change the needle with a standard i.m. injection needle.
- Remove air bubbles by pushing the piston and wipe the needle with a sterile pad.
- Immediately, inject the whole volume of suspension intra-muscularly to the patient.

#### 6.6.1.2 Everolimus administration

Everolimus will be dispensed by the study center personnel on an outpatient basis. Patients will be provided with an adequate supply of everolimus for self-administration at home.

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance).

The patient will take the first dose of everolimus at the center. Everolimus will be dosed starting on Day 1 (Visit 2). Patients will be instructed to take one 10 mg tablet or, alternatively, two 5 mg tablets of everolimus QD orally with a glass of water, at the same time each day either consistently with food or consistently without food. Any dietary habits around the time of everolimus intake should be as consistent as possible throughout the study. The tablet/tablets should be swallowed as a whole and not be chewed or crushed. In cases where the tablet/tablets can not be swallowed, it/they should be disintegrated in water just prior being taken. Approximately 30 mL of water should be put into a glass. The tablet/tablets should then be added and the contents stirred gently (for a maximum of 7 minutes) until the tablet/tablets are disintegrated. The contents should then be drunk. Afterwards, the glass should be rinsed with an additional 30 mL of liquid and drunk.

If vomiting occurs, no attempt should be made to replace the vomited dose unless two everolimus tablets (or one 10 mg tablet) are clearly visible. If two everolimus tablets (or one 10 mg tablet) are clearly visible, then the patient should replace the everolimus dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

If the patient misses a dose at the scheduled time, the administration of the study drug can:

- occurr within 8 hours after the normal time of administration, and the new time of administration can be considered as a reference for the next administration (eg. if the normal time of administration is 8 am, the 8 am missing dose could be administered by 4 pm of the same day)

  or

[redacted]

- be skipped until the next day.

On days on which there are visits scheduled, patients should be reminded not to take their study drug until advised to do so during the visit. At visits, when laboratory blood samples are drawn, patients should not take the daily study drug dose until the blood sample has been drawn and after all safety assessments have been performed.

Patients are to bring their unused everolimus, as well as the empty blister packs, to the clinic on each visit, and a new pack of everolimus will be dispensed on that visit. Compliance should be verified by the investigator's staff by counting the number of tablets consumed between visits.

The investigator (or his/her designee) will document dosage administration and all dose changes during the study in the CRF. The site must maintain an overall drug accountability log for the study, as well as individual accountability records for each patient. The dose, amount dispensed, amount received, and amount remaining unused must be recorded in the source document. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

The patient will be asked to return all unused everolimus tablets at eachstudy visit.

Patients will receive treatment with study drug during the duration of the study, or until progressive disease occurs, or until the occurrence of unacceptable toxicity, or until the investigator or patient decides that continuation is not in the best interest of the patient.

Interruption for toxicity should follow the instructions in Table 6-8.

#### 6.6.1.3 Combination therapy pasireotide LAR and everolimus

Patients assigned to this treatment arm will be given a combination therapy based on pasireotide LAR 60 mg i.m. and everolimus 10 mg p.o. q.d. as described for each study drug above.

### 6.6.2 Study drug packaging and labeling

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

### 6.6.3 Drug supply and storage

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, pasireotide LAR and everolimus should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol. Details are listed in Table 6-14.

[redacted]

**Table 6-14 Supply and storage of study treatments**

| Study treatments | Supply | Storage |
|---|---|---|
| Pasireotide LAR | Centrally supplied by Novartis | Refer to study treatment label |
| Everolimus | Centrally supplied by Novartis, or by local commercial stock, once available | Refer to study treatment label |

#### 6.6.3.1 Pasireotide LAR

Study drug pasireotide LAR i.m. depot injections will be supplied in open-label packaging by Novartis as a powder in vials containing 20 mg, 40 mg and 60 mg, with ampules containing 2 mL of vehicle (for reconstitution). No syringes or needles will be provided with the pasireotide study drug supplies.

#### 6.6.3.2 Everolimus

Study drug everolimus will be supplied in open-label packaging by Novartis (centrally or by local commercial stock, once available) as tablets of either 10 mg or 5 mg strength, blister-packed under aluminium foil in units of 10 tablets and dosed on a daily basis. Everolimus tablets should be opened only at the time of administration as the drug is both hygroscopic and light-sensitive.

### 6.6.4 Study drug compliance and accountability

#### 6.6.4.1 Study drug compliance for everolimus

Compliance will be assessed by the investigator and/or study personnel at each visit using tablet counts. Records of study medication used, treatment administered, and intervals between visits will be kept during the study. This information should be captured in the source document at each patient visit.

- Patients will be requested to bring their unused medication including empty packaging to the clinic at each visit, at the end of the study and at the time of study treatment discontinuation.
- All doses taken by the patient and all dose changes during the study must be recorded on the CRF.

#### 6.6.4.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger (overall drug accountability log for the study as well as individual study drug accountability records for each patient) of tablets administered, tablets used, dose changes, dates dispensed and intervals between visits. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

[redacted]

### 6.6.5 Disposal and destruction

The drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

# 7 Visit schedule and assessments

## 7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category column").

[redacted]

**Table 7-1 CORE STUDY – Visit evaluation schedule (12 months)**

| | Category | Reference to Section 7.2 | Screening Baseline | Core study | | | | | | | | | | | | | | | | End of core study/Early withdran (EOS) | Safety FU visit ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | |
| **Study Day** | | | **-28 to-1** | **1** | **15** | **21** | **29** | **49** | **57** | **85** | **113** | **141** | **169** | **197** | **225** | **253** | **281** | **309** | **337** | | |
| **Week** | | | | | **2** | **3** | **4** | **7** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** | |
| Obtain Informed Consent | D | | X | | | | | | | | | | | | | | | | | | |
| Patient history | D | | X | | | | | | | | | | | | | | | | | | |
| Demography | D | | X | | | | | | | | | | | | | | | | | | |
| Relevant medical history/current medical conditions incl. cancer-related conditions and symptoms | D | | X | | | | | | | | | | | | | | | | | | |
| Diagnosis and extent of cancer | D | | X | | | | | | | | | | | | | | | | | | |
| Prior antineoplastic therapies, therapy for lung/thymus NET | D | | X | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | S | | X | | | | | | | | | | | | | | | | | | |
| Prior/concomitant medications | D | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination | S | 7.2.2.1 | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |

[redacted]

| | Category | Reference to Section 7.2 | Screening Baseline | Core study | | | | | | | | | | | | | | | | End of core study/Early withdran (EOS) | Safety FU visit ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | |
| **Study Day** | | | **-28 to-1** | **1** | **15** | **21** | **29** | **49** | **57** | **85** | **113** | **141** | **169** | **197** | **225** | **253** | **281** | **309** | **337** | | |
| **Week** | | | | | **2** | **3** | **4** | **7** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** | |
| WHO Performance status | D | 7.2.2.4 | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Height | D | 7.2.2.3 | X | | | | | | | | | | | | | | | | | | |
| Weight | D | 7.2.2.3 | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Vital signs | D | 7.2.2.2 | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Chest X-ray, or chest CT scan | D | 7.2.2.6.1 | As medically indicated | | | | | | | | | | | | | | | | | | |
| Hepatitis screening (HBV-DNA, HBsAg, HBsAb, HBcAb, HCV RNA-PCR) | D | 7.2.2.5.10 | X | | | | | | | | | | | | | | | | | | |
| Monitoring for HBV-DNA, HCV RNA-PCR every 4 weeks (if applicable) | D | 7.2.2.5.10 | | | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Anti-HAV, IgM, HbsAg, Anti-HBc, anti-HCV (if positive, PCR viral load should be assessed), Anti-HEV, ANA antibodies, anti-smooth muscle anti-bodies, CMV and | D | | | If LFTs meet criteria reported in Section 6.1.5 | | | | | | | | | | | | | | | | | |

[redacted]

| | Category | Reference to Section 7.2 | Screening Baseline | Core study | | | | | | | | | | | | | | | | End of core study/Early withdran (EOS) | Safety FU visit ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | |
| **Study Day** | | | -28 to-1 | 1 | 15 | 21 | 29 | 49 | 57 | 85 | 113 | 141 | 169 | 197 | 225 | 253 | 281 | 309 | 337 | | |
| **Week** | | | | | 2 | 3 | 4 | 7 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | |
| EBV | | | | | | | | | | | | | | | | | | | | | |
| Laboratory evaluations | | 7.2.2.5 | | | | | | | | | | | | | | | | | | | |
| Hematology | D | 7.2.2.5.1 | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Coagulation (INR) | D | 7.2.2.5.2 | X | X | | X* | X | X* | X | X | | X | | X | | X | | X | | X | |
| Coagulation (PTT) | | 7.2.2.5.2 | X | | | | | | | | | | | | | | | | | | |
| Biochemistry | D | 7.2.2.5.3 | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Fasting glucose/insulin/ HbA1c (everolimus monotherapy) | D | 7.2.2.5.4 | X | X | X | X | X | If medically indicated | X | X | X | X | X | X | X | X | X | X | X | X | |
| Fasting glucose/insulin/ HbA1c (combination) | D | 7.2.2.5.4 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Fasting glucose/insulin/ HbA1c pasireotide LAR monotherapy | D | 7.2.2.5.4 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Blood glucose self monitoring (if applicable) | | 7.2.2.5.4 | Continuous | | | | | | | | | | | | | | | | | | |
| Liver Function Tests | D | 7.2.2.5.5 | X | X | X | X* | X | X* | X | X | X | X | X | X | X | X | X | X | X | X | |

[redacted]

| | Category | Reference to Section 7.2 | Screening Baseline | Core study | | | | | | | | | | | | | | | | End of core study/Early withdran (EOS) | Safety FU visit ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | |
| **Study Day** | | | **-28 to-1** | **1** | **15** | **21** | **29** | **49** | **57** | **85** | **113** | **141** | **169** | **197** | **225** | **253** | **281** | **309** | **337** | | |
| **Week** | | | | | **2** | **3** | **4** | **7** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** | |
| ACTH | D | 7.2.2.5.3 | X | | | Every 3 months, if ACTH hypersecretion at baseline | | | | | | | | | | | | | | | |
| Serum lipid profile | D | 7.2.2.5.6 | X | | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Thyroid function test | D | 7.2.2.5.7 | X | | | | | | | X | | | X | | | | | | | X | |
| Urinalysis | D | 7.2.2.5.8 | X | X | X | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Pregnancy test | D | 7.2.2.5.9 | X | X | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | |
| CgA and 5HIAA | D | 7.2.1.2 | X | | | | | | | X | | | X | | | X | | | X | X | |
| **Imaging/Other assessments** | | | | | | | | | | | | | | | | | | | | | |
| Tumor evaluation | D | 7.2.1.1 | X | | | | | | | X | | | X | | | X | | | X | X | |
| Gallbladder assessment | D | 7.2.2.6.4 | X | | | | | | | X* | | | X* | | | X* | | | X* | X* | |
| Pulmonary Function Test | D | 7.2.2.6.2 | As medically indicated | | | | | | | | | | | | | | | | | | |
| Bronchoscopy | D | 7.2.2.6.3 | As medically indicated | | | | | | | | | | | | | | | | | | |
| ECG | D | 7.2.2.7.1 | X | X | | X | | | X | | X | | | X | | | X | | | X | |
| Cardiac imaging (ECHO or MUGA scan) | D | 7.2.2.7.2 | X | As medically indicated | | | | | | | | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | | | | | | | | | |
| Adverse events | D | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

[redacted]

[redacted]

| | Category | Reference to Section 7.2 | Screening Baseline | Core study | | | | | | | | | | | | | | | | End of core study/Early withdran (EOS) | Safety FU visit ** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | |
| **Study Day** | | | **-28 to-1** | **1** | **15** | **21** | **29** | **49** | **57** | **85** | **113** | **141** | **169** | **197** | **225** | **253** | **281** | **309** | **337** | | |
| **Week** | | | | | **2** | **3** | **4** | **7** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** | |
| [redacted] | | | | | | | | | | | | | | | | | | | | | |
| Contact IVRS for randomization | | | X | | | | | | | | | | | | | | | | | | |
| Pasireotide LAR injections (q28d) | D | | | X | | | X | | X | X | X | X | X | X | X | X | X | X | X | X*** | |
| Everolimus administration (daily) | D | | | Daily*** | | | | | | | | | | | | | | | | | |
| Core study completion | D | | | | | | | | | | | | | | | | | | | X | |

*Only for patients treated with pasireotide LAR
** The safety FU visit should be performed only for patients who prematurely discontinue study treatment or experience disease progression at week 52. The visit should be performed 56 days after the last dose of pasireotide LAR or everolimus, whichever comes last.
***Pasireotide LAR injection and everolimus should be given at V18 only to patients that continue the extension phase

[redacted]

**Table 7-2 EXTENSION PHASE - Visit evaluation schedule**

| | Category | Reference to Section 7.2 | Extension phase | | | | | End of extension phase /Early withdrawn | Safety FU visit** |
|---|---|---|---|---|---|---|---|---|---|
| **Visit No.** | | | 1 | 2 | 3 | 4 | | | |
| **Month of extension phase** | | | 3 | 6 | 9 | 12 | Every 3 mos | | |
| Vital signs | D | 7.2.2.2 | X | X | X | X | X | X | |
| Physical examination | S | 7.2.2.1 | X | X | X | X | X | X | |
| Weight | D | 7.2.2.3 | X | X | X | X | X | X | |
| WHO performance status | D | 7.2.2.4 | X | X | X | X | X | X | |
| Tumor evaluation, frequency at investigator's discretion*** | D | 7.2.1.1 | X | X | X | X | X | X | |
| Gallbladder assessment, frequency as per tumor evaluation at investigator's discretion | D | 7.2.2.6.4 | X* | X* | X* | X* | X* | X* | |
| Pulmonary Function Test | D | 7.2.2.6.2 | As medically indicated | | | | | | |
| Bronchoscopy | D | 7.2.2.6.3 | As medically indicated | | | | | | |
| Chest X-ray, or Chest CT scan | D | 7.2.2.6.1 | As medically indicated | | | | | | |
| ECG | D | 7.2.2.7.1 | X | X | X | X | X | X | |
| Cardiac imaging (ECHO or MUGA scan) | D | 7.2.2.7.2 | As medically indicated | | | | | | |
| Hematology | D | 7.2.2.5.1 | X | X | X | X | X | X | |
| Biochemistry | D | 7.2.2.5.3 | X | X | X | X | X | X | |
| Fasting glucose/insulin/HbA1c (everolimus monotherapy) | D | 7.2.2.5.4 | X | X | X | X | X | X | |
| Fasting glucose/insulin/HbA1c (combination) | D | 7.2.2.5.4 | X | X | X | X | X | X | |
| Fasting glucose/insulin/HbA1c pasireotide LAR monotherapy | D | 7.2.2.5.4 | X | X | X | X | X | X | |
| Blood glucose self monitoring (if applicable) | | 7.2.2.5.4 | Continuous | | | | | | |
| Liver Function Tests | D | 7.2.2.5.5 | X | X | X | X | X | X | |

[redacted]

| | Category | Reference to Section 7.2 | Extension phase | | | | | End of extension phase /Early withdrawn | Safety FU visit** |
|---|---|---|---|---|---|---|---|---|---|
| **Visit No.** | | | 1 | 2 | 3 | 4 | | | |
| **Month of extension phase** | | | 3 | 6 | 9 | 12 | Every 3 mos | | |
| Coagulation (INR) | D | 7.2.2.5.2 | X | X | X | X | X | X | |
| CgA and 5HIAA**** | D | 7.2.1.2 | | X | | X | | | |
| Urinalysis | D | 7.2.2.5.8 | X | X | X | X | X | X | |
| Serum lipid profile | D | 7.2.2.5.6 | X | X | X | X | X | X | |
| Pregnancy test | D | 7.2.2.5.9 | X | X | X | X | X | X | |
| Monitoring of HBV-DNA, HCV RNA-PCR (if applicable) | D | | Every 4 weeks as indicated in Section 6.1.4.8 | | | | | | |
| Anti-HAV, IgM, HbsAg, Anti-HBc, anti-HCV (if positive, PCR viral load should be assessed), Anti-HEV, ANA antibodies, anti-smooth muscle antibodies, CMV and EBV | D | | If LFTs meet criteria reported in Section 6.1.5 | | | | | | |
| Pasireotide LAR injections (q28d) | D | | Every 28 days from V18 of Core phase | | | | | | |
| Everolimus administration (daily) | D | | Daily from V18 of Core phase | | | | | | |
| Adverse events | D | | X | X | X | X | X | X | X |
| Concomitant medications | D | | X | X | X | X | X | X | X |
| Study completion | D | | | | | | | X | |

*Only for patients treated with pasireotide LAR
**The safety follow up visit should be performed 56 days after the last dose of pasireotide LAR or everolimus, whichever comes last.
*** Patients who discontinue study treatment after 12 months of treatment without evidence of progression or for reasons other than disease progression will continue to have tumor evaluation assessments until disease progression or last patient last visit (LPLV) whichever occurs first.
**** CgA and 5HIAA will only be collected until extension visit 4.

[redacted]

### 7.1.1 Pre-screening assessments

Not applicable.

### 7.1.2 Screening

#### 7.1.2.1 Eligibility screening

The principal investigator is responsible for patient's eligibility.

#### 7.1.2.2 Information to be collected on screening failures

Patients who complete the informed consent process and do not meet all entry criteria and therefore who do not receive first dose of study drug(s) will be considered screen failures. For screening failure patients, no data will be entered in the clinical database, except for the reasons of screening failure.

#### 7.1.2.3 Patient demographics and other baseline characteristics

Patient demographics and baseline characteristics will include the following: demography, medical history/current medical conditions (including cancer-related conditions and symptoms), diagnosis and extent of cancer, prior anticancer therapies taken, disease-related symptoms, prior/concomitant medication taken, physical examination, WHO performance status, vital signs, weight and height, hepatitis B and C screening, hematology, blood chemistry, coagulation panel, urinalysis, pregnancy test required for women of childbearing potential, ECG.

### 7.1.3 Treatment period

This study has a treatment duration of 12 months (core study). Patients will either start pasireotide LAR or everolimus treatment or a combined treatment of both pasireotide LAR and everolimus regimens at visit 2.

### 7.1.4 End of core study visit, including premature withdrawal and study discontinuation visit

Patients who discontinue study treatment should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the end of core study visit/early withdrawn will be performed. Study treatment discontinuation in the pasireotide LAR plus everolimus arm is defined as the withdrawal of both study drugs; the date and reason for stopping the study treatment should be reported in the CRF. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations 56 days after the last dose of pasireotide LAR or everolimus, whichever comes last.

#### 7.1.4.1 Criteria for premature patient withdrawal

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

1. Disease progression
2. Unacceptable toxicity / adverse events which are not listed below
3. Clinically significant abnormal lab values
4. Clinically significant abnormal test procedure results
5. Protocol violation
6. Administrative problems
7. Pregnancy
8. Patient withdrawing informed consent
9. New anticancer therapy
10. Patient lost to follow-up
11. Death

In addition to the general withdrawal criteria, the following **study specific criteria** will also require study treatment discontinuation:

1. Patients experiencing unacceptable toxicity as described in Table 6-1, Table 6-2, Table 6-4, Table 6-5, Table 6-6 and Table 6-7.
2. Patient with blood glucose values consistently in excess of 250 mg/dL persisting after interruption of study drug in spite of continuous, appropriate therapeutic intervention(s).
3. Confirmed QTcF >470 msec and discontinuation recommended by a cardiologist after examination of cardiovascular risk factors.
4. Mean QTcF >500 msec measured by triplicate ECGs, and discontinuation recommended by a cardiologist, after ECG re-evaluation and confirmation of a mean QTcF value >500 msec.
5. Significant arrhythmia findings from Holter monitoring such as:
   - Any ventricular or supra-ventricular tachyarrhythmia associated with symptoms of hemodynamic compromise
   - Sustained ventricular tachycardia (>30 sec) irrespective of symptoms
   - Recurrent non-sustained VT (≥ 3 beats) during any 24-hour monitoring period
   - Torsades de Pointes (TdP)
   - Cardiac arrest
   - Pause >5 seconds
   - Second or third degree AV block.
6. New occurrence of clinically significant/symptomatic bradycardia.
7. Increased risk of QT prolongation by use of QT prolonging medication.
8. Hypokalemia (<3.5 mmol/L) or hypomagnesaemia (<0.7 mmol/L or below the LNR as provided by the laboratory) confirmed by repeat testing that is either a new finding or accompanied by vomiting or diarrhea and not corrected by treatment.

[redacted]

9. Abnormal Liver Function Tests such as:
   - ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN and ALP < 2 x ULN;
   - ALT or AST > 5 x ULN and ≤ 8 x ULN persistent for more than 2 weeks;
   - ALT or AST > 8 x ULN.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the CRF.

All patients who discontinue study treatment must have safety evaluations 56 days after the last dose of pasireotide LAR or everolimus, whichever comes last.

All cancer medications/therapies given to a patient up to 56 days after the last dose of study treatment must be recorded in the CRF.

#### 7.1.4.2 Replacement policy

Not applicable.

### 7.1.5 Extension period

Patients who are presenting clinical benefit from the treatment with combination or monotherapy with pasireotide LAR or everolimus and who are not experiencing unacceptable toxicity are permitted to continue treatment after the 12 month treatment period. Patients will have the option to receive therapy as long as they continue to demonstrate benefit and do not fulfill any of the study discontinuation criteria (see Section 7.1.4.1 criteria for premature patient withdrawal) or until the Clinical Trial ceases to be in the interests of the health of the Clinical Trial Subjects, based on the DMC recommendations (see Section 8.6), or until the pasireotide and/or everolimus development programs are discontinued, whichever comes first (see reference to Section 4.4 "Early study termination") .

All patients who discontinue study treatment must have safety evaluations 56 days after the last dose of pasireotide LAR or everolimus, whichever comes last.

All cancer medications/therapies given to a patient up to 56 days after the last dose of study treatment must be recorded in the CRF.

Patients who discontinue study treatment after 12 months of treatment, without evidence of progression or for reasons other than disease progression will continue to have tumor evaluation assessments until disease progression or LPLV whichever occurs first.as described in Section 7.2.1.

Patients lost to follow up should be recorded as such in the CRF. For these patients, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

[redacted]

## 7.2 Assessment types

### 7.2.1 Efficacy assessments

#### 7.2.1.1 Primary efficacy assessment

The primary efficacy endpoint is defined as the proportion of patients who are progression free (i.e. disease control rate) at 9 months according to RECIST V. 1.1 criteria (Eisenhauer et al. 2009).

##### 7.2.1.1.1 Tumor Evaluation

Tumor evaluation (chest, abdomen and pelvis) will be assessed at baseline by means of triphasic CT or MRI. CT scan is the preferred modality and should be used wherever possible. Measurable lesions -i.e., target lesions and the non-target lesions by which subsequent response assessments will be judged- must be identified during tumor assessment at baseline; the disease must be staged and progression confirmed at this time.

The tumor evaluation is to be repeated every 3 months or at EOS if reached earlier. During the extension period, tumor evaluation is recommended every 3 months

All images will be read locally at the site by the reviewer. Clinical decisions will be done locally by the investigator with the local radiologist.

All images will be saved on a CD-rom and locally stored at the site in order to allow any future double check of the tumor assessment, if needed.

Evaluation of the endpoints will be done by a local radiologist together with the investigator.

All patients with bone pain or bone uptake at Octreoscan guided imaging at baseline should repeat the assessment while on treatment (including MRI).

##### 7.2.1.1.2 Response evaluation by RECIST V. 1.1

The same method of assessment and the same technique should be used throughout the study to characterize each identified and reported lesion at baseline and during follow-up.

Each center must have a designated radiologist or other physician responsible for the interpretation of X-rays, MRI or CT scans and the response evaluation according to RECIST V. 1.1 criteria. The same physician should perform the evaluation for the entire duration of the study. All radiology evaluations will be performed by the local physician.

Scans to allow measurement of all target lesions will be performed routinely every 3 months. If an initial observation of partial or complete response is made, a confirmation scan should be obtained no less than 4 weeks and no more than 6 weeks after the initial observation.

Response evaluation will be performed according to the RECIST V. 1.1 criteria (Eisenhauer et al. 2009).

[redacted]

#### 7.2.1.1.3 Baseline requirement

All patients should have at least one measurable disease lesion. Measurable disease lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with minimum lesion size of:

- 10 mm by CT scan (irrespective of scanner type and MRI) (no less than double the slice thickness and a minimum of 10 mm).

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

#### 7.2.1.1.4 Measurement technique

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

#### 7.2.1.1.5 Target lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum of the longest diameter. The baseline sum of the diameters will be used as reference by which to characterize the objective tumor response.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological lymph nodes can be identified as target lesions when measurable (i.e. short axis ≥ 15mm by CT scan). Only the short axis (perpendicular to longest diameter) of these nodes will contribute to the baseline sum.

#### 7.2.1.1.6 Response assessment

Regarding the target lesions:

- partial response (PR) requires at least a 30% decrease in the sum of the diameter of all target lesions, taking as reference the baseline sum of diameters;
- complete response (CR) requires disappearance of all target lesions. Any pathological lymph nodes must have a reduction in short axis to <10 mm. To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeated assessments that should be performed not less than 4 weeks after the criteria for response are first met;

- progressive disease (PD) requires at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Regarding the non-target lesions:

- complete response (CR) is defined as the disappearance of all non-target lesions, and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis);
- non-CR/non-PD is defined as the persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits;
- progression is is defined as unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

For more details on tumor response criteria, please look at RECIST V. 1.1 evaluation criteria (Eisenhauer et al. 2009), and at Appendix 1 (Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival - based on RECIST V. 1.1).

#### 7.2.1.2 Secondary efficacy assessment

##### 7.2.1.2.1 Response assessment

Regarding the response assessment for the secondary efficacy endpoints, please look at the previous section for the primary endpoint ("Response assessment") for more details.

##### 7.2.1.2.2 Biochemical response rate (BRR)

The biochemical response rate (BRR) and biochemical progression will be evaluated on the basis of serum chromogranin A (CgA) levels.

Additionally, the biochemical response on the basis of urine 5-hydroxyindole acetic acid (5HIAA) will be assessed.

Response of CgA is defined as normalization or a ≥30% reduction of serum CgA levels compared to baseline (Kouvaraki et al. 2004; Yao et al. 2010).

Response of 5HIAA is defined as normalization or a ≥50% reduction of urinary 5HIAA levels compared to baseline (Bajetta et al. 1993; Bajetta et al. 2006).

Biochemical progression is defined as an increase of serum CgA levels ≥25% *vs*. baseline (Bajetta et al. 1999; Brizzi et al. 2009).

**CgA / 5HIAA**

The serum parameter CgA and urine 5HIAA will be assessed for all patients at screening, on visits 8, 11 14, 17 and at the end of core study visit/early withdrawn. In patients treated in the extension phase, serum and urine samples will be collected on visits 2, 4. In the course of the study, CgA and 5HIAA are collected at the same time points. In case of an unscheduled tumor evaluation, an additional blood and urine sample will be collected.

[redacted]

For CgA measurements in serum, 5.5 mL blood will be collected. For 5HIAA measurements, urine will be collected for 24 h. From this measurement, 10 mL urine will be analyzed. Serum and urine samples will be analyzed centrally.

[redacted]

It is worth underlining that some foods contain significant amounts of hydroxyindoles that may influence 5HIAA measurements. Thus, patients will be asked to amend their diet for three days before starting urine collection and during the collection to avoid interference with the test. Specifically, patients should avoid food containing high levels of indoles such as avocados, bananas, tomatoes, plums, walnuts, peanuts, almonds, pineapples, eggplants, and smoked fish. Patients will be also asked not to consume coffee, tea, alcohol, vanilla, chocolate, and tobacco for three days before and during urine collection.

### 7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing hematology, blood chemistry, vital signs, ECG tracings, WHO performance status, gallbladder assessment (at baseline for all patients, on treatment only for patients treated with pasireotide LAR), and physical conditions as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

These assessments should be performed ± 7 days during monthly visit period and ± 2 days during the weekly visit period as outlined in Table 7-1, and in Table 7-2 except for adverse events that will be evaluated continuously throughout the study.

Safety and tolerability will be assessed according to the NIH/NCI CTC guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf).

#### 7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

#### 7.2.2.2 Vital signs

Vital signs include blood pressure, pulse, respiration rate and temperature measurements. They will be measured as indicated in Table 7-1 and in Table 7-2 and will be recorded on source documents, repeated at each visit. Other vital signs will be recorded on the CRF if they represent an adverse event.

After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting

[redacted]

measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

#### 7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening visit only; weight will be recorded on the case report form at screening visit and at each visit.

#### 7.2.2.4 Performance status

WHO performance status will be measured as indicated in the assessment schedules (Table 7-1, and Table 7-2), and recorded on the CRF and in the source documents.

**Performance status WHO grade**

| Grade | Status |
|---|---|
| Grade 0 | Fully active, able to carry out all normal activity without restriction. |
| Grade 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| Grade 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| Grade 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| Grade 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| Grade 5 | Dead |

#### 7.2.2.5 Laboratory evaluations

All standard clinical laboratory analyses described below are to be performed by the local laboratory as outlined in Table 7-1 and in Table 7-2. Unscheduled abnormal laboratory evaluations which are clinically relevant (e.g. require dose modification and/or interruption of study drug, indicate changes in previously abnormal values) must be recorded on the Adverse Event page of the CRF. For clinically relevant laboratory values from different local labs, please record actual laboratory value and provide local lab ranges on the CRF, as appropriate.

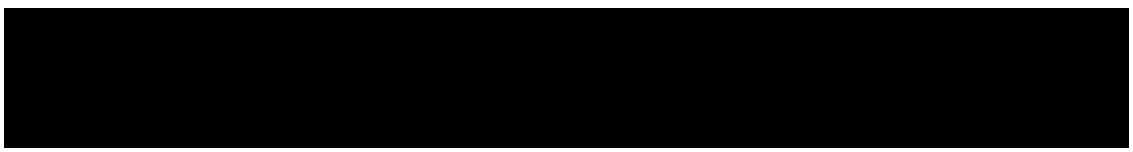
##### 7.2.2.5.1 Hematology

Hematology tests are to be performed at each scheduled visit (± 7 days during monthly visit period and ± 2 days during the weekly visit period) as indicated in Table 7-1 and in Table 7-2. These must include: hemoglobin, hematocrit, platelets, total white blood cell (WBC) count (absolute and, if available, differential including neutrophils, lymphocytes, monocytes, eosinophils, basophils).

If the hematology tests of Visit 1 have been done less than 7 days before treatment start, they should not be repeated on Cycle 1 Day 1.

##### 7.2.2.5.2 Coagulation

The international normalized ratio (INR) will be determined at screening/baseline, at Visits 2, 5, 7, 8 and every 8 weeks thereafter and reported in CRF. It will be determined also at Visits 4 and 6 for patients treated with pasireotide LAR. During the Extension phase, the INR will be



determined every three months. The partial thromboplastin time (PTT) will be determined only at screening/baseline.

#### 7.2.2.5.3 Biochemistry

The following tests will be performed at each scheduled visit (± 7 days during monthly visit period and ± 2 days during the weekly visit period) as indicated in Table 7-1 and in Table 7-2 and will include sodium, potassium, chloride, bicarbonate, creatinine, total protein, uric acid, BUN (or urea, if BUN cannot be directly evaluated), calcium, magnesium, phosphate. If the biochemistry tests of Visit 1 have been done less than 7 days before treatment start, they should not be repeated on Cycle 1 Day 1.

One pre-dose, blood draw for plasma ACTH will be taken at visit 1 (baseline). In patients with ACTH hypersecretion at baseline, ACTH will be tested during the study every 3 month (± 7 days).

#### 7.2.2.5.4 Glucose, Insulin and HbA1c

Glucose, insulin, and glycated hemoglobin (HbA1c) will be assessed in fasting conditions at the visits outlined in Table 7-1 and in Table 7-2.

Blood glucose will not be assessed at visit 6 in patients treated with everolimus monotherapy, unless medically indicated.

Please refer to Section 6.1.4.5 for additional detailed guidance on the combination and pasireotide LAR monotherapy arms.

For patients in the combination and pasireotide LAR monotherapy arms with normal glucose metabolism at baseline, fasting blood glucose will be self-measured once daily for the first 2 month, then twice a week for the next 2 months and once a week thereafter throughout the study.

All patients with abnormal glucose metabolism or at risk to develop this condition at screening or later at any time will self-measure blood glucose by fingerstick twice daily (one fasting and one 2-hour post-prandial). All patients will enter the results in the patient diary. Patient diaries will not be collected by the sponsor.

#### 7.2.2.5.5 Liver Function Tests

The following tests will be performed at each scheduled visit (± 7 days during monthly visit period and ± 2 days during the weekly visit period) as indicated in Table 7-1, and in Table 7-2 and will include albumin, SGOT (AST), SGPT (ALT), total bilirubin (fractionate to direct/indirect bilirubin if total bilirubin is > 2.0 x ULN), alkaline phosphatase and GGT.

For patients treated with pasireotide LAR: the Day 21 and Day 49 LFTs should be available and assessed prior to dosing on Day 29 (2$^{nd}$ LAR injection) and Day 57 (3$^{rd}$ LAR injection).

#### 7.2.2.5.6 Lipid profile

A lipid profile (cholesterol, triglycerides, LDL, HDL) will be determined at screening/baseline, at visit 3 and repeated every month (± 7 days). During the Extension phase,

[redacted]

lipide profile will be determined every three months. The patient must be in a fasting status at the time of blood sampling for this evaluation.

#### 7.2.2.5.7 Thyroid Function Test

Thyroid function test (TSH, free T3 and T4), and B12 vitamin will be collected at screening/baseline, at week 12 (visit 8) (± 7 days), at week 24 (visit 11) (± 7 days) and at EOS.

#### 7.2.2.5.8 Urinalysis

A standard urinalysis assessment (pH, protein, glucose, blood, ketones, and leukocytes) using a dipstick will be performed at screening/baseline and at each scheduled visit as indicated in Table 7-1, and in Table 7-2. If any positive findings, a microscopic laboratory urinalysis has to be performed.

#### 7.2.2.5.9 Pregnancy and assessments of fertility

All females of childbearing potential should have a negative serum pregnancy test at screening (i.e., within 14 days of randomization) and a negative urine/serum pregnancy test at visit 2 (i.e., randomization visit). **Highly effective contraception must be used while on study and up to 56 days (8 weeks) after last dose of pasireotide LAR and/or everolimus treatment, whichever comes last.**

Postmenopausal women must have been amenorrheic for at least 12 months or have a serum FSH >40 mIU/ml to be considered "of non-childbearing potential" or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception;
- Female sterilization: have had surgical bilateral oophorectomy with or without hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment;
- Male sterilization: with appropriate post-vasectomy documentation of the absence of sperma in the ejaculateat least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Combination of any two of the following (a+b or a+c, or b+c):
  a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception;
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

[redacted]

Sexually active males must use a condom during intercourse while taking the treatment and for 2 months after the last dose of study treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. Female partners of male patients must be also advised to use one of the following contraception methods:

- Use of oral, injected or implanted hormonal methods of contraception or other approved hormonal methods of contraception;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Total abstinence or patient sterilization (male or female).

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

A serum/urine pregnancy test should be repeated every month while on treatment and at the end of the core study visit. If the patient continues treatment in the extension phase, a serum/urine pregnancy test should be repeated at each scheduled visit, i.e., every 3 months.

#### 7.2.2.5.10 Hepatitis screening

**Screening for Hepatitis B**

Prior to randomization, all patients must be tested for Hepatitis B viral load and serologic markers, that is: Hepatitis B Virus –Deoxyribonucleic acid (HBV-DNA), Hepatitis B surface antigen (HBsAg), Hepatitis B surface Antibody (HBsAb), and Hepatitis B core Antibody (HBcAb).

If a patient tests positive for the presence of HbsAg and/or HBV-DNA, he/she will be considered ineligible for the study according to Exclusion Criterion #16. In case of eligibility, the results from the other two tests (HBsAb and HBcAb) will detect which patients have to be monitored for the risk of hepatitis B reactivation approximately every 4 weeks (± 1 week) during the study.

Please note that patients whose test is negative for HBV-DNA, HBsAg, and HBcAb but positive for HBsAb with prior history of vaccination against Hepatitis B will be eligible. The fact that the patient had been vaccinated should be entered in the patient's eCRF ("Medical history" page).

Management guidelines for the risk of hepatitis B reactivation are provided in Section 6.1.4.8 according to the results of the baseline assessments of viral load and serological markers for hepatitis B.

**Screening for Hepatitis C**

Prior to randomization, all patients will be tested for the presence of HCV-RNA-PCR..

[redacted]

If a patient tests positive for HCV-RNA-PCR, he/she will be considered ineligible for the study according to Exclusion Criterion #16.

Patients known to have a history of HCV infection, despite a negative viral load test at baseline (including those that were treated and are considered "cured") should be monitored every 4 weeks (± 1 week) for the risk of hepatitis C reactivation.

Management guidelines for the risk of hepatits C reactivation are provided in Section 6.1.4.8..

#### 7.2.2.6 Radiological examinations

##### 7.2.2.6.1 Monitoring for pneumonitis

If the baseline scan shows signs suggestive of interstitial lung disease (ILD)/non-infectious pneumonitis, it is at the discretion of the investigator to follow the patient with appropriate chest imaging. For all other patients, chest X-ray or chest CT scans are to be performed during the study if clinically indicated e.g. if there is suspicion of non-infectious pneumonitis, in the investigator's discretion.

##### 7.2.2.6.2 Monitoring for Pulmonary Function Test

At screening/baseline, prior to administration of study drug, pulmonary function tests (PFT) can be performed, if clinically indicated. During study treatment, all PFTs (spirometry, DLCO and room air $O_2$ saturation at rest) must be performed if the patient develops non-infectious pneumonitis, according to the management guidelines addressed in Table 6-2.

##### 7.2.2.6.3 Bronchoscopy

A bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL) will be performed only when medically necessary for ensuring patient care. When non-infectious pneumonitis is diagnosed, consultation with a pulmonologist should be considered. Further details are provided in Section 6.1.4.7.

##### 7.2.2.6.4 Gallbladder Assessment

The gallbladder evaluation (MRI/CT) will be performed together with the radiological tumor assessment at baseline for all patients, on treatment only for patients treated with pasireotide LAR as outlined in Table 7-1 and in Table 7-2.

If the patient discontinues treatment, an EOS visit MRI/CT scan has to be performed only if the EOS visit occurred 3 months or more after the previous MRI/CT scan.

Significant findings that are present prior to the start of study treatment must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant findings made after the patient signed the ICF or worsening of those reported at screening/baseline and which meet the definition of an AE must be recorded on the AE CRF.

[redacted]

### 7.2.2.7 Cardiac assessments

#### 7.2.2.7.1 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at baseline and at the visits outlined in Table 7-1 and in Table 7-2.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported in CRF. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study.

ECG may be repeated at the discretion of the investigator at any time, as clinical indicated. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

Safety data captures should include the following:

- Any abnormal ECG findings (please refer to Section 6.1.4.9);
- Abnormal vital signs;
- All arrhythmias, including: Torsades de Pointes, ventricular tachycardia, ventricular fibrillation, and ventricular flutter;
- Syncope, near-syncope and fainting;
- Convulsions or loss of central function (sudden incontinence, dizziness, vision disturbances).

#### 7.2.2.7.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

All patients will have an echocardiogram or MUGA scan at screening and when it is indicated clinically during the study.

### 7.2.3 Pharmacokinetics

Not applicable.

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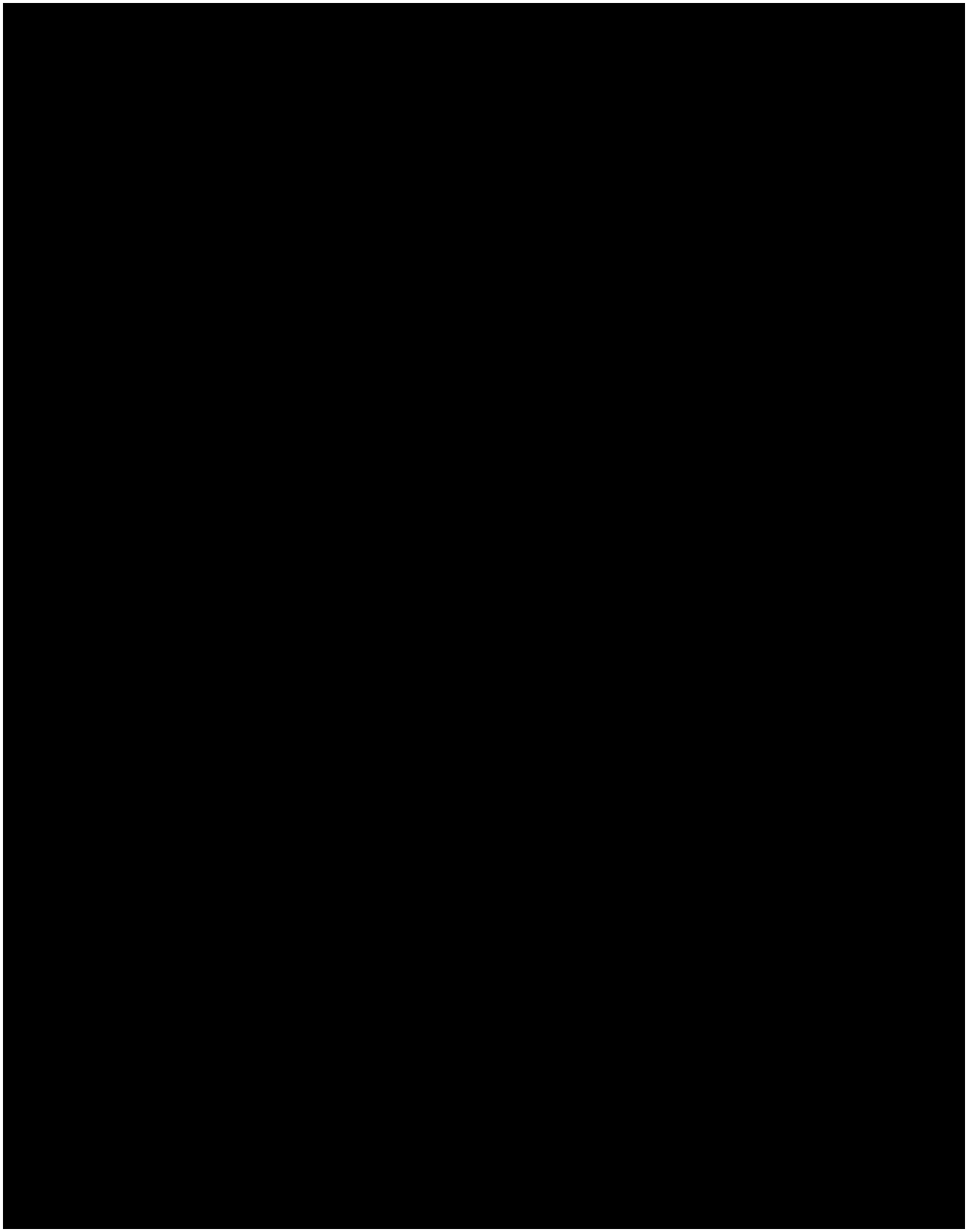
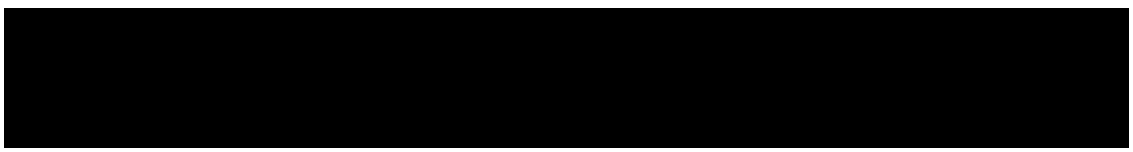
[redacted]





### 7.2.5 Other assessments

No additional tests will be performed on patients entering this study.

# 8 Safety monitoring and reporting

## 8.1 Adverse events

### 8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the CRF. Adverse event monitoring should be continued for at least 56 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the "Study evaluation completion – Core"form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4);
2. Its duration (Start and end dates);
3. Its relationship to pasireotide LAR or everolimus or combination pasireotide LAR and everolimus (Reasonable possibility that AE is related: No, Yes);
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable);
5. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy);

[redacted]

6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown);
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (as per RECIST criteria), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about common adverse effects already known about the investigational drug can be found in the [Investigator's Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

### 8.1.2 Laboratory test abnormalities

#### 8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

### 8.1.3 Adverse events of special interest

Not applicable.

[redacted]

## 8.2 Serious adverse events

### 8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly/birth defect;
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above;
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Protocol exempt SAEs: SAEs specifically defined in the protocol and where there has been a clear agreement with regulators not to collect these SAEs in the safety database, provided the information is collected elsewhere. For example, this may include serious adverse events that are also a primary outcome measure, such as mortality, survival rate or number of flares of the condition being studied.

### 8.2.2 Reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and until 56 days after the patient received the last dose of treatment, respectively must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder

[redacted]

provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

## 8.3 Emergency unblinding of treatment assignment

Not applicable.

## 8.4 Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Preclinical data regarding reproductive toxicity of everolimus is described in the most recent Investigator Brochure. Based on non-clinical findings (rats), male and female fertility may be compromised by treatment with everolimus. In addition, this agent crosses the placenta and is toxic to the conceptus. In rats, everolimus caused embryo/fetotoxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced fetal weight.

The potential for everolimus to cause infertility or reproductive risk in male and female patients is unknown. However, due to the observed malformations in rats, everolimus should be considered potentially teratogenic. In addition, menstrual irregularities, amenorrhea (including secondary amenorrhea), and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed.

[redacted]

Regarding pasireotide, there are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity, and effects on female reproductive parameters when pasireotide was administered via the subcutaneous route; however, the potential risk for humans is not known.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus or pasireotide and up to 8 weeks after treatment has been stopped. If a pregnancy occurs while on study treatment, the newborn will be followed for at least 12 months.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

It is not known whether everolimus and pasireotide are excreted in human breast milk. However, in *in vivo* studies everolimus (and/or its metabolites) and pasireotide readily passed into the milk of lactating animals. Women taking everolimus should therefore not breast-feed.

## 8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

## 8.6 Data Monitoring Committee

An external Data Monitoring Committee (DMC) will be instituted before study start. It is expected that the DMC will consist of at least two physicians and one independent statistician. The DMC will review safety-related issues and will be entitled to make recommendations for changes in study conduct. Details on the function of the DMC will be laid out in a separate DMC Charter prepared and approved by both Novartis and the DMC.

Member of the DMC will not be involved in patient recruitment or trial conduct.

## 8.7 Steering Committee

The general role of the study Steering Committee (SC) is to oversee and provide guidance on study conduct and to help ensure delivery of study data. The SC will support the Novartis clinical team on a continuous basis when questions arise in the trial. The SC will monitor and supervise the progress of the trial towards its objectives. The members of the SC will be appointed by Novartis and comprise of three investigators. The SC will also include two Novartis physicians (one covering the role of Clinical Trial Head), a statistician, and the Clinical Trial Manager. Clinical experts not directly involved in the clinical trial may be added after consultation with the SC. The committee will be chaired and co-chaired by an external (non-Novartis) expert.

The SC chair will play a specific role in controlling the flow of the trial information, in being the primary contact to receive the recommendations from the IDMC at any safety data

[redacted]

review and at the interim analyses, and in further communicating this information as appropriate.

Additional details on the safety monitoring and the role of the Steering Committee will be provided in the Steering Committee charter.

# 9 Data collection and management

## 9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

## 9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

[redacted]

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

No information in source documents about the identity of the patients will be disclosed.

## 9.3 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements; Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check have been created to detect data discrepancies in the eCRFs and to allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

[redacted]

## 9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

# 10 Statistical methods and data analysis

This is a multicenter, phase II trial evaluating the treatment of pasireotide LAR and everolimus in patients with well differentiated neuroendocrine carcinoma of the lung and thymus randomized to one of the following arms:

[redacted]

- Arm 1: pasireotide LAR alone;
- Arm 2: everolimus alone;
- Arm 3: pasireotide LAR and everolimus.

The study is designed to assess the activity, safety, and tolerability of the therapy with pasireotide LAR and/or everolimus in each arm separately following a Fleming single-stage design. Each arm is independently evaluated using the decision rules given in the sample size calculation (see Section 10.8). If 2 or 3 arms are accepted the selection of the best arm will be based on a risk/benefit evaluation including the incidence of grade 3-4 adverse events, the incidence of serious adverse events, the frequency of treatment modifications as key safety parameters to be taken into account in the final decision.

The data will be analyzed by Novartis and/or by the designated CRO. Any data analysis carried out independently by the investigator(s) should be submitted to Novartis before publication or presentation. It is planned that the data from participating centers in this protocol will be combined within each of the arms, so that an adequate number of patients will be available for analysis.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements. Categorical data will be presented as absolute frequencies and percentages. For continuous data, N, mean, standard deviation, minimum, median, and maximum will be presented. Time to event data will be analyzed using the Kaplan-Meier methodology and will be presented as Kaplan-Meier plots and/or Kaplan-Meier estimates.

Efficacy and safety analyses will be conducted on all patient data at the time all patients who are still receiving study drug will have completed 12 months of treatment. The additional data for any patients continuing to receive study drug past this time, as allowed by the protocol, will be further summarized in a report once these patients completed the study (extension phase of the clinical study report).

## 10.1 Analysis sets

The following analysis sets will be defined for each study arm separately:

### 10.1.1 Full Analysis Set

The full analysis set (FAS) consists of all patients who received at least one dose of study drug. Following the intent-to-treat (ITT) principle, patients will be analyzed according to the treatment and stratum they were assigned to at randomization.

### 10.1.2 Safety Set

It consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the safety set. Patients will be analyzed according to the study treatment (regimen) they actually received.

[redacted]

### 10.1.3 Per-Protocol Set

It consists of all FAS patients without major protocol violations, such as: (1) no histologically confirmed diagnosis of unresectable advanced well differentiated neuroendocrine carcinoma, (2) prior therapy with mTOR inhibitors (e.g sirolimus, temsirolimus, everolimus) (3) prior treatment with long-acting somatostatin analogs (not as rescue medication) within one month prior randomization (4) sign of recurrence of prior or concomitant malignancies (within the last 3 years or requiring active treatment) other than NET with the exception of previous basal cell skin cancer, previous cervical carcinoma in situ (5) any current or prior medical condition that may interfere with the conduct of the study, (6) study treatment received different from treatment assigned by randomization. Further protocol violations leading to exclusion from the per-protocol (PP) set will be eventually specified in the Novartis Validation and Planning (VAP) document.

The PP set will be identified prior to database lock.

### 10.1.4 Dose-determining analysis set

Not applicable.

### 10.1.5 Pharmacokinetic analysis set

Not applicable.

### 10.1.6 Other analysis sets

Not applicable.

## 10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, the number of valid observations, the number of missing observations, mean, standard deviation, minimum, median, and maximum will be presented.

Baseline characteristics include prior medication, past/current medical conditions, diagnosis and extent of cancer, ECOG performance status and tumor evaluation at baseline.

Medical history will be coded using MedDRA and will be presented by system organ class and MedDRA preferred term. Separate tables will be provided for past medical condition and current medical condition. Prior medication will be coded according to WHO Drug Reference List.

## 10.3 Treatments (study treatment, concomitant therapies, compliance)

The duration of study treatment exposure, dose intensity and relative dose intensity will be summarized descriptively. Frequency of dose reduction (including temporary dose interruption) will be presented together with the reasons for dose adjustments/interruptions.

Concomitant medications and significant non-drug therapies after the start of the study drug will be coded according to the WHO Drug Reference List and will be summarized by ATC class and ATC preferred term.

## 10.4 Primary objective

The primary objective of this trial is to evaluate the efficacy of pasireotide LAR and everolimus alone or in combination in patients with a well differentiated neuroendocrine tumor of the lung or thymus.

### 10.4.1 Variable

The primary efficacy endpoint is defined as the proportion of patients who are progression free at Month 9, based on RECIST 1.1.

All CT scans and MRI will be assessed and validated at the local sites throughout the trial.

### 10.4.2 Statistical hypothesis, model, and method of analysis

Let $p_0$ be the highest proportion of patients progression-free at Month 9 which would indicate that the procedure or treatment is clearly ineffective, and $p_1$ be the minimum required proportion of patients progression-free. The trial tests the null hypothesis H0 that the proportion of patients progression-free, $p$, is less than or equal to $p_0$ against the alternative hypothesis H1 that $p$ is greater than or equal to $p_1$. It consists of entering a predetermined number of subjects and deciding in favor of $p_0$ or $p_1$ based on the success rate observed by using an appropriate cut-off between $p_0$ or $p_1$. In a single-stage design, if the number of responses is greater than or equal to R+1, the hypothesis that $p$ is less than or equal to $p_0$ is rejected. If the number of responses is less than or equal to R, the hypothesis that $p$ is greater than or equal to $p_1$ is rejected. Details on $p_0$, $p_1$ and R are reported in Section 10.8.

The number and percentage of patients progression-free at Month 9 will be presented for the FAS together with the appropriate exact confidence interval.

### 10.4.3 Handling of missing values/censoring/discontinuations

The definition of the primary variable is based on RECIST 1.1 criteria.

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, nontarget lesion response and presence of new lesions as shown below in Table 10-1.

**Table 10-1 Overall lesion response at each assessment**

| Target lesions | Non-target lesions | New Lesions | Overall lesion response |
|---|---|---|---|
| CR | CR | No | CR[1] |
| CR | Non-CR/Non-PD | No | PR |
| CR, PR, SD | UNK | No | UNK |
| PR | Non-PD and not UNK | No | PR[1] |
| SD | Non-PD and not UNK | No | SD[1, 2] |
| UNK | Non-PD or UNK | No | UNK[1] |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |
| CR, PR, SD | UNK | No | UNK |

[redacted]

| Target lesions | Non-target lesions | New Lesions | Overall lesion response |
|---|---|---|---|
| [1]This overall lesion response also applies when there are no non target lesions identified at baseline.<br>[2]Once confirmed PR was achieved, all these assessments are considered PR. | | | |

The evaluation of overall lesion response at Month 9 will be used for the assessment of the primary efficacy endpoint.

Patients discontinuing the study for any reason prior to the 9 month assessment, or with missing tumor assessment, or with overall lesion response "unknown" will be considered as "non progression-free". Only patients in CR, PR or SD at Month 9 will be considered as "progression-free". Therefore, the proportion of patients who are progression free at 9 months is equivalent to the disease control rate (DCR).

### 10.4.4 Supportive analyses

The number and percentage of patients progression-free will be presented additionally for the PP set together with the appropriate exact confidence interval. Results of supportive analyses will be interpreted purely exploratory.

## 10.5 Secondary objectives

Secondary efficacy variables will be analyzed in the FAS. Time to event endpoints will be analyzed by Kaplan-Meier (KM) method. Frequencies will be reported together with the appropriate exact confidence intervals. All listings and tables will be presented by study arm

### 10.5.1 Key secondary objective(s)

Not applicable.

### 10.5.2 Other secondary efficacy objectives

**Progression-free survival (PFS)** is defined as the time from first study drug administration to objective tumor progression or death from any cause. If a patient has not had an event, PFS is censored at the date of the last adequate tumor assessment. PFS will be analysed in the FAS and PP set by presenting the Kaplan-Meier curve and estimators.

**Disease control rate** (i.e. the proportion of patient showing a best overall response of CR, PR or SD) at 12 months. It will be calculated and displayed with 95 percent exact confidence intervals.

**Time to response** will be defined as the time from start of treatment to the first objective tumor response (PR or CR) observed according to RECIST V. 1.1 criteria. Patients who did not achieve a confirmed PR or CR will be censored using one of the following options:

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case, the PFS event is the worst possible outcome as it means the patient cannot subsequently respond;
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding.

Time to response will be explored by presenting the Kaplan-Meier curve and estimators.

[redacted]

**Duration of response** is defined as the time from onset of the first objective tumor response (CR/PR) to objective tumor progression or death from any cause. Patients not experiencing progression or death will be censored with the date of their last adequate tumor assessment. Duration of response will be explored by presenting the Kaplan-Meier curve and estimators.

**Objective response rate** is defined as the proportion of patients showing a best overall response of CR or PR at 9 and 12 months, according to RECIST V. 1.1 criteria.The objective response rate will be calculated and displayed with 95 percent exact confidence intervals for the full analysis set.

**Best overall response** is defined as the best response recorded from the start of the treatment until disease progression/recurrence, taking as reference for PD the smallest measurements recorded since the treatment started.

**Biochemical response (BR)** is defined in Section 7.2.1.2. BR rate (BRR) is the percentage of patients showing a ≥30% decrease or normalization of serum CgA levels compared to baseline. Additionally, parameters of biochemical response as well as absolute and relative changes from baseline in these parameters will be descriptively summarized .

Additionally, the biochemical response on the basis of urine 5-hydroxyindole acetic acid (5HIAA) will be assessed, with a response being defined as normalization or a ≥ 50% reduction of 5HIAA levels from baseline

**Duration of biochemical response (DBR)** is defined as the time from the first documentation of biochemical response to the first documentation of biochemical progression or to death due to any cause, whichever occurs first. Biochemical progression is defined as an increase of serum CgA levels ≥25% *versus* baseline. DBR data will be censored on the date of the last tumor marker assessment on study for subjects who do not have biochemical progression and who do not die due to any cause while on study.

**Biochemical progression free survival (BPFS)** is the time from first study drug administration to the first documentation of biochemical progression or to death due to any cause, whichever occurs first. BPFS data will be censored on the date of the last tumor marker assessment on study for subjects who do not have biochemical progression and who do not die due to any cause while on study.

### 10.5.3 Safety objectives

#### 10.5.3.1 Safety parameters and analyses

Safety will be evaluated using assessment of adverse events and laboratory data. The assessment of safety will be based mainly on the frequency of adverse events. Other safety data (e.g. vital signs) will be considered as appropriate.

##### 10.5.3.1.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by study arm

The overall observation period will be divided into three mutually exclusive segments:

[redacted]

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 56 days after last dose of study medication
3. Post-treatment period: starting at day 56+1 after last dose of study medication.

#### 10.5.3.1.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Adverse events will be coded using MedDRA. The incidence of treatment-emergent adverse events will be summarized by system organ class, severity (based on CTC grades), type of adverse event, and relation to the study drug by study arm. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and study arm.

All information pertaining to AE noted during the study will be listed by treatment group and patient, detailing verbatim given by the investigator, the preferred term, the body system, start/end dates, severity, seriousness, relationship to study drug and action taken. The AE onset will also be displayed relative (in number of days) to the day of the first dose of study medication. AE occurring before start of study drug or 57 or more days after the discontinuation of study medication will not be considered as treatment-emergent and will not be included in AE summary tables but will be listed only.

#### 10.5.3.1.3 Laboratory abnormalities

All laboratory values will be converted into SI units; for laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see NCI 2009), the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Frequency table for newly occurring on-treatment grades 3 or 4.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high /(low and high) classification to compare baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

#### 10.5.3.1.4 Other safety data

**ECG**

- Data from ECG will be listed and notable values will be flagged.
- Shift table from baseline to worst on-treatment result and summary statistics of changes from baseline will be provided for QTcF.

Number and percentage of patients with clinically notable QTcF interval values will be summarized.

**Vital signs**

Vital signs variables include measurements of oral body temperature, systolic and diastolic blood pressures, pulse and body weight.

Data on vital signs will be descriptively analysed and listed. Notable values will be flagged; definitions of notably abnormal results will be specified in the statistical analysis plan.

#### 10.5.3.1.5 Supportive analyses for secondary objectives

Not applicable.

#### 10.5.3.1.6 Tolerability

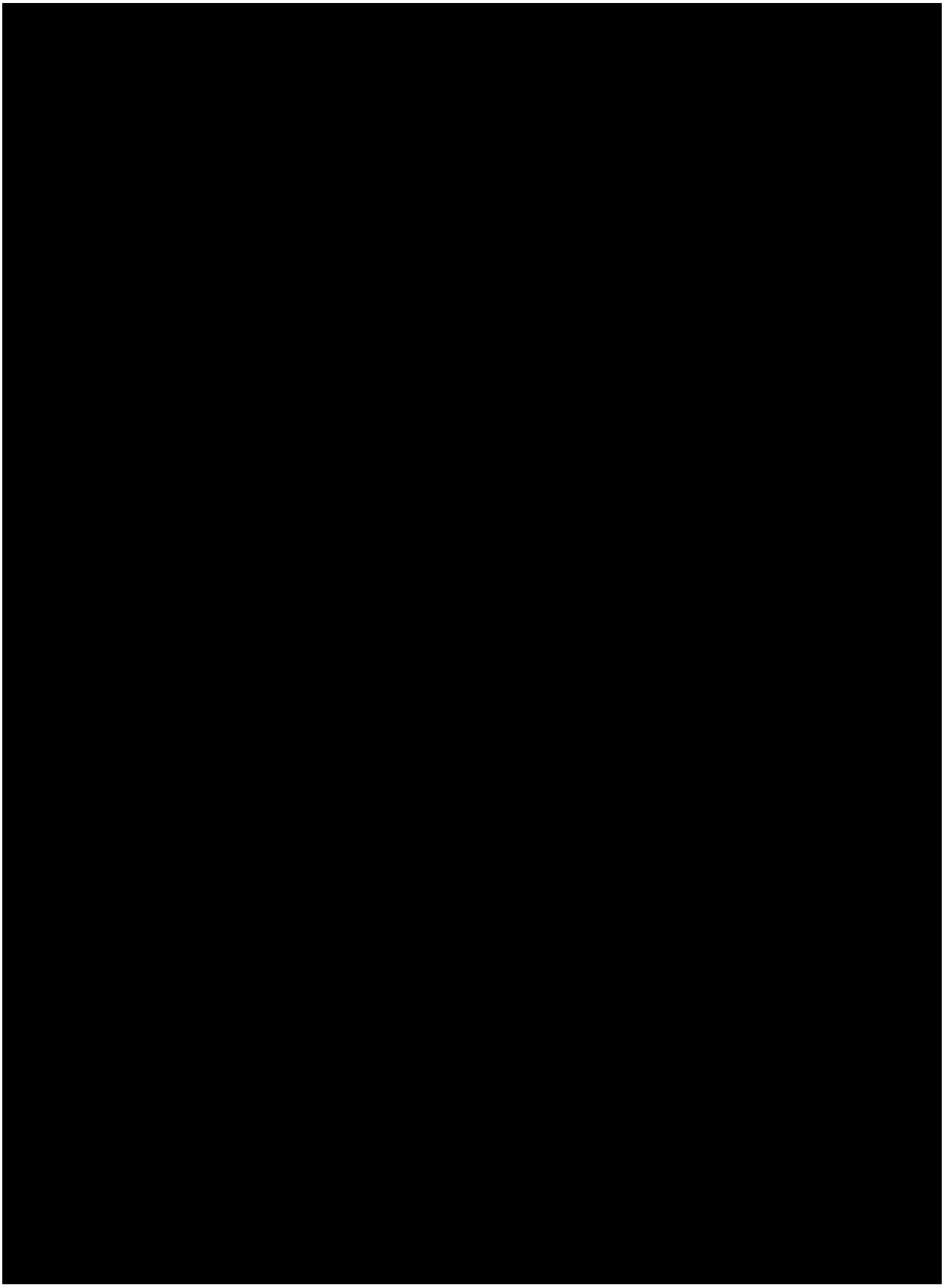
Not applicable.

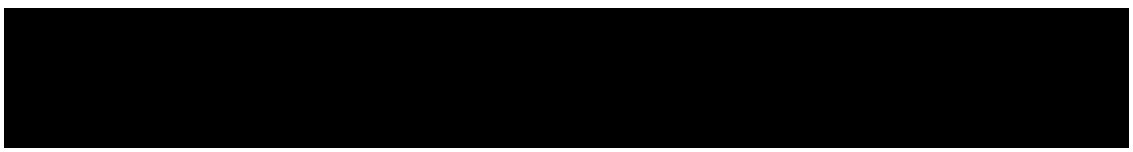
### 10.5.4 Pharmacokinetics

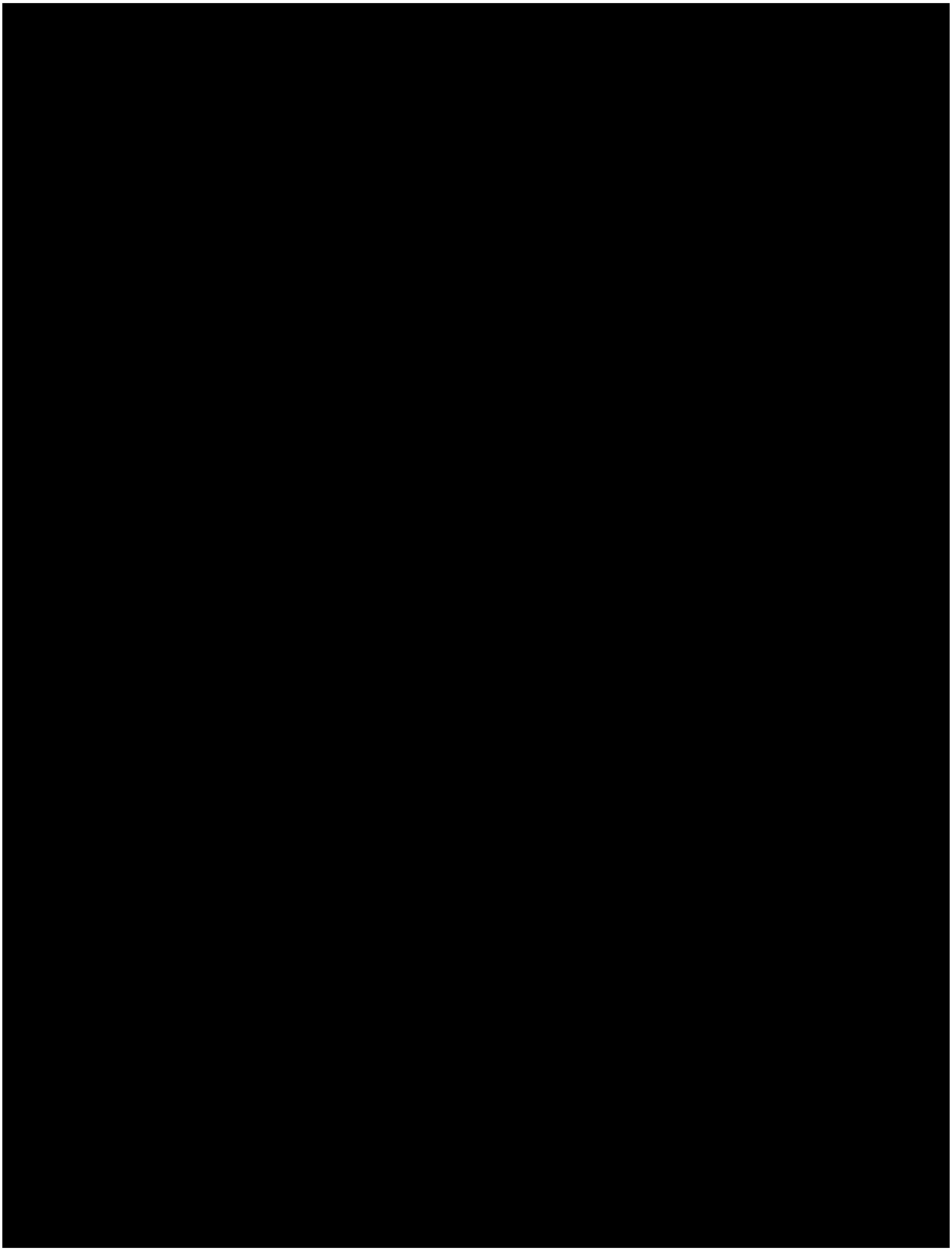
Not applicable.

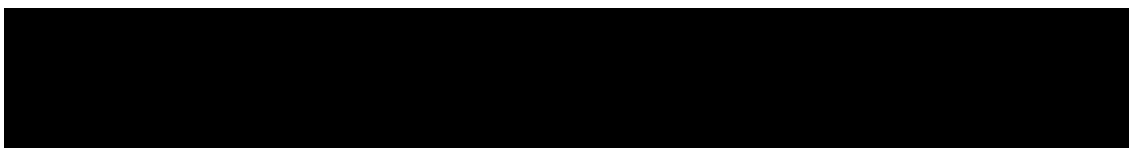
[redacted]

[redacted]









## 10.7 Interim analysis

Not applicable. No interim analysis will be performed.

## 10.8 Sample size calculation

A Fleming single stage design will be employed for each arm. Let $p_0$ be the highest proportion of patients progression-free at Month 9 which would indicate that the treatment is clearly ineffective, and $p_1$ be the minimum required proportion of patients progression-free. The trial tests the null hypothesis H0 that the observed proportion of patients progression-free, p, is less than or equal to $p_0$ against the alternative hypothesis H1 that p is greater than or equal to $p_1$. It consists of entering a predetermined number of subjects and deciding in favor of $p_0$ or $p_1$ based on the success rate observed by using an appropriate cut-off between $p_0$ and $p_1$. If the number of responses is greater than or equal to R+1, $p_0$ is rejected. If the number of responses is less than or equal to R, $p_1$ is rejected.

In this trial, p0 and p1 have been set equal to 0.20 and 0.45, respectively. Forty (40) patients are planned to be randomized in each treatment group. If the number of responses is 13 or more, the hypothesis that $p \leq p0 = 20\%$ is rejected with a target alpha error rate of 5% and an actual alpha error rate of 4.3%; if the number of responses is 12 or less, the hypothesis that $p \geq p1 = 45\%$ is rejected with an actual beta error rate of 4%.

**Table 10-2 Design features for single-arm trials**

| p0 | p1 | Target | | Cut-Off R + 1 | N | Actual | |
|---|---|---|---|---|---|---|---|
| | | alpha | beta | | | alpha | beta |
| 20% | 45% | 5% | 10% | 13 | 40 | 4.3% | 4% |

## 10.9 Power for anal ysis of key secondary variables

Not applicable.

# 11 Ethical considerations and administrative procedures

## 11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

## 11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a

[redacted]

protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

## 11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide investigators in a separate document with a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

## 11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Other specific conditions for terminating the study are outlined in Section 4.4.

## 11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

[redacted]

## 11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

## 11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

[redacted]

## 11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

## 11.9 Financial disclosures

Financial disclosures should be provided by study personnel who is directly involved in the treatment or evaluation of patients at the site - prior to study start.

# 12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## 12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

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# 14 Appendices

## 14.1 Appendix 1

# Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1) – RECIST Guidelines version 3.1, released on November 29, 2011

Document type: TA Specific Guideline

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Version 3:0: 19-Oct-2009
Version 2:0: 18-Jan-2007
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Authors (Version 3.1): [redacted]

Authors (Version 3): [redacted]

Authors (Version 2): [redacted]

Authors (Version 1): [redacted]

[redacted]

### 14.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.4 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

### 14.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

#### 14.1.2.1 Definitions

##### 14.1.2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.1.3.2.

**Measurable lesions** (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

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- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

#### 14.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.1.3.2.8.

### 14.1.2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

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- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

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- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

#### 14.1.2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- Target lesions: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

##### Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.1.2.1.1.
- **Nodal target**: See Section 14.1.2.1.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

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#### 14.1.2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

##### 14.1.2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

###### 14.1.2.4.1.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

###### 14.12.4.1.2 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a “non-zero size” will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

[redacted]

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

#### 14.1.2.4.2 Determination of target lesion response

**Table 14-1 Response criteria for target lesions**

| Response Criteria | Evaluation of target lesions |
|---|---|
| Complete Response (CR): | Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1] |
| Partial Response (PR): | At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. |
| Progressive Disease (PD): | At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 $mm^2$. |
| Stable Disease (SD): | Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD. |
| Unknown (UNK) | Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3] |

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. Methodology change See Section 14.1.2.2.

### Notes on target lesion response

**Reappearance of lesions**: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.

[redacted]

- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

[redacted]

#### 14.1.2.4.3 Determination of non-target lesion response

**Table 14-2 Response criteria for non-target lesions**

| Response Criteria | Evaluation of non-target lesions |
|---|---|
| Complete Response (CR): | Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis) |
| Progressive Disease (PD): | Unequivocal progression of existing non-target lesions.[1] |
| Non-CR/Non-PD: | Neither CR nor PD |
| Unknown (UNK) | Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline. |

1. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

### Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.1.2.4.2 for assigning PD following a CR for thenon-target lesion response in the presence of non-target lesions nodal lesions should be pplied.

#### 14.1.2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion

[redacted]

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.2.2.

### 14.1.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-3.

**Table 14-3 Overall lesion response at each assessment**

| Target lesions | Non-target lesions | New Lesions | Overall lesion response |
|---|---|---|---|
| CR | CR | No | CR[1] |
| CR | Non-CR/Non-PD[3] | No | PR |
| CR, PR, SD | UNK | No | UNK |
| PR | Non-PD and not UNK | No | PR[1] |
| SD | Non-PD and not UNK | No | SD[1, 2] |
| UNK | Non-PD or UNK | No | UNK[1] |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 14.1.2.4.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

## 14.1.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

[redacted]

#### 14.1.3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status

[redacted]

other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

**Overall response rate (ORR)** is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

**Disease control rate (DCR)** is the proportion of patients with a best overall response of CR or PR or SD.

[redacted]

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

**Early progression rate (EPR)** is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

### 14.1.3.2 Time to event variables

*The protocol should state which of the following variables is used in that study.*

#### 14.1.3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

**Progression-free survival (PFS)** is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

#### 14.1.3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

**Overall survival (OS)** is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

#### 14.1.3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

[redacted]

**Time to progression (TTP)** is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

#### 14.1.3.2.4 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

**Time to treatment failure (TTF)** is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

#### 14.1.3.2.5 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates... If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

**Duration of overall response (CR or PR)**: For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

[redacted]

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

**Duration of overall complete response (CR)**: For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

**Duration of stable disease (CR/PR/SD)**: For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

#### 14.1.3.2.6 Time to response

**Time to overall response (CR or PR)** is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

**Time to overall complete response (CR)** is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

#### 14.1.3.2.7 Definition of start and end dates for time to event variables

**Assessment date**

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the

[redacted]

assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

### Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

### End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.3.2.8).

**Example** (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

#### 14.1.3.2.8 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies

[redacted]

with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

**Table 14-4 Overall lesion response at each assessment: patients with non-target disease only**

| Non-target lesions | New Lesions | Overall lesion response |
|---|---|---|
| CR | No | CR |
| Non-CR/Non-PD[1] | No | Non-CR/non-PD |
| UNK | No | UNK |
| PD | Yes or No | PD |
| Any | Yes | PD |

[1] As defined in Section 14.1.2.4

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

**For ORR** it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

**For PFS**, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

#### 14.1.3.2.9 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

[redacted]

Based on definitions outlined in Section 14.1.3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

**Table 14-5 Options for event dates used in PFS, TTP, duration of response**

| Situation | | Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP | Outcome |
|---|---|---|---|
| A | No baseline assessment | (1) Date of randomization/start of treatment[3] | Censored |
| B | Progression at or before next scheduled assessment | (1) Date of progression<br>(2) Date of next scheduled assessment[2] | Progressed<br>Progressed |
| C1 | Progression or death after **exactly one** missing assessment | (1) Date of progression (or death)<br>(2) Date of next scheduled assessment[2] | Progressed<br>Progressed |
| C2 | Progression or death after **two or more** missing assessments | (1) Date of last adequate assessment[2]<br>(2) Date of next scheduled assessment[2]<br>(3) Date of progression (or death) | Censored<br>Progressed<br>Progressed |
| D | No progression | (1) Date of last adequate assessment | Censored |
| E | Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim | (1) N/A<br>(2) Date of discontinuation (visit date at which clinical progression was determined) | Ignored<br>Progressed |
| F | New anticancer therapy given | (1) Date of last adequate assessment<br>(2) Date of secondary anti-cancer therapy<br>(3) Date of secondary anti-cancer therapy<br>(4) N/A | Censored<br>Censored<br>Event<br>Ignored |
| G | Deaths due to reason other than deterioration of 'Study indication' | (1) Date of last adequate assessment | Censored (only TTP and duration of response) |

1. =Definitions can be found in Section 14.1.3.2.7.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.3.2.7.
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

[redacted]

**Situation E: Treatment discontinuation due to 'Disease progression' without documented progression**: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

**Situation F: New cancer therapy given**: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

### Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

## 14.1.4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

### 14.1.4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

### 14.1.4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source

[redacted]

documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

#### 14.1.4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

[redacted]

#### 14.1.4.4 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

#### 14.1.4.5 Programming rules

The following should be used for programming of efficacy results:

##### 14.1.4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

##### 14.1.4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

[redacted]

#### 14.1.4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

#### 14.1.4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

#### 14.1.4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

#### 14.1.4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 3-2)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.1.3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-

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cancer therapy) has occurred more than the specified period following the last adequate assessment.

- This reason will also be used to censor in case of no baseline assessment.

### 14.1.5 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

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