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Statistical Analysis Plan

Study BLU-285-1101

Study Title: A Phase 1 Study of BLU-285 in Patients with Gastrointestinal Stromal Tumors (GIST) and other Relapsed and Refractory Solid Tumors

Document Date: 26 October 2018

NCT Number: 02508532

STATISTICAL ANALYSIS PLAN

A Phase 1 Study of BLU-285 in Patients with Gastrointestinal Stromal Tumors (GIST) and other Relapsed and Refractory Solid Tumors

Protocol Number: BLU-285-1101

SAP Version:	Date of Statistical Analysis Plan:
Final 1.0	26 Oct 2018

Approval Signatures:

Date

Prepared by:
[redacted]

26 Oct 2018
Date

[redacted]
Prepared by:
[redacted]
Associate Director of Biostatistics, Blueprint Medicines Corporation

26 OCT 2018
Date

[redacted]
Approved by:
[redacted]
Director of Biostatistics, Blueprint Medicines Corporation

26 Oct 2018
Date

[redacted]
Senior Vice President of Clinical Development, Blueprint Medicines Corporation

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
2L	Second-line
3L+	Third-line or later
4L+	Fourth-line or later
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
BP	Blood pressure
C3D1	Cycle 3 Day 1
CBR	Clinical benefit rate
CI	Confidence interval
CR	Complete response
CS	Clinically significant
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CXDX	Cycle X Day X
D842V	Aspartic acid to valine at amino acid 842
DD	Dose-determining
DE	Dose escalation
DOR	Duration of response
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMA	European Medicines Agency
EOT	End-of-treatment
FDA	Food and Drug Administration
GIST	Gastrointestinal stromal tumors
KIT	V-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
KM	Kaplan-Meier
MAF	Mutant allele fractions
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST 1.1	Modified Response Evaluation Criteria in Solid Tumors version 1.1
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NCS	Not clinically significant
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression free survival

Abbreviation	Term
PDGFRα	Platelet-derived growth factor receptor alpha
PK	Pharmacokinetic
PGDx	Personal Genome Diagnostics
PR	Partial response
PT	Preferred term
QD	Once daily
RDI	Relative dose intensity
RE	Response-evaluable
R/R	Relapsed or refractory
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
StdDev	Standard deviation
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumor/lymph nodes/metastasis
TTR	Time to response
US	United States (of America)

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis and data presentations to be performed for Blueprint Medicines Corporation, Protocol Number. BLU-285-1101 (amendment 8 dated 28 Feb 2018) "A Phase 1 Study of BLU-285 in Patients with Gastrointestinal Stromal Tumors (GIST) and other Relapsed and Refractory Solid Tumors." It contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety.

This Phase 1 study consists of Dose Escalation (DE) (Part 1) and Expansion (Part 2).

The Part 2 further breaks down into 3 groups:

- Group 1: Patients who have received treatment with imatinib and at least one other tyrosine kinase inhibitor (TKI) for the treatment of GIST (third-line or later [3L+]), and whose tumor lacks an aspartic acid to valine at amino acid 842 (D842V) mutation in platelet-derived growth factor receptor alpha (PDGFRα)
- Group 2: Patients whose tumor contains a PDGFRα D842V mutation
- Group 3: Patients who have received imatinib and no other TKI for the treatment of GIST (second-line [2L]), and whose tumor lacks a PDGFRα D842V mutation.

The study data will be analyzed and reported based on all patients' data from the Part 1 DE, and the combined Part 1 and Part 2 data by mutation type and/or line of therapy and dose levels with a data cutoff date of 16 Nov 2018 for the clinical study report (CSR). The database will be locked after the completion of the medical review of the data, and identification of protocol deviations, and the data cleaning. The SAP will be finalized and approved prior to the clinical database lock.

At the time of the data cutoff date, the planned enrollment in Part 2 Groups 1 and 2 will be complete, however enrollment to Part 2 Group 3 might be ongoing. An addendum to the CSR analysis will therefore be conducted when all patients in the study have been enrolled and had sufficient treatment duration.

All statistical analyses will be conducted using SAS version 9.3 or higher.

Pharmacokinetic (PK), pharmacodynamic, and analyses of patients who undergo continuous Holter monitoring are not within the scope of this SAP and will be addressed separately.

1.1 Study Design

This is a Phase 1, open-label, first-in-human dose escalation (DE) /dose expansion study designed to evaluate the safety, tolerability, PK, pharmacodynamic, and preliminary antineoplastic activity of avapritinib (also known as BLU-285), administered orally, once daily (QD) in patients with unresectable GIST or other relapsed or refractory (R/R) solid tumors.

The study includes a DE part to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D); and an expansion part to further evaluate the safety and tolerability, and to assess the clinical efficacy of avapritinib at the MTD/RP2D (Figure 1).

Dose Escalation (Part 1)

The DE part of the study will enroll patients with unresectable GIST or a R/R solid tumor. Patients with GIST must have disease that has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase-inhibitor agent, or disease with an D842V mutation in the PDGFRα gene. Patients with an advanced solid tumor other than GIST must have R/R disease without an available effective therapy. A standard 3+3 DE design using cohorts of 3 patients will be employed.

The first cohort of patients will receive avapritinib at a starting dose of 30 mg QD. The DE increment for the first escalation step will be a maximum of 100%; all subsequent DE increments will be a maximum of 50%.

Three patients will be enrolled initially in each cohort and an additional 3 patients (for a total of 6) will be enrolled should the cohort require expansion due to dose limiting toxicity (DLT). After the current escalation cohort is full, up to 3 additional patients, all of whom must have the diagnosis of GIST, may be enrolled into an enrichment cohort that included only 3 patients evaluable for DLT, was reviewed at a DE meeting, and did not exceed the MTD. Enrollment of patients into an enrichment cohort requires written approval from the Sponsor. Data from these patients will allow for further exploration of PK, pharmacodynamic, safety, , and anit-tumor activity in patients with GIST.

In cohorts in which the administered dose is <100 mg QD, enrolled patients may have the diagnosis of either GIST or a R/R solid tumor. To assure that the safety profile of avapritinib is adequately described in patients with GIST, at least 2 of 3 patients in each cohort (4 of 6 patients if the cohort is expanded) dosed at ≥100 mg QD must have the diagnosis of GIST.

Dose escalation will continue until the MTD or a RP2D below the MTD has been determined.

Additional details on the DE process, estimation of the MTD/RP2D, and DLTs are provided in Section 6.4 of the protocol.

Expansion (Part 2)

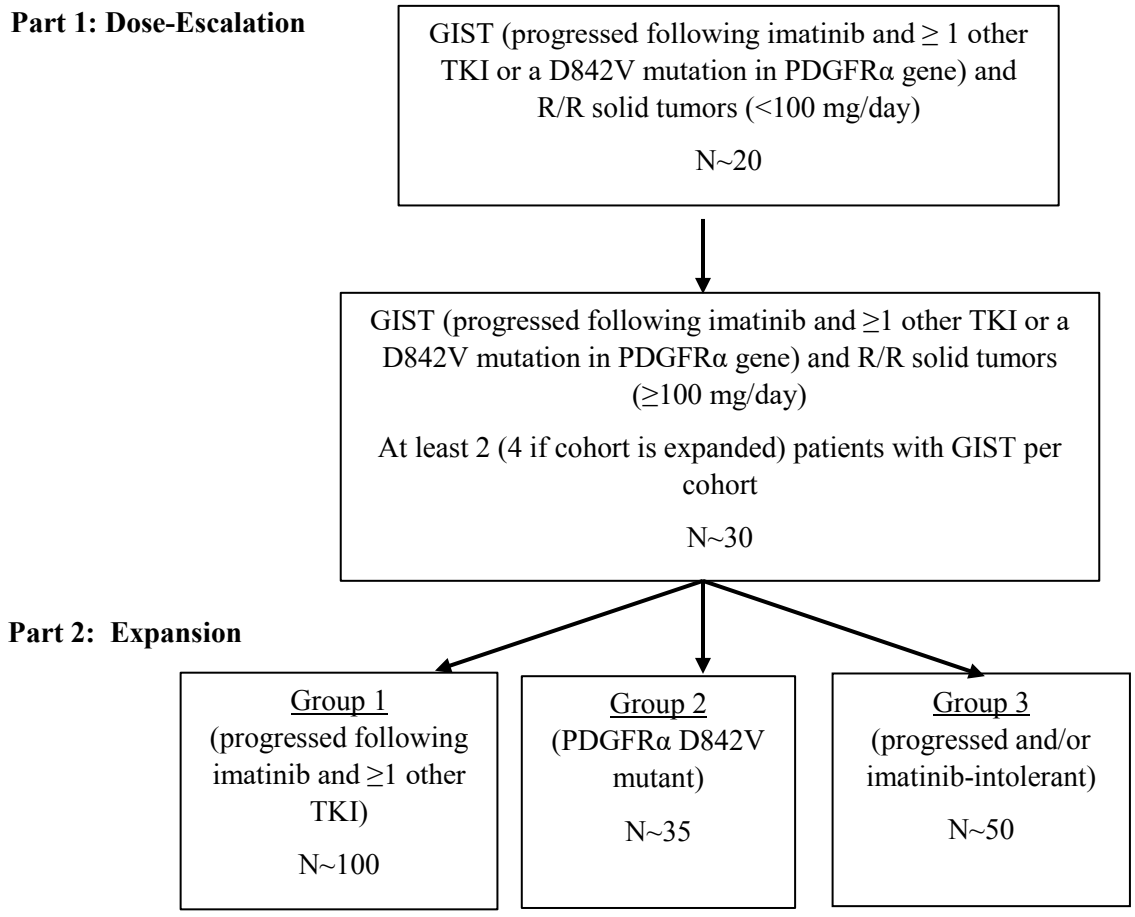
Once the MTD or RP2D has been determined, 3 groups of patients with the following characteristics will be enrolled and treated with avapritinib:

- Group 1: Patients with unresectable GIST that has progressed following treatment with imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase-inhibitor therapy and who do not have a D842V mutation in PDGFRα (N~100)
- Group 2: Patients with unresectable GIST harboring a D842V mutation in the PDGFRα gene (N~35). The PDGFRα mutation will be identified by local and central

assessment, either in archival tissue or a new tumor biopsy obtained, prior to treatment with avapritinib

- Group 3: Patients with unresectable GIST that has progressed and/or those who have experienced intolerance following treatment with imatinib (including in the adjuvant setting) and who have not received additional kinase-inhibitor therapy and do not have a known D842V mutation in PDGFRα (N~50).

Figure 1: Study Schematic



Abbreviations: D842V = aspartic acid to valine at amino acid 842; GIST = gastrointestinal stromal tumor; N = Approximate number of patients to be enrolled; PDGFRα = platelet-derived growth factor receptor alpha; R/R = relapsed/refractory; TKI = tyrosine kinase inhibitor.

1.2 Study Objectives

1.2.1 Primary Objectives

Part 1:

- To determine the MTD and RP2D of avapritinib
- To determine the safety and tolerability of avapritinib.

Part 2:

- To determine the overall response rate (ORR) per modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST 1.1) (Eisenhauer, 2009) at the MTD/RP2D of avapritinib in patients with GIST who have a D842V mutation in PDGFRα
- To determine the ORR by mRECIST 1.1 at the MTD/RP2D of avapritinib in patients with GIST that has progressed following treatment with imatinib and at least another kinase-inhibitor agent, and who are not known to have a D842V mutation in PDGFRα
- To determine the ORR by mRECIST 1.1 at the MTD/R2PD of avapritinib in patients with GIST who have progressed or who experienced intolerance to imatinib, including in the adjuvant setting, and who have not received additional kinase-inhibitor therapy and do not have a known D842V mutation in PDGFRα
- To determine the safety and tolerability of avapritinib.

1.2.2 Secondary Objectives

- To characterize the PK profile of avapritinib, and correlate drug exposure with safety assessments, including changes in electrocardiogram (ECG) intervals
- To assess evidence of antineoplastic activity of avapritinib as measured by duration of response (DOR), progression free survival (PFS), and clinical benefit rate (CBR)
- To assess antitumor activity as measured by Choi criteria
- To compare PFS on avapritinib with PFS on last prior anticancer therapy
- To assess mutations in v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) and PDGFRα in tumor tissue at baseline and at Cycle 3 Day 1 (C3D1)
- To assess the KIT and PDGFRα gene mutant allele fractions (MAF) measured in circulating tumor deoxyribonucleic acid (ctDNA) at baseline, and changes in the MAF measured in ctDNA after treatment with avapritinib

[redacted]

1.3 Sample Size Justification

The total number of patients to be enrolled in Part 1 depends upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of DEs required to achieve the MTD or identify the RP2D. It is expected that approximately 50 patients who meet the criteria for the Dose-Determining (DD) Population (defined in Section 2) will be enrolled in Part 1.

In Part 2 Group 1, a sample size of 100 non-D842V 3L+ patients will allow testing the null hypothesis of ORR ≤5% versus the alternative hypothesis of ORR ≥15% using exact binomial test with 90% power assuming a 2-sided type I error rate of 0.05. An observed ORR of ≥11% in 100 patients will result in an exact binomial 95% confidence interval (CI) with a lower bound greater than 5%) (Table 1), which is clinically meaningful and exceeds the ORR expected with available therapies (Kang, 2013; Stivarga®, 2017).

Table 1: Sample Size for Part 2 by Group

Part 2	Sample Size	Null ORR	Alternative ORR	Observed ORR Needed to Reject Null (95% CI)
Group 1	100	≤5%	≥15%	11% (5.62%, 18.83%)
Group 2	31	≤10%	≥35%	26% (11.86%, 44.61%)
Group 3	50	≤10%	≥25%	20% (10.03%, 33.72%)

Abbreviations: CI = confidence interval; ORR = overall response rate.

In Part 2 Group 2, a sample size of 31 D842V patients will allow testing the null hypothesis of ORR ≤10% versus the alternative hypothesis of ORR ≥35% using exact binomial test with 90% power assuming a 2-sided type I error rate of 0.05. An observed ORR of ≥26% in 31 patients will result in an exact binomial 95% CI with a lower bound greater than 10% (Table 1), which is clinically meaningful, and exceeds the ORR expected with available therapies (Cassier, 2012; Yoo, 2016). We target to enroll up to 35 D842V patients.

In Part 2 Group 3, a sample size of 50 non-D842V 2L patients will allow testing the null hypothesis of ORR ≤10% versus the alternative hypothesis of ORR ≥25% using exact binomial test with 83% power assuming a 2-sided type I error rate of 0.05. An observed ORR of >20% in 50 patients will result in an exact binomial 95% CI with a lower bound greater than 10% (Table 1), which is clinically meaningful, and exceeds the ORR expected with available therapies (Goodman, 2007; Sutent®, 2014).

2. POPULATIONS FOR ANALYSIS

2.1 Safety Population

The Safety Population includes all patients who have received at least 1 dose of study drug. The Safety Population will be the primary population for efficacy and safety analysis unless otherwise specified. Patients will be analyzed based on the dose they receive on Day 1.

2.2 Dose-Determining Population

The DD Population includes all patients in Part 1 who have received at least 75% of their prescribed doses (*i.e.* ≥21 doses) of the study drug in cycle 1 (C1) and completed follow-up through C1 Day 28 (C1D28) or experienced a DLT regardless of the extent of study drug exposure. The DD Population will be the default analysis population for the DE phase for all MTD related analyses. Patients will be analyzed according to the dose they receive on Day 1.

2.3 Response-Evaluable Population

The Response-Evaluable (RE) Population included all patients in the Safety Population who have at least 1 target lesion at baseline by central radiology review per mRECIST 1.1, have at least 1 post-baseline disease assessment by central radiology per mRECIST 1.1, and have experienced no major protocol deviations. Selected efficacy analysis may be performed using the RE Population. Patients will be analyzed according to the dose they receive.

Major protocol deviations leading to exclusion from the RE Population include:

- Patient has history of another primary malignancy within 1 year
- Patient received concomitant treatment for the underlying malignancy while taking avapritinib prior to the efficacy assessment of interest.

2.4 Sub-Populations

Selected analyses may be conducted on sub-populations of safety or RE based on line of TKI therapy and GIST mutation types, which are determined in the order of Qiagen, Sysmex or Personal Genome Diagnostics [PGDx], and local when available.

- Qiagen D842V: PDGFRα D842V patients determined by the Qiagen assay
- D842V: PDGFRα D842V patients
- Exon 18: PDGFRα exon 18 patients
- 4L+: all patients regardless of mutation type, who received 3 or more prior lines of TKI
- Non-D842V 4L+: non-PDGFRα D842V 4L+ patients

- Non-D842V 3L+: non-PDGFRα D842V patients, who received 2 or more prior lines of TKI
- Non-D842V 2L: non-PDGFRα D842V patients, who received imatinib as the only prior TKI therapy.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1 Randomization, Stratification and Blinding

This is an open label, single arm study with no randomization or stratification.

3.2 Data Analysis General Information and Definition

Summary statistics for continuous variables will include n (non-missing observations), mean, standard deviation (StdDev), minimum, median, and maximum. Summary statistics for categorical variables will be presented in terms of frequencies and percentages. Time to event data will be summarized using Kaplan-Meier (KM) method, which will include the estimated median with 95% CIs and 25th and 75th percentiles.

3.2.1 Study Drug

Study drug or study treatment used in the rest of the document refers to avapritinib (BLU-285).

3.2.2 Day 1 and Other Days

Date of first dose of avapritinib (or Day 1) is defined as the day of the first administration of study drug in the study, *i.e.* after enrollment. First dose refers to first dose in study unless specified otherwise.

Date of last dose of avapritinib is defined as the date of last administration of study drug (last dose) in the study. For patients who have not end treatment and last dose date is missing, the cutoff date will be used.

3.2.3 Calculation Using Dates

Calculations using dates will adhere to the following conventions:

- Study day for a date of interest (TARGET DATE) is calculated as

  STUDY DAY = TARGET DATE – Day 1 + 1 if TARGET DATE is on or after Day 1;

  STUDY DAY = TARGET DATE – Day 1 otherwise.

  Note that negative study days are reflective of observations obtained during the screening period. Partial dates for the first study drug administration are not imputed in general.

- Age (in days) is calculated as

  AGE = CONSENT DATE – BIRTH DATE (DOB) + 1.

  Age (in years) = (year of consent) - (year of DOB) if passed Birthday;

  Age (in years) = (year of consent) - (year of DOB) - 1 if otherwise.

This is equivalent to the following:

[(year of consent) - (year of DOB)] – [(month of consent) ≤ (month of DOB)] + [(month of consent) = (month of DOB) and (day of consent) ≥ (day of DOB)]

3.2.4 Duration Derivation

Unless otherwise specified for a specific panel or variable, duration variables will be derived according to the following rules:

- Duration (in days) = [end date – start date +1]
- Duration (in weeks) = [end date – start date +1]/ 7
- Duration (in months) = [end date – start date +1]/ 30.4375
- Duration (in years) = [end date – start date +1]/ 365.25.

Duration variables which are to be expressed in units greater than day will be rounded to 1 decimal place.

3.2.5 Baseline Values

Baseline is defined as the last observation prior to first dose of study drug, *i.e.* Day 1 pre-dose value or the last available (including unscheduled) value before Day 1 if Day 1 pre-dose value is unavailable.

3.2.6 Last Contact

Last contact is the date of last measurement or assessment upon the patient.

3.3 Methods for Handling Missing Data

Refer to Section 7.1 for detailed date imputation guidelines.

3.4 Windowing of Visits

Visits will be windowed. Data are summarized by visit following the visit windows reported in Table 2 and Table 3 when appropriate (*e.g.* lab parameters). If multiple assessments occur within a visit window, the assessment closest to the target day will be used. In case of ties, with equal number of days on either side of target day, the value from the day before target day shall be used.

Table 2: Visit Windows for Patients Who Participate in a 3-Day Pharmacokinetic-Lead in Stage

Visit	Start Day (time)	Target Day (time)	End Day (time)
Week 1 (C1D8)	1	11 ± 1	14
Week 2 (C1D15)	15	18 ± 2	21
Week 3 (C1D22)	22	25 ± 2	28
Week 4 (C2D1)	29	32 ± 3	39
Week 6 (C2D15)	40	46 ± 3	51
Week 8 (C3D1)	52	60 ± 7	74
Week 12 (C4D1)	75	88 ± 7	102
Week 16 (C5D1)	103	116 ± 7	130
Week 4*X (C(X+1)D1)	28*X-9	(28*X+4) ± 7	28*X+18

Note: Visit window for Week 1 will not consider Day 1 if Day 1 observation is marked as baseline; X can be 4, 5, 6… until cover all visit windows.

Table 3: Visit Windows for Other Patients

Visit	Start day (time)	Target Day (time)	End day (time)
Week 1 (C1D8)	1	8 ± 1	11
Week 2 (C1D15)	12	15 ± 2	18
Week 3 (C1D22)	19	22 ± 2	25
Week 4 (C2D1)	26	29 ± 3	36
Week 6 (C2D15)	37	43 ± 3	48
Week 8 (C3D1)	49	57 ± 7	71
Week 12 (C4D1)	72	85 ± 7	99
Week 16 (C5D1)	100	113 ± 7	127
Week 4*X (C(X+1)D1)	28*X-12	28*X+1 ± 7	28*X+15

Note: Visit window for Week 4 will not consider Day 1 if Day 1 observation is marked as baseline; X can be 4, 5, 6… until cover all visit windows.

3.5 Withdrawals, Dropouts, Lost to Follow-Up

Patients may withdraw or be withdrawn from study treatments at any time for any of the following reasons:

- Withdrawal of consent
- Adverse event (AE)
- Disease progression
- Death
- Investigator decision

- Protocol deviation
- Pregnancy
- Lost to follow-up.

3.6 Protocol Deviations

Deviations from the protocol, as defined in the protocol and protocol deviation plan, will be documented in Insight on an ongoing basis by the study monitors and project manager throughout the study period.

Prior to database lock, protocol deviations will be reviewed and categorized as major or minor for summarization.

Major protocol deviations will be summarized descriptively for the Safety Population.

A by-patient listing of patients with protocol deviations in the Safety Population will be provided. A separate listing of patients with major protocol deviations that lead to exclusion from the RE Population will also be provided.

4. STATISTICAL METHODOLOGY

All primary analyses in this section will be conducted and presented by starting daily dose (grouped as '<300 mg', '300 mg', '400 mg', '300/400 mg', and 'all doses') for the Safety Population and/or its sub-populations which refer to those specified in Section 2.4. Selected sensitivity analyses will be conducted for the RE sub-populations by the same starting dose grouping.

Analyses based on the DD Population, e.g. MTD, DLT analyses, will be presented by starting daily dose without grouping, and 'all doses'.

4.1 Analysis Populations

A summary of analysis populations by starting dose will be presented for the following:

- Safety Population and its sub-populations
- RE Population and its sub-populations
- DD Population.

4.2 Patient Disposition

The number of patients treated, discontinued from treatment and study and the reasons for discontinuations, will be summarized by starting dose for the Safety Population.

Reasons for treatment discontinuation and study discontinuation will be summarized with the following categories collected on the electronic case report form (eCRF):

- Disease progression
- AE
- Death
- Lost to follow-up
- Protocol deviation
- Withdrew consent
- Pregnancy
- Investigator decision
- Administrative/other
- Sponsor decision.

Listings will be provided for discontinued patients with reason for treatment discontinuation, study discontinuation.

4.3 Demographics and Baseline Disease Characteristics

Demographic and baseline disease characteristic data will be summarized by starting dose based on the Safety Population and its sub-populations, and the DD Population when appropriate. Medical history data will be summarized similarly.

4.3.1 Demographics

The number and percentage of patients in each of the following categories will be presented:

- Age group (<65 years or ≥65 years)
- Sex
- Ethnicity
- Race.

Patients' age (years), height (cm), weight (kg), body mass index (BMI) (kg/m^2), and other continuous demographic variables will be summarized descriptively.

BMI will be calculated as: BMI (kg/m^2) = (weight in kg) / (height in m)^2.

4.3.2 Baseline Disease Characteristics

The number and percentage of patients in each of the following categories will be presented:

- The Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2, 3...)
- GIST subtype:
  - KIT mutant (all, exon 13 or 14, exon 17 or 18, V654 and T670)
  - PDGFRα exon 18 mutants (all, D842V, non- D842V)
  - PDGFRα exon 14 mutants (all, N659K)
  - KIT & PDGFRα wild type
- Metastatic disease (Yes, No)
- Largest target lesion size (≤5 cm, >5 to ≤10 cm, >10 cm) by central radiographic assessment
- Patient staged at screening by tumor/lymph nodes/metastasis (TNM) system (Yes, No)
- Current stage at screening by TNM
- Prior imatinib (Yes, No)
- Prior sunitinib (Yes, No)
- Prior regorafenib (Yes, No)

- Primary tumor site of GIST at the time of diagnosis
- Site of metastatic disease
- Prior surgical resection (Yes, No), and type of resection (total, partial, other).

Continuous baseline disease characteristics will be summarized using descriptive statistics.

4.3.3 Medical History

Ongoing medical history data will be summarized by system organ class (SOC) and preferred term (PT) per Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. All medical history data will be listed.

4.4 Prior and Concomitant Medications and Prior Therapies

4.4.1 Prior and Concomitant Medications

Prior medications are those that started and stopped before exposure to study drug. Concomitant medications are all medications taken at any time from first dose date of study drug to last dose date of study drug + 30 days. If the last dose date of study drug is not available, the cutoff date is used in place of the last dose date.

The number and percentage of patients taking concomitant medications and significant non-drug therapies will be summarized and listed by therapeutic area (ATCText3) and preferred drug name for the Safety Population. A patient taking the same medication multiple times is counted only once under that preferred drug name.

Prior (with clear flag) and concomitant medications will be listed for the Safety Population.

Medications are coded using the World Health Organization Drug dictionary B2 enhanced, version Mar 2017.

4.4.2 Prior Therapies for the Underlying Malignancy

Prior therapy is defined as all treatment that started and ended on or before first dose date of avapritinib.

The number and percentage of patients for each category below will be summarized by PT:

- Prior antineoplastic therapy (Yes, No)
- Prior chemotherapy (Yes, No)
- Prior Lines of TKI (0, 1, 2, 3, 4+)
- Prior Distinct TKI(s) (0, 1, 2, 3, 4+)
- Prior radiation therapy (Yes, No)
- Prior cancer related surgery-procedures (Yes, No)

- Best response to any prior TKI (CR, PR, SD, progressive disease, NE)
- Best response to last prior TKI (CR, PR, SD, progressive disease, NE).

Continuous variables to be summarized include:

- Time between diagnosis to first dose of avapritinib
- Time between end of last prior line of antineoplastic therapy to the first dose date of avapritinib
- Duration of previous exposure to TKI.

The duration of previous exposure to TKI will be the sum of exposure from each prior TKI therapy, which is number of days from start date to end date captured on the prior cancer therapy eCRF page.

No overlap between the exposure to prior therapies and avapritinib will be allowed and any overlap of exposure will be queried at data review stage. The end date of the last prior therapy will be imputed to 'first dose date of avapritinib – 15' if the imputation of partial dates is within 14 days of Day 1. However, if Day 1 of study drug is within the first half of the month, and last prior therapy ended on the same month as study drug start, the day component of last prior therapy end date will be imputed as 1.

4.5 Study Treatments and Extent of Exposure

A summary of study drug exposure, including number of doses administered, cumulative dose, dose intensity, relative dose intensity (RDI), duration of treatment, and the proportion of patients with dose modifications will be produced.

Exposure data will be summarized descriptively by time (every 4 weeks and entire duration) and by starting dose in the safety, and the DD Population when appropriate.

Duration in every 4 weeks is defined as the time from first day of the 4 weeks to the day prior to the first day of the subsequent 4 weeks; for the last 4 weeks, the end date is the date of last dose.

4.5.1 Treatment Duration and Exposure

Duration of treatment (days) = (treatment end date– treatment start date + 1).

Duration of treatment (weeks) = (treatment end date– treatment start date + 1) / 7.

The treatment start date is the first dose date of study drug, and the treatment end date is the last dose date of study drug or data cutoff date, whichever is earlier.

Descriptive statistics will be provided for treatment duration in weeks.

4.5.2 Cumulative Dose

Cumulative dose (mg) is defined as sum of all dose taken. The dosage will be counted as 0 for days when the study drug is not taken.

4.5.3 Average Daily Dose

Average daily dose (mg) is defined as the cumulative dose divided by the number of days dosed. Each patient has an average daily dose.

4.5.4 Dose Intensity

Dose intensity (mg/day) is defined as the cumulative dose divided by the treatment duration (in days).

4.5.5 Relative Dose Intensity

Relative dose intensity is defined as the ratio: dose intensity / planned dose intensity. Planned dose intensity is based on initial assigned daily dose.

Relative dose intensity will be summarized descriptively as a continuous variable and be categorized into <75%, 75% to <90%, 90% to 120%, 120 to 150%, and ≥150%.

A by-patient listing of study drug including treatment duration, cumulative dose, average daily dose, dose intensity, planned initial dose, RDI will be provided.

4.5.6 Dose Modification

Frequency of dose modification will be summarized as follows:

Dose reduction due to AE will be summarized using the number and percent of patients with 0, 1, 2, or >2 dose reduction during the entire treatment period.

Dose increase will be summarized using the number and percent of patients with 0, 1, 2, or >2 dose increase during the entire treatment period.

A bivariate table will summarize (number and percentage) both dose reduction and increase.

The number of patients whose dose escalates from total daily dose of 300 mg to 400 mg, and the number of patients who have dose modification and types of dose modification after the DE will be summarized.

The number of patients whose dose reduces from total daily dose of 400 mg or 300 mg, and the number of patients who have dose modification and types of dose modification after the dose reduction will be summarized.

Time to first dose reduction among patients with at least one dose reduction, is the time in weeks elapsed from the date of first dose of study drug to the date when the first dose reduction occurred. It will be summarized as a continuous variable.

Dose interruption/missing due to AE will be summarized using the number and percentage of patients who have 0, 1, 2, or >2 dose interruptions/missing, by starting dose and the dose the patient was on at the time of interruption.

Details of dose modifications will be provided in listings.

4.6 Efficacy Analyses

All efficacy analyses will be conducted by daily starting dose ('<300 mg', '300 mg', '400 mg', '300/400 mg', and 'all doses) for the safety sub-populations primarily. Supportive analyses may be conducted in the RE sub-populations. Endpoints involving response assessment will be primarily based on central radiology per mRECIST 1.1. Investigator assessment per mRECIST 1.1, or central radiology assessment per Choi criteria will only be supportive. Logistic regression and Cox proportional hazards model may be based on the overall Safety Population.

4.6.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint of ORR is defined as the proportion of patients with a confirmed (CR/PR for at least two assessments with no progression in between) best response of complete response (CR) or partial response (PR).

The primary analysis of ORR will be assessed by central radiology per mRECIST 1.1. ORR will be estimated using frequency, percentage, and two-sided 95% CI based on the exact binomial distribution (Clopper-Pearson) for the Safety Population.

Additionally, the best overall response following the hierarchical order of CR, PR, stable disease (SD), progressive disease (PD), and not evaluable (NE) will be tabulated for the prespecified sub-populations in the Safety Population. Non-CR/Non-PD will be treated as SD.

The following sensitivity analysis will be conducted on the response to assess the robustness of the primary analysis:

- ORR by starting dose within sub-populations specified in Section 2.4 in the Safety Population for patients who have had the opportunity for at least 8 months of follow-up or have discontinued study treatment
- ORR by starting dose within sub-populations specified in Section 2.4 in the RE Population
- ORR as assessed by the Investigator in the Safety Population will be summarized for best overall response. Tables of concordance between best overall response by central radiology assessment and by the Investigator will be reported.

Logistic regression will be fit to assess the effect of factors individually on the ORR, including starting dose, maximum daily dose level, dose intensity, age, ECOG status, size of largest tumor mass, *etc.*, stratified by mutation type (exon 18 vs not). Factors that are significant at 0.2 level in univariable models will be entered in the final multivariable model.

Unstratified analysis based on the Safety Population may be conducted.

4.6.2 Analysis of Secondary Efficacy Endpoints

4.6.2.1 Duration of Response

Duration of response is defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever occurs first. The date of disease progression will be per mRECIST 1.1. Patients without confirmed CR or PR will be excluded from this analysis. Patients who are still in response at time of data cutoff will be censored at their last valid assessment. Complete censoring rules (both European Medicines Agency [EMA] and United States [US] Food and Drug Administration [FDA]) are specified in Table 4. The analysis will be primarily based on FDA Guidance for Cancer Trial Endpoints (FDA, 2007). The censoring rules based on the EMA Guideline on the evaluation of anticancer medicinal products in man will be used as sensitivity analysis (EMA, 2017).

Duration of response will be analyzed using KM methods and will include the estimated median with two-sided 95% CI and 25th and 75th percentiles. DOR at specific time-points (*e.g.* 3-, 6-, and 12-month, *etc.*) will be computed, along with the standard errors using Greenwood's formula (Klein, 2003).

Sensitivity analysis will be conducted for DOR based on Investigator assessment per mRECIST 1.1, or central radiology assessment per Choi criteria for the Safety Population by mutation types. Both FDA and EMA censoring rules will be applied.

4.6.2.2 Progression Free Survival

Progression free survival is defined as the time from the start of treatment to the date of first documented disease progression or death due to any cause, whichever occurs first. The date of disease progression will be per mRECIST 1.1. Specifically, if not all scans were done on the same date, the first scan date will be used. If a patient has not had an event, PFS is censored at the date of last valid assessment that is stable or better. See Table 4 for censoring rules.

The KM method will be used to estimate the survival distribution function. The median PFS along with its two-sided 95% CI and 25th and 75th percentiles will be estimated. In addition, the event rates (or event-free) at specific time-points (*e.g.* 3-, 6-, and 12-month, *etc.*) will be computed, along with the standard errors using Greenwood's formula (Klein, 2003). The plots of survival curves using the KM method will be presented.

A Cox proportional hazards model will be used to estimate hazard ratios of factors like starting daily dose, maximum daily dose level, dose intensity, age, ECOG status, size of largest tumor mass, *etc.*, along with 95% CIs. The model will be stratified by mutation type (exon 18 vs not). Factors that are significant at 0.2 level in univariable models will be enter the final multivariable model.

Unstratified analysis based on the Safety Population may be conducted.

Table 4: Duration of Response and Progression Free Survival Censoring Rules

Situation	Date of Progression or Censoring	FDA Censoring Rules	EMA Censoring Rules
No baseline assessments and alive after 2 scheduled assessments (defined by 140 days)	Date of first dose	Censored	Censored
Progression documented between scheduled visits	Date of last radiological assessment showing new lesions or an increase in measured lesions	Event	Event
No progression	Date of last radiological assessment with evidence of no progression (or first dose date if no assessment)	Censored	Censored
New anticancer/ non-protocol treatment started prior to progression	Date of last radiological assessment with evidence of no progression prior to the start of new anticancer treatment	Censored	Event at date of disease progression/death
Death before the second scheduled post-baseline assessment (defined by within 140 days after first dose)	Date of death	Event	Event
Death between scheduled assessments	Date of death	Event	Event
Death or progression immediately after an extended lost to follow-up time (2 more missed scheduled assessments defined by at least x[1] days)	Date of last radiological assessment with evidence of no progression (first dose date if first 2 scheduled assessments are missing)	Censored	Event at date of disease progression/death

[1] x= 140 days if the death or progression date is ≤336 days from first dose date; x=210 days if the death or progression date is ≥337 days from first dose date.

4.6.2.3 Clinical Benefit Rate

Clinical benefit rate is defined as the proportion of patients with a confirmed CR/PR, or SD lasting for 4 cycles. The response will be assessed per mRECIST 1.1. Clinical benefit rate will be estimated using frequency, percentage, and two-sided 95% CI based on the exact binomial distribution.

4.6.2.4 Response Rate by Choi Criteria

Overall response rate per Choi response criteria (Weng, 2013) will be estimated using frequency, percentage, and two-sided 95% CI based on the exact binomial distribution (Clopper-Pearson).

The best overall response per Choi criteria following the hierarchical order of CR, PR, SD, progressive disease, and NE will be tabulated.

4.6.2.5 Progression Free Survival on Last Prior Anti-Cancer Therapy

Progression free survival on last prior anticancer therapy is defined as the time from the start of last prior anticancer therapy to progression on that therapy.

Patient is considered PD on the last prior anti-cancer therapy if its best response was PD, or discontinuation was due to progressive disease. If the date of PD is partially missing, the imputation rule is the same as that for incomplete stop date for AE (Appendix 7.1.4); if the date of PD is completely missing, last dose date will be used as the disease progression date. Imputation rule for partial missing last dose date is in Appendix 7.1.3. PD date of on last prior therapy will be imputed to first dose date of study drug – 1 if the progression is on or after the first dose date of the study drug due to partial dates imputation. For patients who have no documented disease progression on the last prior anti-cancer therapy, PFS will be censored at 1 day before the first dose of avapritinib.

The KM method will be used to estimate the survival distribution function. The median PFS along with its two-sided 95% CI and 25th and 75th percentiles will be estimated. In addition, the event rates (or event-free) at specific time-points (*e.g.* 3-, 6-, and 12-month, *etc.*) will be computed, along with the standard errors using Greenwood's formula (Klein, 2003). The plots of survival curves using the KM method will be presented.

Statistical testing will be conducted between the PFS on study drug and PFS on last prior anticancer therapy. Methods that accounts for paired censored data, *e.g.* paired Prentice-Wilcoxon test will be performed due to the in-patient correlation of the two PFSs.

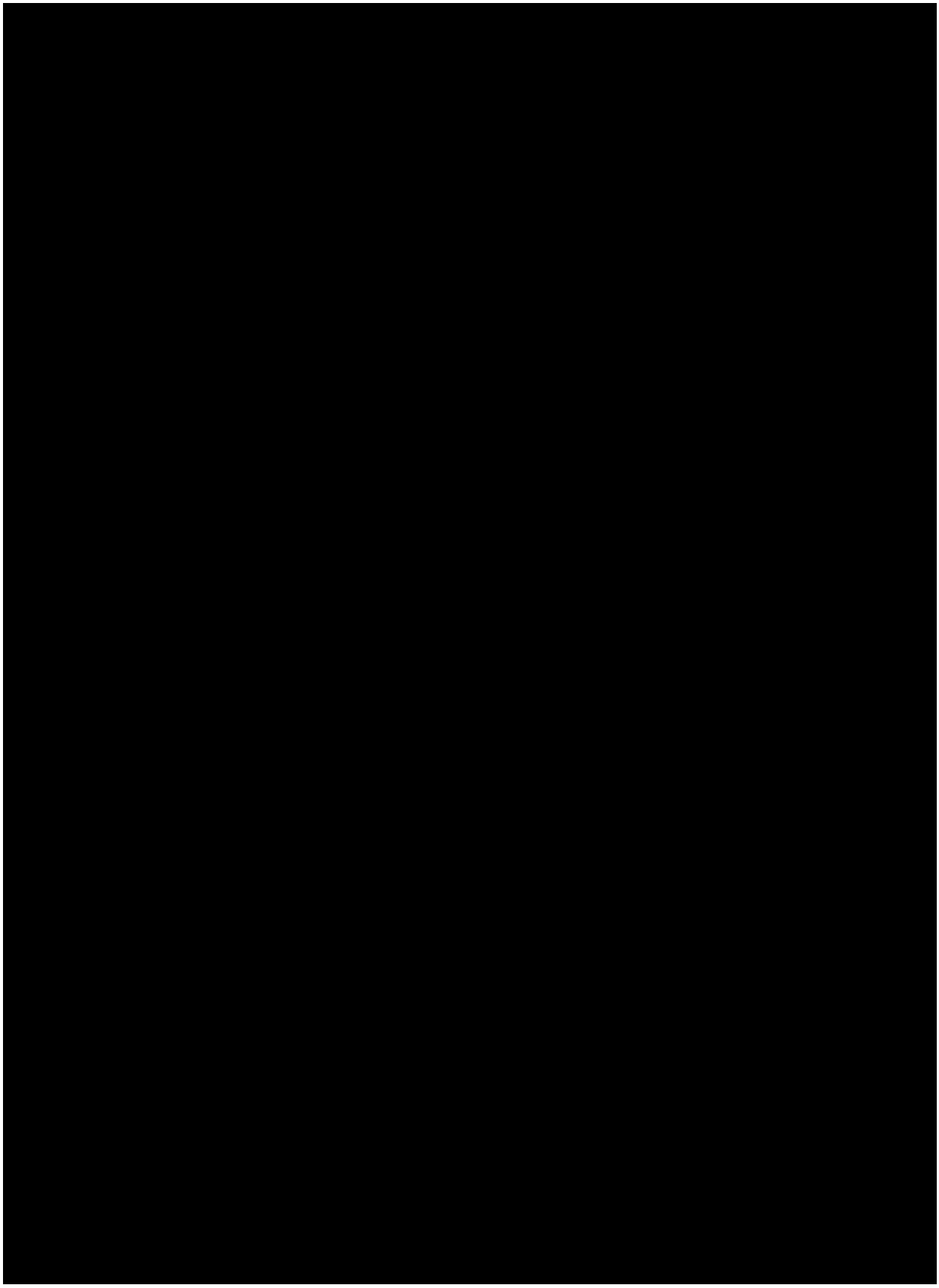
The analyses described will apply to safety sub-populations of Qiagen D842V, D842V, and exon-18.

4.6.2.6 Mutation Analysis

KIT and PDGFRα mutations present in tumor tissue and ctDNA will be analyzed.

Baseline mutations will be summarized descriptively including those documented by Qiagen assay (tumor), Sysmex/PGDX assay (tumor and ctDNA), and on the CRF (tumor) in the order of presence.

Change (in percentage) from baseline to C3D1 in MAF including KIT and PDGFRα will be summarized for mutations documented by Sysmex ctDNA assay in DD population. For patients with multiple mutations, the minimum change in MAF will be used.



4.6.4 Subgroup Analysis

For ORR, DOR, PFS as assessed by central radiology, and OS, the following subgroup analyses will be conducted for safety sub-populations of PDGFRα exon-18, and 4L+ and limited to patients with starting dose of 300/400 mg. Corresponding forest plots will be provided based on the odds ratio or hazard ratio for each subgroup.

- Age (<65 years, ≥65 years)
- Gender (male, female)
- Region (US, Europe, Asian)
- Race (White, non-White)
- Largest target lesion (≤10 cm, >10 cm).

4.7 Safety Analyses

Safety data will be summarized and presented by starting dose ('<300 mg', '300 mg', '400 mg', '300/400 mg', and 'all doses') for the Safety Population, unless otherwise specified. The analyses for MTD and DLT will be summarized by starting dose without grouping, and "all doses" descriptively for patients in the DD Population.

4.7.1 Adverse Events

Adverse Events will be analyzed in terms of treatment-emergent adverse events (TEAEs) which are defined as any AE that occurs during or after administration of the first dose of study drug through 30 days after the last dose of study drug, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens intensity or is subsequently considered study drug-related by the Investigator.

Adverse Event refers to TEAEs unless otherwise specified throughout this document. All AEs will be coded using MedDRA version 18.1. The severity will be graded per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

Relationship of **AE** to treatment is defined as AE that is considered (possibly or probably) to be related to the study drug by the Investigator according to the following criteria:

- Not Related: Exposure to the study treatment did not occur, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to the study treatment
- Possibly Related: The study treatment and the AE were reasonably related in time, and the AE could be explained equally well by causes other than exposure to the study treatment
- Probably Related: The study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the study treatment than by other causes, or the study treatment was the most likely cause of the AE.

A patient experiencing multiple AEs under the same PT (SOC) will be counted only once for that PT (SOC) by maximum severity. A patient experiences the same AE more than once with more than one relationship to study drug, the strongest causal relationship to study drug will be given precedence. Any missing severity, causality, or outcome will not be imputed and classified as 'Missing'. Detailed imputation rule for missing AE dates are in Section 7.1.

Number of patients with at least one AE will be summarized (Table 5). The following tables summarizing incidence of various aspects of AEs and serious adverse events (SAEs) by descending frequency of SOC and PT:

1. AE Summary (including all subsequent items)
2. AE by PT/ by SOC and PT
3. AE related to study drug by PT/by SOC and PT
4. SAE by PT/by SOC and PT
5. SAE related to study drug by PT/by SOC and PT
6. Grade 3/4/5 AE by PT/by SOC and PT
7. Grade 3/4/5 AE related to study drug by PT/by SOC and PT

8. AE by PT/by SOC and PT, and NCI CTCAE Grade
9. AE related to study drug by PT/by SOC and PT, and NCI CTCAE Grade
10. SAE by PT/by SOC and PT, and NCI CTCAE Grade
11. SAE related to study drug by PT, and NCI CTCAE Grade
12. AE leading to interruption of study drug regardless of causality by PT/ by SOC and PT
13. AE leading to reduction of study drug regardless of causality by PT/ by SOC and PT
14. AE leading to permanent discontinuation of study drug regardless of causality by PT/ by SOC and PT.

All AEs will be listed by patient.

Dose limiting toxicities will be presented by dose level and PT in the DD Population.

Subgroup analysis will be conducted for endpoints 1 – 7 above (details in Table 5) for patients with a starting dose of 300/400 mg in the Safety Population. Corresponding forest plots will be provided based on the odds ratio for each of the following subgroups:

- Age (<65 years, ≥65 years)
- Gender (male, female)
- Region (US, Europe, Asian)
- Race (White, non-White).

4.7.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be summarized by category (cognitive effects and intracranial bleeding) and relevant PTs.

- Cognitive effects consisting of 3 PTs: cognitive disorder, memory impairment, confusional state
- Intracranial bleeding consisting of 3 PTs: haemorrhage intracranial, cerebral haemorrhage, subdural haematoma.

The general rules for summarizing AE specified in Section 4.7.1 apply for AESIs for avapritinib. The following tables will be presented by AESI Category and PT:

- AESI by AESI category and PT
- Serious AESI by AESI category and PT
- AESI by AESI category and PT and NCI CTCAE Grade
- AESI leading to permanent discontinuation of study drug regardless of causality by PT.

Table 5 Summary of Adverse Event Tables:

Safety Endpoint	Main Table	by PT		by SOC, PT		by PT, CTCAE	by SOC, PT, CTCAE
		Overall	Subgroup[1]	Overall	Subgroup[1]	Overall	Overall
Summary Table (each item below one row)	X[2]						
AE		X	X	X	X	X	X
SAE		X	X	X	X	X	X
Grade 3+ AE		X	X	X	X		
Related AE		X	X	X	X	X	X
Related SAE		X	X	X	X	X	
Related Grade 3+ AE		X	X	X	X		
DLT		X					
AE Leading to Permanent Study Discontinuation		X		X			
Adverse Events Leading to Dose Interruption		X		X			
Adverse Events Leading to Dose Reduction		X		X			
Listing (Death, Discontinuation, SAE, DLT)	X						
AESI by Category and		X				X	
Serious AESI by Category and		X				X	
AESI Leading to Permanent Study Discontinuation		X					
Time to Onset of AESI	X						
Cumulative Incidence of AESI	X						

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; DDP = Dose determining Population; DLT = dose limiting toxicity; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TKI = tyrosine kinase inhibitor.

1 Among patients with 300/400 mg starting dose by Subgroup of Age at Informed Consent, Gender, Region, Race, and Number of prior lines of TKIs.

2 Subgroup analysis will be conducted among patients with 300/400 mg starting dose by Subgroup of Age at Informed Consent, Gender, Region, Race, and Number of prior lines of TKIs.

4.7.3 Deaths

Death will be summarized during the active treatment phase and within 30 days after the last date of the study treatment by SOC and PT.

A listing of patients who died will be provided specifying the date of death, the cause, and the date of last study treatment dose. On treatment death (from first dose date to last dose date + 30 days) will be clearly marked.

4.7.4 Clinical Laboratory Evaluations

The laboratory parameters with both baseline and post-baseline assessments will be summarized by starting dose ('<300 mg', '300 mg', '400 mg', '300/400 mg', and 'all doses') and visit for the Safety Population. If there are repeated values for a specific visit, the last reported value will be used for that visit. Baseline is defined as the last assessment prior to start of study treatment.

Clinical laboratory values will be graded according to NCI CTCAE version 4.03 for applicable parameters. Shift tables of laboratory data from baseline to worst grade during treatment will be presented. For serum chemistry parameters (including sodium, potassium, magnesium, and glucose) shift tables in maximum CTCAE grades of worst (high) and worst (low) assessment will be presented separately.

Overall summary and changes from baseline will be presented for hematology and serum chemistry (including coagulation) laboratory values.

Listings will be provided for each laboratory parameter. All results outside predefined normal ranges, and CTCAE grade will be flagged in the data listings.

Urinalysis will be presented in listing only.

Boxplot of selected lab tests (including leucocytes, neutrophils, platelets, hemoglobin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin) values will be presented by visit.

4.8 Vital Signs

Results for height, weight, BMI, systolic and diastolic blood pressure (BP), heart rate, and body temperature will be summarized by starting dose and visit for the Safety Population. Changes in BP, pulse rate, and body temperature from baseline will be summarized by starting dose ('<300 mg', '300 mg', '400 mg', '300/400 mg', and 'all doses') and visit.

4.9 Electrocardiograms

Electrocardiogram overall interpretation (normal, abnormal not clinically significant [NCS], abnormal clinically significant [CS], and NE) will be presented for actual values and changes from baseline [expressed as improvement, no change, and deterioration] by dose level

summarized by starting dose (‘<300 mg’, ‘300 mg’, ‘400 mg’, ‘300/400 mg’, and ‘all doses’) and visit for the Safety Population.

- Improvement = abnormal CS to abnormal NCS/normal, abnormal NCS to normal
- Deterioration = normal to abnormal NCS/CS, abnormal NCS to abnormal CS
- No change = normal to normal, abnormal NCS to abnormal NCS, abnormal CS to abnormal CS.

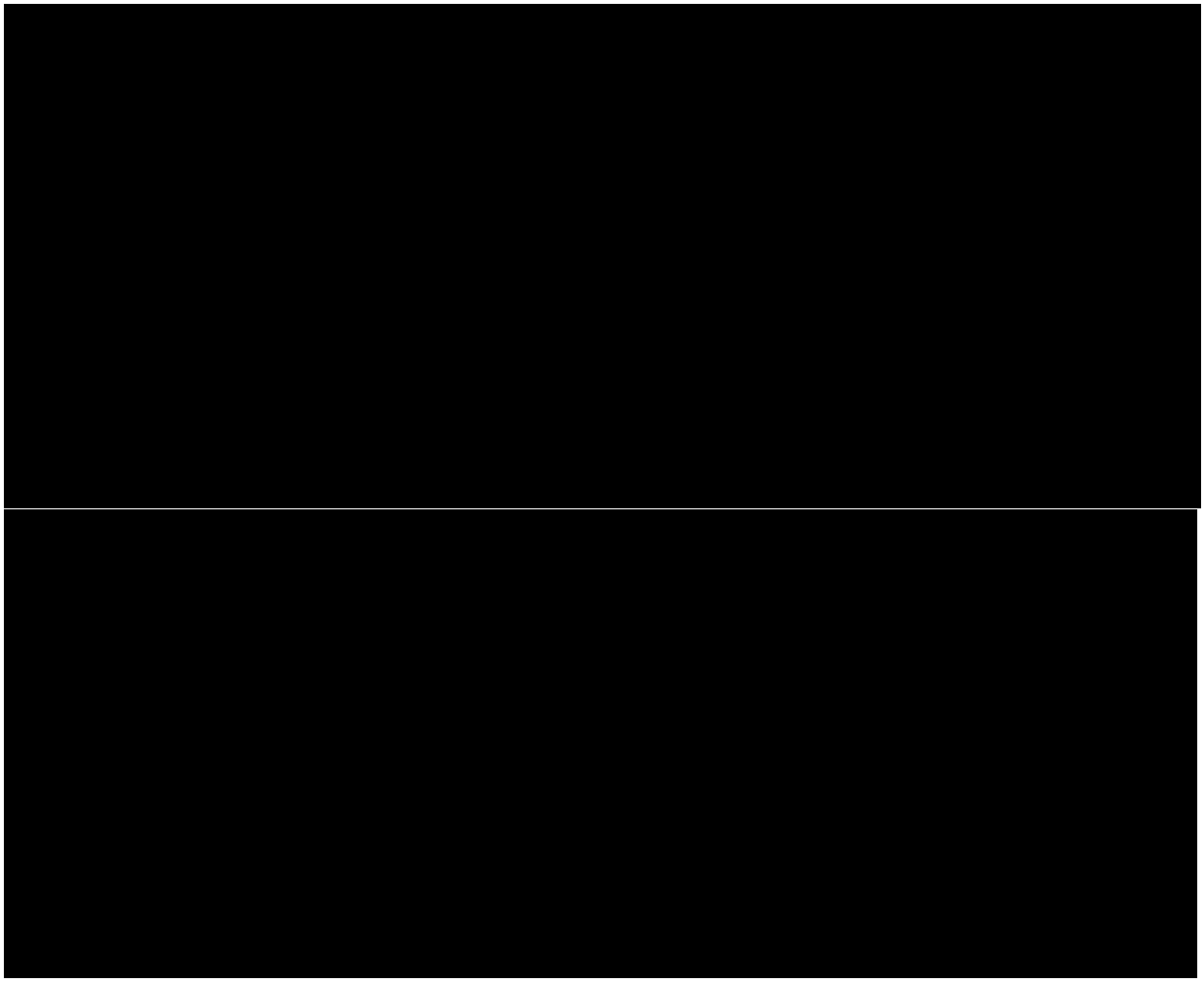
If either result is missing for any patient, then an ‘Unknown’ category will be presented.

4.10 ECOG Performance Status

Overall summary and changes from baseline will be presented for ECOG performance by starting dose (‘<300 mg’, ‘300 mg’, ‘400 mg’, ‘300/400 mg’, and ‘all doses’) and visit for the Safety Population.

5. INTERIM ANALYSES

No interim analysis is planned for this study.



7. APPENDICES

7.1 Data Imputation Guidelines

No imputation will be made for completely missing date unless otherwise specified. General imputation rules mentioned below apply to partially missing or impossible dates:

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date
- If the start date is not missing, and the imputed stop date is before the start date, then the imputed stop date will be equal to the start date
- Any imputed dates need to be logical. For example, last dose date should not be later than death date.

When imputation rules in subsequent sections contradicts the general rule, always follow the general rule.

7.1.1 Adverse Event Date Imputation

Follow the general rule specified in Section 7.1.

Incomplete Start Date:

Missing day, month, and year

- No imputation will be made; the corresponding AE will be included.

Missing day and month

- If the year is the **same** as the year of the first dose date, then impute day and month as the day and month of the first dose date
- If the year is **prior to** the year of the first dose date, then impute day and month as 31 Dec
- If the year is **after** the year of the first dose date, then impute day and month as 01 Jan.

Missing day only

- If the month and year are the **same** as those of the first dose date, then impute day as the day of the first dose date
- If either the year of partial date is **before** the year of the first dose date, or the years are the same, but the month of partial date is **before** the month of the first dose date, then impute day as last day of the month
- If either the year of partial date is **after** the year of the first dose date, or the years are the same, but the month of partial date is **after** the month of the first dose date, then impute day as first day of the month.

Incomplete Stop Date:

Missing day, month, and year

- No imputation will be made.

Missing day and month

- If the year is the **same** as the year of the last dose date, then impute day and month as the day and month of the last dose date
- If the year is **prior to** the year of the last dose date, then impute day and month as 31 Dec
- If the year is **after** the year of the last dose date, then impute day and month as 01 Jan.

Missing day only

- If the month and year are the **same** as those of the last dose date, then impute day as the day of the last dose date;
- If either the year of partial date is **not the same as** the year of the last dose date, or the years are the same, but the month of partial date is **not the same as** the month of the last dose date, then impute day as last day of the month.

7.1.2 Concomitant Medication Date Imputation

Follow the general rules specified in Section 7.1 and rules in Section 7.1.1.

7.1.3 Prior Therapies Date Imputation

Follow the general rule specified in Section 7.1.

For start date partial as month and year are available, then impute day as '01'. *E.g.* impute partial date of 'DEC2013' as '01DEC2013'.

For start date partial as year only is available, then impute day and month as '01JAN'. *E.g.* impute partial date of '2013' as '01JAN2013'.

For end date partial as month and year are available, then impute day as last day of the month. *E.g.* impute partial date of 'JUN2013' as '30JUN2013'.

For end date partial as year only is available, then impute day and month as the last day of the year. *E.g.* impute partial date of '2013' as '31DEC2013'.

If the imputed starting date is earlier than initial diagnosis date, it should be set as the initial diagnosis date. No overlap between the exposure to prior therapies and study drug will be allowed and any overlap of exposure will be queried at data review stage. The end date of prior therapies will be imputed to first dose date of study drug – 15 if there is overlap due to imputation of partial dates. When there are multiple lines of prior therapies, the end date of prior therapies will be imputed to first dose date of the subsequent line of therapy -1 if there

is overlap due to imputation of partial dates. If the end year for one prior therapy is the same as the start year for the next prior therapy, impute Jun 30 and Jul 1 of that year for the end and start days if missing months and days.

7.1.4 Death Date Imputation

- If death date is completely missing, will use latest alive date + 1
- If both month and day are missing, then use the first date (01 JAN) of the year, or latest alive date + 1, whichever is later
- If only day is missing, then use the first day of the month, or latest alive date + 1, whichever is later.

7.1.5 Post-Therapies Date Imputation

Follow the general rule specified in Section 7.1.

7.1.6 Other Imputations

Follow the general rule specified in Section 7.1.

7.2 Table, Listing, and Figure Format

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmer user identification, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is for both table and listing presentations for post-text tables. A *portrait* layout is for in text table.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9 cm from the right. The *top and bottom margins* will be a minimum 2.92 cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size = 141 and page size = 44 for *8-point* font size, and line size = 161 and page size = 50 for *7-point* will be used to fit on both United Kingdom and US paper sizes.

In a listing, in the case that a patient's record has been continued to the next page, an appropriate identification (e.g. the patient identification number) must be presented at the beginning of that page.

7.3 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the StdDev will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place (XX.X%).

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.

Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by analysis group, patient and visit and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

8. REFERENCES

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