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Clinical Protocol

Study BLU-285-1303

Study Title: An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU-285 vs Regorafenib in Patients With Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)

Document Date: 20 June 2019

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CLINICAL RESEARCH PROTOCOL

DRUG:	Avapritinib (formerly BLU-285)
STUDY NUMBER:	BLU-285-1303
PROTOCOL TITLE:	An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU-285 vs Regorafenib in Patients with Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)
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Study No:	**BLU-285-1303**
Original Protocol Date:	**25 October 2017**
Protocol Version No:	**Amendment 3**
Protocol Version Date:	**20 June 2019**

This study protocol was subject to critical review and has been approved by the Sponsor. The information contained in this protocol is consistent with the current risk-benefit evaluation of the investigational product.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

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20 Jun 2019

Date

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STUDY SUMMARY

Title:	An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU-285 vs Regorafenib in Patients with Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)
Study Centers:	The study will be conducted at multiple centers in North America, Europe, Australia, and Asia.
Rationale:	Approximately 90% of patients with GIST have a tumor that is dependent on a mutation in either V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) (75%-80%) or the highly related protein platelet-derived growth factor receptor alpha (PDGFRα) (10%-15%). On a molecular level, the most common sites for oncogenic mutations at the time of diagnosis are in the juxtamembrane domain (exon 11 [60%-70%]) and extracellular domain (exon 9 [5%-15%]) for KIT and in the activation loop (Exon 18) for PDGFRα where the most common activation loop mutation is D842V. The current treatment paradigm for advanced GIST involves successive use of tyrosine kinase inhibitors (TKIs) that target KIT or PDGFRα. Avapritinib (formerly BLU-285), a highly potent and selective oral kinase inhibitor, was designed to treat imatinib-resistant GIST by targeting KIT/PDGFRα activation loop mutants. Avapritinib has potent activity on the KIT and PDGFRα activation loop mutants (exon 17/18), including the D842V mutation, with biochemical half-maximal inhibitory concentration (IC_{50}) against all activation loop mutants of less than 2 nM. In addition, avapritinib has demonstrated considerable potency across a wide array of disease-relevant KIT mutants found in patients with GIST including those that appear as secondary mutants after imatinib treatment and those found as primary mutants in imatinib-naïve GIST. No currently approved TKI selectively and potently inhibits activation loop mutations of KIT and PDGFRα. Thus, GISTs linked to either of these mutations represent an important medical need especially in patients who did not respond to imatinib and 1 other TKI and who have not been treated with regorafenib.
Number of Patients:	Approximately 460 patients will be enrolled and randomized in a 1:1 ratio, stratified by TKI treatment (third vs. fourth), geographic region (Asia vs. rest of the world), and mutation status (PDGFRα D842V mutation present vs. absent) including: • Approximately 230 patients randomized to receive avapritinib (Arm A). • Approximately 230 patients randomized to receive regorafenib (Arm B). At least 70% of the patients enrolled should be receiving their third distinct TKI treatment for GIST, ie, no more than 30% of patients should be receiving a fourth distinct TKI treatment for GIST. Enrollment will be restricted to include only patients receiving their third distinct TKI treatment once 30% of the targeted 460 patients who are receiving their

fourth distinct TKI treatment have been enrolled.

Objectives:

Primary Objective:

- The primary objective is to demonstrate the efficacy of avapritinib based on progression-free survival (PFS) determined by central radiological assessment per modified Response Evaluation Criteria in Solid Tumors (mRECIST), version 1.1 in patients with advanced GIST following 2 or 3 prior TKI therapies, including imatinib, compared to patients treated with regorafenib.

Secondary Objectives:

The key secondary objectives are:

- To evaluate objective response rate (ORR) determined by central radiology assessment per mRECIST, version 1.1 in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
- To evaluate overall survival (OS) in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.

To preserve study-wide Type I error, the key secondary objectives will be tested in the order presented, as part of the sequential testing scheme for the study if the primary analysis is significant.

Additional secondary objectives are:

- To evaluate the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-C30) individual scores in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
- To evaluate the safety and tolerability of avapritinib compared to regorafenib.
- To evaluate disease response rate as assessed by the Investigator per mRECIST, version 1.1 and determined by central radiological assessment per Choi criteria in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
- To evaluate disease control rate (DCR) per mRECIST, version 1.1 in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
- To evaluate duration of response (DOR) per mRECIST, version 1.1 in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
- To determine steady state systemic exposure of avapritinib.
- To assess the patient-reported perception of abdominal pain.

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Study Design:

This is an open-label, randomized, Phase 3 study in patients with locally advanced unresectable or metastatic GIST (advanced GIST) of avapritinib versus regorafenib in patients previously treated with imatinib and 1 or 2 other TKIs.

All study visits are intended to be conducted on an outpatient basis. After provision of written informed consent, patients will be evaluated for study eligibility during the screening period within 4 weeks (28 days) before study drug administration on Cycle 1 Day 1 (C1D1). During the screening period, eligibility will be confirmed; management of baseline concomitant conditions will be recorded and stabilized; and baseline symptoms will be assessed. Hematology, blood chemistry, mutation status, brain imaging (computed tomography [CT] scan or magnetic resonance imaging [MRI]), and baseline tumor assessments (CT scan or MRI) will be performed within 28 days of C1D1.

Patients will be randomly assigned, in a 1:1 ratio, to 1 of 2 treatment arms: Arm A (avapritinib) or Arm B (regorafenib) stratified by TKI treatment (third vs. fourth), geographic region (Asia vs. rest of the world), and mutation status measured in ctDNA or a tumor sample (PDGFRα D842V mutation present vs. absent). Patients randomized to Arm A will receive avapritinib 300 mg orally (PO) once daily (QD). Patients who experience disease progression on avapritinib, based on central review, will be offered the opportunity to continue taking treatment with avapritinib if there is no clinical evidence of disease progression (including worsening of laboratory values); the patient is not experiencing rapid progression of disease or a progressive tumor requiring urgent alternative medical intervention at critical anatomical sites (eg, spinal cord compression); and there has been no decline in Eastern Cooperative Oncology Group Performance Status (ECOG PS). Patients randomized to Arm A must consent to continue avapritinib treatment after disease progression.

	Patients randomized to Arm B will receive regorafenib 160 mg PO QD for 3 weeks out of every 4 weeks (28 days) cycle (ie, 3 weeks on/1 week off). Patients who experience disease progression on regorafenib (Arm B), as confirmed by central radiology review, may be offered the opportunity to cross over to the avapritinib treatment arm (Arm A) after an evaluation of their disease progression and a washout period of 7 to 28 days after their last dose of regorafenib. Patients randomized to Arm B must consent to cross over to avapritinib treatment after disease progression. At least 70% of the patients enrolled should be receiving the study drug as their third distinct TKI treatment for GIST, ie, no more than 30% of patients should be receiving the study drug as their fourth distinct TKI treatment for GIST. In addition, patients will receive best supportive care, excluding any additional anticancer therapy such as any systemic antineoplastic therapy (including kinase inhibitors and chemotherapy), radiation therapy, or surgery. All patients will present to the study center on C1D1 for the first dose of study drug, vital sign measurements, safety monitoring, quality-of-life (QoL) assessment, PRO assessments, electrocardiogram (ECG) assessment, and AE recording. On Cycle 2 Day 1 (C2D1) and Cycle 3 Day 1 (C3D1), patients will present to study centers for physical examination, laboratory assessments, QoL assessments, PRO assessments, and AE/concomitant medication recording. For all subsequent cycles, all patients will attend study center visits every other cycle on Day 1 of odd cycles (ie, C5D1, C7D1 etc.) for safety monitoring including ECG, hematology, blood chemistry, QoL assessments, PRO assessments, and AE recording. At any point in time between treatment cycles patients should attend or contact the study center for AE reporting, evaluation, and medical intervention. Tumor assessments will be performed at Baseline and then every 8 weeks (± 1 week) counting from C1D1, regardless of the scheduled treatment cycles, ie, if study treatment is interrupted or discontinued for any reason, tumor imaging should continue according to an 8-week schedule until tumor progression is confirmed by central radiology review. Computed tomography with intravenous contrast is the preferred imaging modality, unless a site of disease is better evaluated by MRI. All patients will attend an End-of-Treatment (EOT) visit within 14 (±7) days after the last dose of study drug. A safety Follow-up visit for resolution of any ongoing AE will be made on Day 30 (±7 days) after the last dose of study drug, or at the time the patient initiates another antineoplastic therapy. Patients who discontinue study treatment before disease progression will undergo tumor assessments every 8 weeks until disease progression, death, or patient withdrawal of consent. After documentation of disease progression by central radiology review, patients are to be followed for subsequent antineoplastic therapy and survival approximately every 2 months until death, withdrawal of consent or closure of the study by the Sponsor.
Duration of Treatment:	It is anticipated that patients will receive at least 1 cycle of avapritinib if randomized to Arm A and regorafenib if randomized to Arm B; no

	maximum treatment duration has been set. After C1, patients may continue to receive study drug until precluded by toxicity, noncompliance, pregnancy, withdrawal of consent, physician decision, progressive disease (PD), death, or closure of the study by the Sponsor.
Duration of Patient Participation:	The minimum duration of patient participation is approximately 3 months, including a screening period to assess study eligibility up to 4 weeks (28 days); a treatment period of at least 1 cycle (28 days); an EOT visit at least 14 ± 7 days after the last dose of study drug; and a Safety Follow-up visit in the clinic for physical examination and resolution of any AEs 30 days (± 7 days) after the last dose of study drug. Thereafter, patients are to be followed for tumor imaging every 8 weeks (± 7 days) until disease progression, death, initiation of new anti-GIST therapy, withdrawal of consent, or closure of the study by the Sponsor and then survival approximately every 2 months until death, withdrawal of consent or closure of the study by the Sponsor.
Duration of Study:	The expected enrollment period is approximately 18 months, and the expected duration of the study to reach the primary analysis timepoint is approximately 24 months until a total number of 264 PFS events are reached. The study will be completed when all patients are no longer receiving study drug and follow-up for OS has been concluded.
Target Population:	Inclusion Criteria: 1. Patients who are ≥18 years of age. 2. Patients who have histologically confirmed metastatic or unresectable GIST. Unresectable GIST must be confirmed to be unresectable by a qualified surgeon. 3. Patients who have received imatinib and 1 or 2 other TKIs for the treatment of GIST, including TKIs used for adjuvant therapy. Each different TKI is counted once regardless of how often it was used, and if 2 different TKIs are used in combination, both TKIs are counted. Patients must have objective disease progression, inadequate clinical benefit, or intolerance to the prior TKIs. Patients must have disease progression prior to enrollment. Prior use of other systemic and local therapies is not restricted. 4. Patients who have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1. 5. Patient, or legal guardian if permitted by local regulatory authorities, who provides informed consent to participate in the study.
Primary Endpoints:	• The primary endpoint is PFS, based on central radiological assessment per mRECIST, version 1.1, in patients with advanced GIST. Progression-free survival is defined as time from randomization to disease progression, or death due to any cause, whichever occurs first.
Secondary Endpoints:	The key secondary endpoints are: • Objective response rate defined as the percentage of patients whose best response is CR or PR as assessed by central radiology using mRECIST, version 1.1.

- Overall survival defined as the time from date of randomization to death due to any cause.

Additional secondary endpoints include:

- All individual EORTC QLQ-C30 scores, eg, physical functioning score, pain score, role functioning score, appetite loss score, etc.

- Adverse events, serious AEs, and changes in safety laboratory parameters, 12-lead ECG evaluations, and ECOG PS. The intensity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

- Response as assessed by Investigator per mRECIST, version 1.1. and assessed by central radiology per Choi criteria.

- Disease control is defined as the rate of CR or PR of any duration, or stable disease (SD) lasting for at least 16 weeks per mRECIST, version 1.1.

- Duration of response defined as the time from first documentation of tumor response to disease progression or death due to any cause.

- Plasma drug concentration at specified time points.

- Abdominal pain as measured by a numeric rating scale (0-10).

Exploratory Endpoints

Pharmacokinetics

Blood samples will be collected to determine circulating plasma concentrations (including any relevant metabolites) of avapritinib.

Statistical Methods and Data Analysis

The primary endpoint of PFS is defined as the time from randomization to disease progression or death due to any cause, whichever occurs first. The primary analysis for PFS is based on the central radiological assessment of PD per mRECIST, version 1.1 in the ITT population.

Patients without disease progression or death at the time of analysis will be censored at their last date of tumor evaluation. Patients who withdraw from the study and receive subsequent antineoplastic therapy without documented PD will be censored at the time of the last adequate (CT or MRI scan available) disease assessment. For PD documented between scheduled evaluations, the actual date of PD will be used, not the date of the next scheduled evaluation. For death or PD after no more than 1 missed evaluation, the date of the event will be the date of PD or death, whichever occurs first. For death or PD after more than 1 missed evaluation, the date of the event will be censored at the last adequate disease assessment.

Detailed censoring methods will be described in the statistical analysis plan.

The Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. The primary treatment comparison is based on a stratified log-rank test in the intent-to-treat population. The hazard ratio, and its 95% confidence interval (CI), are to be estimated based on a stratified Cox's model with treatment as the explanatory variable. Stratification factors include TKI treatment (third vs. fourth), geographic region (Asia vs. rest of the world), and mutation status measured in ctDNA or a tumor sample (PDGFRα D842V mutation present vs. absent).

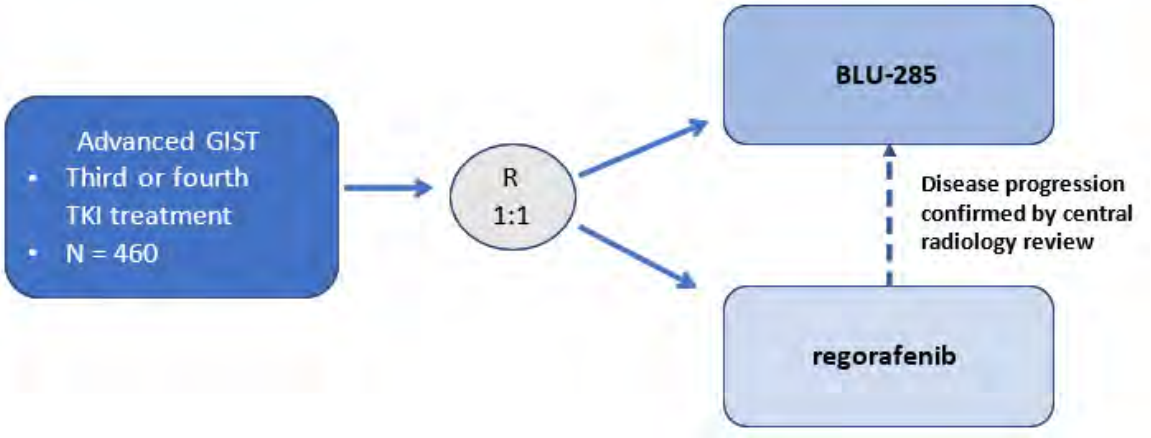
The key secondary endpoints are: ORR and OS. The ORR, as assessed by central radiological assessment according to mRECIST, version 1.1, will be evaluated and analyzed for the intent-to-treat population. A stratified Cochran-Mantel-Haenszel test will be performed to test treatment difference. A logistic regression model will be used to estimate the treatment effect measured in terms of odds ratios.

The primary treatment comparison for OS will be based on a rank preserving structural failure time model to account for treatment crossover effects from regorafenib to avapritinib. The survival time gained/lost by receiving avapritinib after crossover in the regorafenib group will be estimated. Rank preserving structural failure time reconstructs the survival duration of patients as if they had never received avapritinib, assuming treatment is acting by multiplying survival time by a given factor once a patient starts receiving avapritinib (Korhonen et al, 2012). If the patient is alive or the vital status is unknown at the time of analysis, OS will be censored at the date the patient is last known to be alive. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. The hazard ratio and its 95% confidence interval will be estimated based on Cox's regression model with stratification factors as covariates.

A gate-keeping method will be implemented to control Type I error. The ORR will be analyzed when superiority is demonstrated for PFS. The OS will be analyzed when superiority is demonstrated for both PFS and ORR.

Safety will be evaluated by the incidence of AEs, causality, intensity, seriousness, and type of AEs, and by the patient's vital signs, ECOG PS scores, clinical laboratory test results, and ECG data. All safety data will be listed by patient and summarized by treatment arm.

STUDY SCHEMATIC



Abbreviations: GIST = gastrointestinal stromal tumor; N = number of patients; R = randomized; TKI = tyrosine kinase inhibitor.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the systemic plasma concentration versus -time curve from zero through 24 hours
β-hCG	Beta human chorionic gonadotropin
BSC	Best supportive care
CI	Confidence interval
C_{max}	Maximum systemic concentration
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CxDx	Cycle x Day x
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EEG	Electroencephalogram
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life
EOT	End-of-Treatment
EQ-5D-5L	EuroQol 5 Dimension
FACT-Cog	Functional Assessment of Cancer Therapy-Cognitive Function
GCP	Good Clinical Practice
GI	Gastrointestinal

Abbreviation	Definition
GIST	Gastrointestinal stromal tumor
GLP	Good Laboratory Practice
HNSTD	Highest non-severely toxic dose
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive web response system
KIT	V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDGFRα	Platelet-derived growth factor receptor alpha
PFS	Progression-free survival
PGI-C	Patients' Global Impression of Change
PGI-S	Patients' Global Impression of Severity
PK	Pharmacokinetic(s)
PO	Orally (per os; by mouth)
PR	Partial response
PRO	Patient-reported outcome
QD	Once daily
QoL	Quality-of-life
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease

Abbreviation	Definition
STD_{10}	Severely toxic dose for 10% of animals
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal

1 BACKGROUND AND RATIONALE

1.1 Background on Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GIST) are thought to develop from the interstitial cells of Cajal or their stem cell precursors. They are the most common mesenchymal tumors occurring in the gastrointestinal (GI) tract, representing approximately 0.1% to 3.0% of all GI malignancies (Miettinen and Lasota, 2006; Rammohan et al, 2013). GIST is most commonly diagnosed between the ages of 50 and 80 years, with a slight predilection for males (Nilsson et al, 2005).

GIST may develop at any point along the GI tract, with the stomach (60%) and small intestine (30%) being the most common locations; the remaining 10% of GIST arise from the esophagus, colon, rectum, or the mesentery (Nilsson et al, 2005). GIST most commonly presents with GI bleeding, with obstruction or acute tumor rupture occurring more rarely (Rammohan et al, 2013). Slightly fewer than half of patients with GIST present with high-risk characteristics, such as large size, local infiltration, and/or metastasis (Goettsch et al, 2005; Nilsson et al, 2005). GIST typically progresses by local extension from its site of origin, intra-peritoneal spread, and metastases to the hepatic parenchyma. Metastases to lymph nodes are rare.

Surgery is the primary treatment for patients with resectable or potentially resectable GIST with the goal being to obtain histologically negative margins. GIST is not considered sensitive to either systemic cytotoxic chemotherapy or radiation therapy.

1.1.1 Molecular Pathology of GIST

Approximately 90% of patients with GIST have a tumor that is dependent on a mutation in either V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) (75%-80%) or the highly related protein platelet-derived growth factor receptor alpha (PDGFRα) (10%-15%). On a molecular level, the most common sites for oncogenic mutations at the time of diagnosis are in the juxtamembrane domain (exon 11 [60%-70%]) and extracellular domain (exon 9 [5%-15%]) for KIT and in the activation loop (Exon 18) for PDGFRα where the most common activation loop mutation is D842V. The current treatment paradigm for advanced GIST involves successive use of tyrosine kinase inhibitors (TKIs) that target KIT or PDGFRα.

1.1.2 Treatment of GIST

Most patients with GIST present with resectable disease and undergo surgery. Surgery followed by adjuvant imatinib has been demonstrated to result in significantly prolonged recurrent-free survival (Gleevec, 2016). In metastatic, unresectable GIST the first treatment regimen is imatinib, a small molecule oral kinase inhibitor, indicated for the treatment of patients with KIT (CD117) positive unresectable and/or metastatic malignant GIST. Imatinib was assessed initially in a single, open-label trial involving 1 center in Europe and 3 centers in the United States (US). In this randomized study, 73 patients received imatinib 400 mg once daily (QD) and 74 patients received imatinib 600 mg QD.

An objective response was confirmed in 56 patients; the overall response rate for the combined study arms was 38% (95% confidence interval [CI], 30%-46%). These were all partial responses (PRs), and there was no statistically significant difference in response rates between the 2 dose groups (Dagher et al, 2002). After the initial open-label trial, 2 large, identical, open-label, randomized, global phase 3 studies were conducted where 1640 patients were enrolled and randomized to receive imatinib at doses of 400 mg orally (PO) QD or 800 mg PO QD. Patients in the 400 mg QD group who experienced disease progression were permitted to cross over to receive treatment with 800 mg QD. The results showed a response rate of 50% to 69% and a median progression-free survival (PFS) of approximately 19 months (Gleevec, 2016).

Commonly reported adverse events (AEs) included edema, fatigue, nausea, abdominal pain, diarrhea, rash, vomiting, myalgia, anemia, and anorexia. Edema most frequently included periorbital or lower extremity edema; severe edema was observed in 182 patients (11.1%). Other AEs included bone marrow suppression, GI bleeding, and elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin. Imatinib treatment is notably limited by primary resistance among 15% of patients and progressive disease (PD) through secondary resistance driven mutations in over 80% of patients.

In the second treatment regimen setting, based upon data from a randomized, placebo-controlled trial with supportive evidence from a single-arm study, sunitinib, an oral multi-kinase inhibitor, is indicated for the treatment of patients with GIST after disease progression or intolerance to imatinib. In patients treated with imatinib who had refractory or intolerant GIST, time-to-tumor progression of sunitinib-treated patients was superior to that of placebo-treated patients. Median time to tumor progression of sunitinib-treated patients was 27.3 weeks, compared to 6.4 weeks for placebo-treated patients ($p < 0.0001$). Partial responses were observed in 6.8% of sunitinib-treated patients. The most common AEs related to sunitinib included diarrhea, mucositis, skin abnormalities, and altered taste. Reductions in left ventricular ejection fraction and severe hypertension were also more common in sunitinib-treated patients. Sunitinib has also been associated with severe hepatoxicity resulting in liver failure or death. Sunitinib is potent against the wild type KIT kinase compared to a first treatment regimen; however, resistance to this therapy evolves usually within 1 year of treatment.

In the third treatment regimen setting, regorafenib, an oral multi-kinase inhibitor, is indicated for the treatment of patients with locally advanced unresectable or metastatic GIST who have been previously treated with imatinib and sunitinib. The United States Food and Drug Administration (US FDA) approved regorafenib in February 2013 based upon efficacy and safety evaluated in the GRID study, an international, multicenter, randomized, double blind, placebo-controlled trial (Demetri et al, 2013a) in 199 patients with unresectable, locally advanced or metastatic GIST, who had been previously treated with imatinib and sunitinib.

The primary efficacy outcome measure of the GRID study was PFS based on disease assessment by independent radiological review using modified Response Evaluation Criteria in Solid Tumors, version 1.1 (mRECIST, version 1.1). Patients were randomized

to receive 160 mg regorafenib PO QD (N=133) plus best supportive care (BSC) or placebo (N=66) plus BSC for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. At the time of disease progression as assessed by central review, the study blind was broken, and all patients were offered the opportunity to take regorafenib at the Investigator's discretion. Fifty-six (85%) patients randomized to placebo and 41 (31%) patients randomized to regorafenib received open-label regorafenib.

A statistically significant improvement in PFS was demonstrated among patients treated with regorafenib (4.8 months) compared to placebo (0.9 months) at a hazard ratio (HR) of 0.27 and no patients in either group had a complete response (CR), while 6 of the 133 patients in the regorafenib group and 1 of the 66 patients in the placebo group had a PR, giving objective response rates of 4.5% and 1.5%, respectively. Drug-related AEs were reported in 130 patients who received regorafenib (98%) and 45 patients who received placebo (68%). The most common regorafenib-related AEs of Grade 3 or higher were hypertension, hand-foot skin syndrome, and diarrhea. Regorafenib has also been associated with severe hepatoxicity resulting in liver failure or death.

Serious side effects, which occurred in less than 1% of patients, were liver damage, severe bleeding events, blistering and peeling of skin, severe hypertension that required emergency intervention, acute myocardial infarctions, and intestinal perforations.

Although imatinib is effective as a first treatment regimen for the majority of patients with GIST, primary imatinib resistance is a challenge in a subset of patients, and nearly all patients who receive imatinib ultimately develop secondary resistance. Subsequent treatment regimens for those who respond initially to imatinib are less effective. This diminished efficacy may be related to an acquired resistance to imatinib, which can occur due to multiple mutations in KIT, with exon 13 being the most common, and ~23% of activations loop mutations, with exon 17 being the most common. Primary resistance to all available therapies is most often due to wild type KIT and the D842V mutation in exon 18 of PDGFRα (5%-10% in unresectable/metastatic disease). In KIT-mutant GIST, activation loop mutations occur at a rate of ~20% after imatinib and ~90% after imatinib and sunitinib, and no currently approved TKI selectively and potently inhibits the activation loop mutations in KIT (Antonescu et al, 2005; Debiec-Rychter et al, 2006; Heinrich et al, 2003; Liegl et al, 2008; Wardelmann et al, 2006). Likewise, there are no effective therapies that inhibit D842V mutant PDGFRα (Cassier et al, 2012; Corless et al, 2005; Yoo et al, 2016). Thus, GIST, dependent on either of these mutations, represents an important medical need especially in patients who did not respond to imatinib.

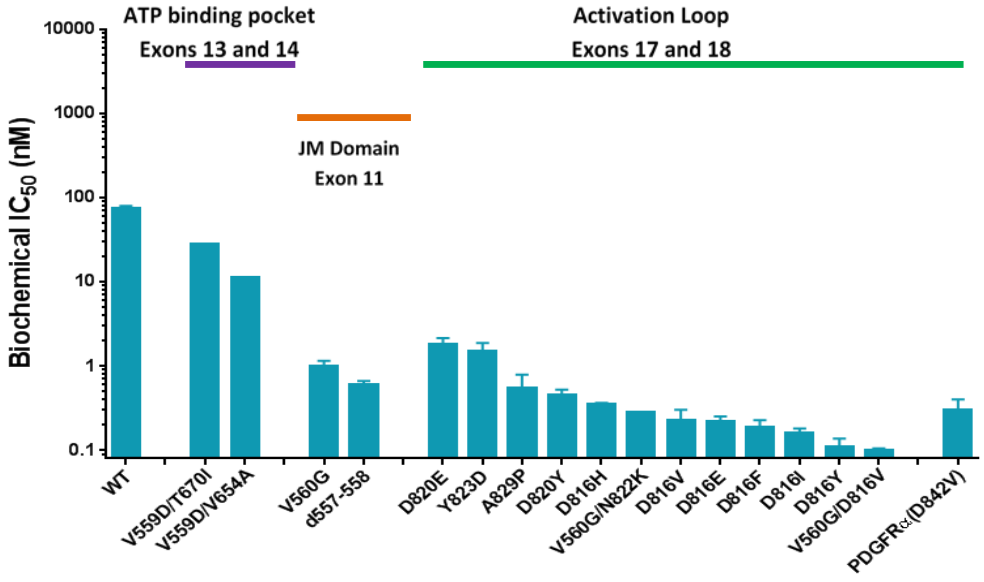
1.2 Avapritinib

1.2.1 Overview

Avapritinib (formerly BLU-285), a highly potent and selective oral kinase inhibitor, was designed to treat imatinib-resistant GIST by targeting KIT/PDGFRα activation loop mutants (exon 17/18). Avapritinib has potent activity on the KIT and PDGFRα activation loop mutants (exon 17/18), including the D842V mutation, with biochemical half-

maximal inhibitory concentration (IC_{50}) against all activation loop mutants of less than 2 nM (Figure 1). In addition, avapritinib has demonstrated considerable potency across a wide array of disease-relevant KIT mutants found in patients with GIST including those that appear as secondary mutants after imatinib treatment as well as the exon 11 mutants most commonly observed in imatinib-naïve GIST.

Figure 1: Biochemical Activity of Avapritinib Against Disease-relevant KIT Mutants



1.2.2 Summary of Nonclinical Information

A summary of the key nonclinical information is provided below. Additional information can be found in the Investigator Brochure (IB) for avapritinib.

1.2.2.1 Pharmacokinetic Drug Interactions

In vitro studies with recombinant human cytochrome P450 (CYP) enzymes demonstrated that avapritinib phase I metabolism is predominantly mediated by CYP3A4, with CYP2C9 playing a minor role. Therefore, CYP3A inhibitors may increase circulating levels of avapritinib and CYP3A inducers may reduce circulating levels of avapritinib.

In vitro, avapritinib is a reversible inhibitor of CYP2C9 and CYP3A4/5 at clinically relevant concentrations. The R_1 values for CYP2C9 and CYP3A4 inhibition and $R_{1,gut}$ value for CYP3A4 inhibition are ≥1.02 and >11, respectively. Avapritinib also demonstrated time-dependent inhibition of CYP3A4/5 in vitro with an estimated K_{inact} and K_I of 0.0301 min^{-1} and 12.3 μM, respectively and estimated R_2 value of ≥1.25. Therefore, clinical drug interactions with comedications for which CYP2C9, or CYP3A-mediated metabolism constitutes the primary mechanism of clearance are likely.

In vitro, avapritinib, at concentrations of 0.3 to 3 μM, induced CYP3A4 mRNA expression with a maximal 3.25-fold induction observed at 3 μM.

In vitro, avapritinib is an inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), and multidrug and toxin extrusion protein (MATE1, MATE2K). Therefore, avapritinib may have the potential to increase plasma concentrations of co-administered substrates of these transporters.

1.2.2.2 Safety Pharmacology

In an Irwin test to evaluate the effects of avapritinib on the gross behavioral, physiological, and neurological state of female Sprague-Dawley rats after 15 days of avapritinib administration, no test article–related effects were noted at a dose level of 15 mg/kg. A dose level of 45 mg/kg resulted in increased touch response, increased corneal reflex, increased pinna reflex, head flicking, exophthalmos, increased startle response, aggressiveness, vocalization, increased pain response, and/or tremors in 2 of 6 animals. These findings show an increase in sensitivity to stimuli and are potentially underlying indictors of preconvulsive activity. Although observed in a minority of treated animals and noted at lethal doses only, these signs were considered test article-related.

Avapritinib inhibited the human ether-à-go-go-related gene (hERG) channel with an IC_{50} of 2.4 μM (~100× the free mean maximum systemic concentration [C_{max}] of 0.0243 μM at the human maximum tolerated dose (MTD) of 400 mg QD). However, in an in vivo study in radiotelemetry-implanted Beagle dogs, avapritinib did not affect any cardiovascular parameter (heart rate, mean arterial blood pressure, and systolic, diastolic, and pulse pressure), body temperature, electrocardiogram (ECG) waveform morphology, duration of PR, QRS, RR, QT, and heart rate corrected QT intervals, respiratory parameters (respiratory frequency, tidal volume, and minute volume), or the clinical condition of the animals. The observed C_{max} of 1650 ng/mL at the high dose of 45 mg/kg in the telemetrized dog study was 1.6-fold higher than the human C_{max} of 1009 ng/mL at the human MTD of 400 mg QD.

1.2.2.3 Toxicology

Sprague-Dawley rats and Beagle dogs were chosen as the nonclinical test species for assessing chemical structure- and pharmacology-mediated toxicity of avapritinib on the basis of the following criteria: a) these species are pharmacologically responsive to the effects of avapritinib; b) these species have historically been used to assess potential human adverse effects; and c) these species are qualitatively similar in hepatocyte metabolism profiles to humans.

Two 28-day Good Laboratory Practice (GLP)-compliant repeated dose toxicology studies were conducted in Sprague-Dawley rats. These studies determined that the severely toxic dose in 10% of animals (STD_{10}) was 30 mg/kg/day (180 mg/m^2/day). The Day last area under the systemic plasma concentration versus -time curve from zero through 24 hours (AUC_{0-24}) of 208000 h•ng/mL at 30 mg/kg/day in rats is approximately 10-fold higher than the steady state (Day 15) $AUC_{0-\tau}$ of 20298 h•ng/mL at the human MTD of 400 mg

QD. The toxicities defining the STD_{10} were inanition and metabolic perturbations (including changes in serum and urine chemistries, body weight loss, decreased food consumption, tissue effects [including gonad effects] and convulsions). All findings reversed after the 2-week recovery period except gonad effect. No morphologic brain alterations were observed.

In a 28-day GLP-compliant toxicology study in male Beagle dogs, the highest non-severely toxic dose (HNSTD) was 7.5 mg/kg/day (150 mg/m^2/day). The Day last AUC_{0-24} of 6115 h•ng/mL at 7.5 mg/kg/day in dogs is approximately 0.3 times the steady state (Day 15) AUC0-τ of 20298 h•ng/mL at the human MTD of 400 mg QD. The toxicities defining the HNSTD were inanition, metabolic perturbations (including changes in urine electrolytes and serum cholesterol and triglycerides) with vomiting, diarrhea, decreased food intake, body weight loss, hematologic and serum chemistry alterations, and microscopic alterations in tissues, including single focal brain hemorrhage in 3 of 10 dogs treated at doses above the HNSTD, decreased bone marrow cellularity, and gonad effects. All findings reversed after the 2-week recovery period, except gonad and brain effects.

GLP-compliant 3-month toxicology studies were conducted to further characterize dose-limiting toxicities (DLTs) in the dog and rat. In the rat study, no DLT was identified and the highest dose tested was identified as the HNSTD. In dogs, central nervous system (CNS) effects including brain hemorrhage were considered dose limiting. The HNSTD in dogs was 7.5 mg/kg/day (150 mg/m^2/day), consistent with the 28-day toxicology study.

Due to the occurrence of convulsions in rats, a study was conducted to determine if the oral administration of avapritinib evokes changes in electroencephalographic (EEG) measures consistent with seizures or altered seizure threshold in rats. Administration of avapritinib at the STD_{10} (30 mg/kg/day) for 9 consecutive days did not result in frank seizures or in EEG changes suggestive of lowered seizure threshold. Convulsions associated with EEG abnormalities were observed when animals were dosed at 50 mg/kg/day, a dose that exceeds the STD_{10}.

In a follow-up, non-GLP-compliant study conducted in the rat, diazepam, a routinely used anti-seizure medication, was observed to ameliorate avapritinib-induced CNS effects in rats. The ameliorative effects of diazepam on avapritinib-induced altered seizure potential were noted in rats at the early stages of pre-seizure effects as well as at the onset of a frank seizure. These data in Sprague-Dawley rats suggest that diazepam may be effective in preventing avapritinib-induced altered seizure potential.

Avapritinib did not cause mutagenesis in the Ames bacterial mutagenesis assay. In the in vitro chromosome aberration test, in cultured human peripheral blood lymphocytes, avapritinib demonstrated minimal potential to cause chromosomal aberrations. However, avapritinib did not demonstrate any potential to induce micronuclei in vivo in rats. As the in vivo micronucleus assay is considered to be a more physiologically relevant and informative indicator of human genotoxicity risk than the in vitro chromosome aberration test, the overall risk of genotoxicity with avapritinib is considered to be low.

1.2.3 Summary of Clinical Studies

The avapritinib clinical development program was initiated in August 2015 and includes 2 ongoing Phase 1 clinical studies:

1. BLU-285-1101: A Phase 1 study of BLU-285 in patients with GIST and other relapsed and refractory solid tumors.

2. BLU-285-2101: A Phase 1 Study of BLU-285 in patients with advanced systemic mastocytosis and relapsed or refractory myeloid malignancies.

In addition, the avapritinib clinical pharmacology development program includes a completed bioavailability study and other ongoing or planned studies to evaluate food effect, drug-drug interaction, and bioequivalence.

Summaries of the data from studies of avapritinib are provided in the IB.

1.2.3.1 Study BLU-285-1101

Study BLU-285-1101 is assessing the safety, PK and clinical activity of avapritinib in adult patients with unresectable GIST. In Part 1 of the study, patients with GIST must have had disease that had progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase-inhibitor agent, or disease with a D842 mutation in the PDGFRα gene. Patients in Part 1 (dose escalation) received avapritinib QD on a 4-week cycle following a 3+3 design, which allowed additional accrual to dose levels demonstrated to be safe. In Part 2 of the study, expansion cohorts dosed at the recommended Phase 2 dose include the following 3 groups of patients:

- 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.

- Group 2: Patients with unresectable GIST harboring a D842V mutation in the PDGFRα gene.

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

Adverse events based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, PK and plasma/tumor mutant DNA levels are being assessed. Response is being determined according to mRECIST, version 1.1 approximately every 8 weeks. This study is currently ongoing.

As of 11 October 2017, 116 patients with GIST have been treated with avapritinib

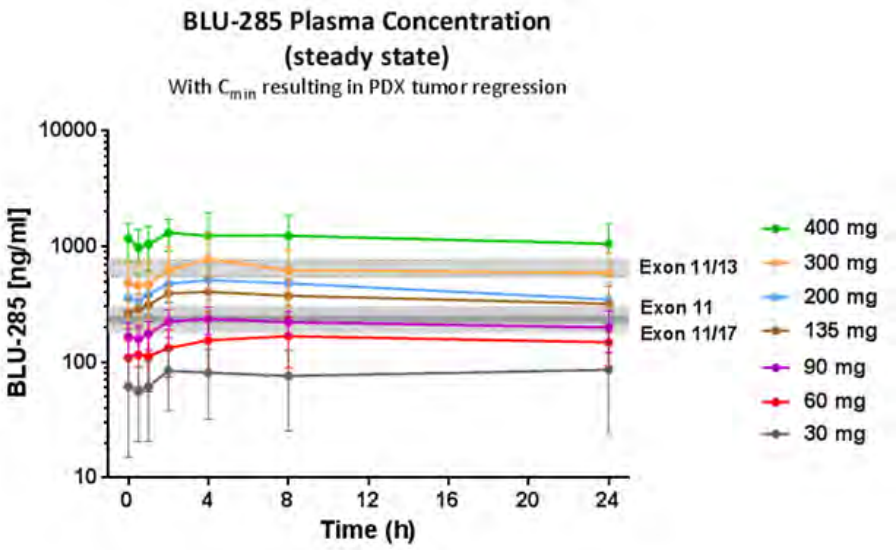
including 46 patients who were enrolled and treated during the dose escalation part of the study, and 70 patients in the expansion part.

Treatment with avapritinib has been well tolerated in patients with GIST. Most AEs have been Grade 1 or 2 in intensity, with the most common (≥ 25%) including nausea (56%), fatigue (53%), periorbital edema (43%), vomiting (41%), peripheral edema (34%), anemia (31%), diarrhea (31%), cognitive effects (consisting of multiple similar AEs aggregated into a single category [30%]), increased lacrimation (30%), and decreased appetite (28%). There were no DLTs until the 600 mg dose cohort was reached and DLTs were noted in 2 patients: 1 patient experienced Grade 2 hypertension, Grade 2 rash, and Grade 2 memory impairment; the other patient experienced Grade 2 hyperbilirubinemia. The maximum tolerated dose was determined to be 400 mg QD.

Overall, 49 patients discontinued avapritinib treatment. Six patients discontinued due to AEs, 40 patients discontinued due to disease progression, and 3 patients discontinued avapritinib due to patient's decision.

The single dose (Cycle 1 Day 1; C1D1) and steady state (Cycle 1 Day 15; C1D15) pharmacokinetics of avapritinib have been evaluated in Study BLU-285-1101. Preliminary unaudited PK data from the 11 April 2018 datacut are presented. After administration of single oral doses of avapritinib ranging from 30 to 400 mg avapritinib, the median time to peak concentration (T_{max}) ranged from 2 to 4 hours postdose, and the mean plasma elimination half-life of avapritinib ranged from 35 hours to 57 hours. After a single dose and repeat dosing of avapritinib, systemic exposure was dose proportional over the dose range of 30 mg to 400 mg QD. The steady state (C1D15) geometric mean C_{max} (%CV) of avapritinib at doses of 300 mg QD and 400 mg QD was 774 ng/mL (49.4%) and 1009 ng/mL (50.9%), respectively, and the corresponding area under the plasma concentration-time curve ($AUC_{0-\tau}$) was 14074 h•ng/mL (45.1%) and 20298 h•ng/mL (41.5%), respectively. The mean accumulation ratio after repeat dosing of avapritinib (dose range: 30 – 400 mg QD) was 3.4 – 5.2. Based on the data collected thus far, and the exposures required for antitumor activity in GIST patient-derived xenograft models (Figure 2), systemic exposure at 300 mg QD - 400 mg QD is predicted to provide broad coverage of the primary (eg, exon 11) and secondary KIT (eg, exon 11/17 and exon 11/13) mutations.

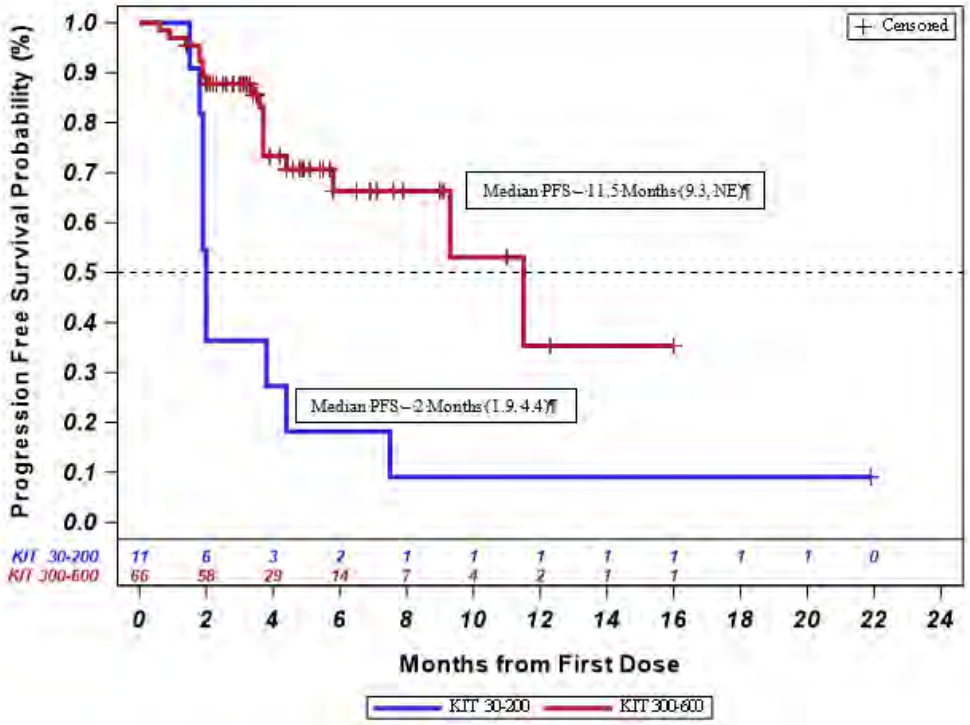
Figure 2: Clinical Exposure of Avapritinib Reaches Levels Projected to be Efficacious Across Multiple KIT-mutant Genotypes



As of 11 October 2017, 74 patients including 31 patients with a PDGFRα D842V mutation and 43 patients with a KIT mutation were evaluable for the analysis of efficacy (ie, had at least 1 mRECIST, version 1.1 response determined by radiographic assessment and evaluated by blinded central review). The median number of prior kinase inhibitor regimens was 4 (ranging from 2 to 11) among patients with a KIT mutation and 1 (ranging from 0 to 6) among patients with a PDGFRα mutation.

Of the 31 patients with a PDGFRα D842V mutation who had a radiographic assessment evaluated by blinded central review, 21 PDGFRα D842V patients had PR (objective response rate [ORR] 71%, 18 confirmed, and 3 pending confirmation) and 9 PDGFRα D842V patients had stable disease (SD). Clinical and molecular response was observed in heavily pretreated patients with KIT – mutant GIST with a median of 4 prior TKIs. Of the 43 efficacy-evaluable patients with a KIT mutation treated at all dose levels, 6 KIT patients had PR (5 confirmed and 1 pending confirmation; ORR 14%) and 23 KIT patients had SD. Among patients treated at or above the Part 2 starting dose of 300 mg, 5 patients have had a PR (ORR 16%). In patients with a KIT mutation treated at doses ≥ 300 mg QD, the median PFS was 11.5 months and in patients treated at doses between 30 mg and 200 mg the median PFS was 2 months. (Figure 3). Overall, decreases in tumor size were observed in patients with a variety of KIT mutations, including mutations in exons 9, 11, 13, 17 and 18 (Heinrich et al, 2017). In this heavily pretreated population, imatinib rechallenge has shown a median PFS of 1.8 months (Kang et al, 2013).

Figure 3: Probability of PFS with Avapritinib in KIT-mutated GIST patients at Low and High Dose Levels.



Abbreviations: GIST = gastrointestinal stromal tumor; KIT = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PFS = progression-free survival.

In summary, treatment with avapritinib has demonstrated potent and selective activity against KIT and PDGFRα mutants in vitro and growth inhibition in TKI-resistant models in nonclinical and clinical studies. It has been shown to be efficacious and tolerable at active doses in nonclinical toxicology and safety pharmacology studies, as well in the Phase 1 clinical program with dose expansion cohorts. Given the poor prognosis and potential risk/benefit of avapritinib for patients with advanced GIST, further development of this agent is warranted in a third treatment regimen setting.

1.3 Study Rationale

No currently approved TKI selectively and potently inhibits the activation loop mutations of KIT and PDGFRα. Thus, GISTs linked to either of these mutations represent an important medical need especially in patients who did not respond to imatinib and 1 other TKI and who have not been treated with regorafenib.

Avapritinib, a highly potent and selective oral kinase inhibitor, was designed to treat imatinib-resistant GIST by targeting KIT/PDGFRα activation loop mutants. Avapritinib has potent activity on the KIT and PDGFRα activation loop mutants with biochemical IC_{50} against all activation loop mutants less than 2 nM. In addition, avapritinib has demonstrated considerable potency across a wide array of disease-relevant KIT mutants found in patients with GIST including those that appear as secondary mutants after

imatinib treatment and those found as primary mutants in imatinib-naïve GIST; it is also potent against D842V mutant PDGFRα, which results in resistance to the available TKIs.

As of 11 October 2017, preliminary Phase 1 clinical data with avapritinib in patients with advanced KIT mutant GIST have shown the compound to be well tolerated with clinically meaningful evidence of anti-tumor activity including radiographic response. Based on the supportive efficacy and safety data (see Section 1.2.3.1), avapritinib may serve as a novel targeted treatment option for patients with previously treated advanced GIST.

Study BLU-285-1303 is an open-label randomized study designed to demonstrate the efficacy and safety of avapritinib in patients with locally advanced unresectable or metastatic GIST previously treated with at least 2 TKIs including imatinib compared to regorafenib. Patients eligible for this study are those who received imatinib and 1 or 2 other TKIs as prior treatment regimens including adjuvant therapy, with objective disease progression, inadequate clinical benefit or intolerance, or had disease progression or intolerance to other systemic therapies including investigational agents and radiotherapy, and have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2. Patients who experienced intolerance to prior therapies must have objective disease progression prior to enrollment onto BLU-285-1303 study.

As regorafenib is the only approved TKI treatment for patients with GIST who have received 2 prior TKIs, patients who experience disease progression on regorafenib during this study, as confirmed by central radiology review, may be offered the opportunity to cross over to the avapritinib treatment arm (see Section 7.6 for additional details).

1.4 Benefit/Risk Assessment

GIST is a sarcoma of the gastrointestinal tract. It commonly presents with GI bleeding and gastrointestinal obstruction. Surgery is the primary therapy for patients with resectable disease. GIST that is metastatic or locally advanced and unresectable is treated with TKIs that target KIT. Imatinib is the standard first-line therapy for patients with metastatic and locally advanced, unresectable GIST. Sunitinib and regorafeninb are the standard second-line therapies, respectively; however, other TKIs targeting KIT are also used in the second- and third-line setting. Therefore, regorafenib is also often used in the fourth-line setting.

This study includes patients with metastatic and locally advanced, unresectable GIST who have been treated with imatinib and one or two other TKIs, but have not received regorafenib. Patients will be randomly assigned to treatment with avapritinib (the experimental group) or regorafenib (the control group). Following treatment with imatinib and a second TKI the outcome for patients with GIST is very poor. Treatment with regorafenib following imatinib and sunitinib provides a median PFS of about 5 months and a response rate of about 5 months. The median survival for patients treated with available TKIs in the third- and fourth-line setting is about 1 year (Ozer-Stillman et al, 2015).

Avapritinib is a selective and potent inhibitor of KIT and PDGFRα. Activating mutations in *KIT* and *PDGFRA* are the primary drivers of GIST in about 90% of patients (75-80% *KIT* and 10-15% *PDGFRA*). As described in Section 1.2.1, avapritinib potently inhibits *KIT* and *PDGFRA* carrying the activating mutations most commonly found in GIST tumors. Avapritinib has demonstrated important clinical activity in an ongoing clinical study, BLU-285-1101, in patients with advanced, heavily pre-treated GIST. As described in Section 1.2.3.1, the response rate with avapritinib was 16% among patients with *KIT*-driven GIST treated at doses of 300-400 mg QD. Importantly, these patients were heavily pre-treated, having received a median of 4 prior lines of therapy. The response rate was 71% among patients with *PDGFRA*-driven GIST across all dose levels. These patients had received a median of 1 prior line of therapy; however, *PDGFRA*-driven GIST is typically not responsive to any of the available TKIs, including imatinib. Based on preliminary data from this ongoing study the median PFS in patients with *KIT*-driven GIST was 11.5 months, and the median PFS in patients with *PDGFRA*-driven GIST was not yet reached.

Overall, avapritinib has been well-tolerated in patients with GIST. Most AEs have been Grade 1 or Grade 2 in severity and consistent with the effects of KIT inhibition. Adverse events occurring in ≥25% of patients (regardless of relationship to avapritinib) included nausea (56%), fatigue (53%), periorbital edema (43%), vomiting (41%), peripheral edema (34%), anemia (31%), diarrhea (31%), cognitive effects (consisting of multiple similar AEs aggregated into a single category [30%]), increased lacrimation (30%), and decreased appetite (28%). Among 116 patients treated with avapritinib in the BLU-285-1101 study as of the 11 October 2017 data cut-off only 6 (5%) have discontinued treatment due to a treatment-related AE.

Overall, the benefit-risk assessment is favorable and warrants continued development of avapritinib in patients with advanced GIST.

2 STUDY OBJECTIVES

2.1 Primary Objective

- The primary objective is to demonstrate the efficacy of avapritinib based on PFS determined by central radiological assessment per mRECIST, version 1.1 in patients with advanced GIST following 2 or 3 prior TKI therapies, including imatinib, compared to patients treated with regorafenib.

2.2 Secondary Objectives

The key secondary objectives are:

- To evaluate ORR determined by central radiology assessment per mRECIST, version 1.1 in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.

- To evaluate overall survival (OS) in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.

To preserve study-wide Type I error, the key secondary objectives will be tested in the order presented, as part of the sequential testing scheme for the study if the primary analysis is significant.

Additional secondary objectives are:

- To evaluate the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-C30) individual scores in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
- To evaluate the safety and tolerability of avapritinib compared to regorafenib.
- To evaluate disease response rate as assessed by the Investigator per mRECIST, version 1.1 and determined by central radiological assessment per Choi criteria in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
- To evaluate DCR per mRECIST, version 1.1 in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
- To evaluate duration of response (DOR) per mRECIST, version 1.1 in patients with advanced GIST treated with avapritinib compared to patients treated with regorafenib.
- To determine steady state systemic exposure of avapritinib.
- To assess the patient-reported perception of abdominal pain.

[redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoints

- The primary endpoint is PFS, based on central radiological assessment per mRECIST, version 1.1, in patients with advanced GIST. Progression-free survival is defined as time from randomization to disease progression, or death due to any cause, whichever occurs first.

3.2 Secondary Endpoints

The key secondary endpoints are:

- Objective response rate defined as the percentage of patients whose best response is CR or PR as assessed by central radiology using mRECIST, version 1.1.

- Overall survival defined as the time from date of randomization to death due to any cause.

Additional secondary endpoints include:

- All individual EORTC QLQ-C30 scores, eg, physical functioning score, pain score, role functioning score, appetite loss score, etc.

- Adverse events, serious AEs (SAEs), and changes in safety laboratory parameters, 12-lead ECG evaluations, and ECOG PS. The intensity of AEs will be assessed by the NCI CTCAE, version 5.0.

- Response as assessed by Investigator per mRECIST, version 1.1. and assessed by central radiology per Choi criteria.

- Disease control is defined as the rate of CR, or PR of any duration, or SD lasting for at least 16 weeks per mRECIST, version 1.1.

- Duration of response defined as the time from first documentation of tumor response to disease progression or death due to any cause.

- Plasma drug concentration at specified time points.

- Abdominal pain as measured by a numeric rating scale (0-10).

[redacted]

4 STUDY PLAN

4.1 Study Design

This is an open-label, randomized, Phase 3 study in patients with locally advanced unresectable or metastatic GIST (advanced GIST) of avapritinib versus regorafenib in patients previously treated with imatinib and 1 or 2 other TKIs.

All study visits are intended to be conducted on an outpatient basis. After provision of written informed consent, patients will be evaluated for study eligibility during the screening period within 4 weeks (28 days) before study drug administration on Cycle 1 Day 1 (C1D1). During the screening period, eligibility will be confirmed; management of baseline concomitant conditions will be recorded and stabilized; and baseline symptoms will be assessed. Hematology, blood chemistry, mutation status, brain imaging (CT scan or MRI), and baseline tumor assessments (CT scan or MRI) will be performed within 28 days of C1D1.

Patients are to be randomly assigned, in a 1:1 ratio, to 1 of 2 treatment arms: Arm A (avapritinib) or Arm B (regorafenib) stratified by TKI treatment (third vs. fourth), geographic region (Asia vs. rest of the world), and PDGFRα D842V mutation status measured in ctDNA or a tumor sample (PDGFRα D842V mutation present vs. absent). Patients randomized to Arm A will receive avapritinib 300 mg PO QD. Patients who experience disease progression on avapritinib, based on central review, will be offered the opportunity to continue taking treatment with avapritinib if there is no symptomatic evidence of disease progression or laboratory abnormalities attributable to disease progression, no rapid progression of disease or a progressive tumor requiring urgent alternative medical intervention at critical anatomical sites, and no decline in ECOG PS. Patients randomized to Arm A must consent to continue avapritinib treatment after disease progression; see Section 7.7 for additional details.

Patients randomized to Arm B will receive regorafenib 160 mg PO QD for 3 weeks out of every 4-weeks (28 days) cycle (ie, 3 weeks on/1 week off). Patients who experience disease progression on regorafenib, as confirmed by central radiology review, may be offered the opportunity to cross over to the avapritinib treatment arm (Arm A); see Section 7.6 for additional details. Prespecified dose modification guidance for AEs related to regorafenib and to avapritinib are described in Section 6.3.1.

At least 70% of the patients enrolled should be receiving the study drug as their third distinct TKI treatment for GIST, ie, no more than 30% of patients should be receiving the study drug as their fourth distinct TKI treatment for GIST. In addition, patients will

receive BSC, excluding any additional anticancer therapy such as any systemic antineoplastic therapy (including kinase inhibitors and chemotherapy), radiation therapy, or surgery.

All patients will present to the study center on C1D1 for the first dose of study drug, vital sign measurements, physical exam, quality-of-life (QoL) assessment, PRO assessments, laboratory assessments, ECG and AE recording. In Cycle 2 Day 1 (C2D1), Cycle 3 Day 1 (C3D1), Cycle 4 Day 1 (C4D1) and Cycle 5 Day 1 (C5D1), patients will present to study centers for physical examination, vital signs measurements, laboratory assessments, QoL assessments, PRO assessments, ECG, and AE/concomitant medication recording. On C1D15 and C2D15, all patients will attend study center visits for vital sign measurements, serum chemistry measurements, and AE reporting. For all subsequent cycles, all patients will attend study center visits every other cycle on Day 1 of odd cycles (ie, C7D1, C9D1 etc.) for physical examination, vital sign measurements, laboratory assessments, QoL assessments, PRO assessments, ECG and AE recording. At any point in time between treatment cycles patients should attend or contact the study center for AE reporting, evaluation, and medical intervention.

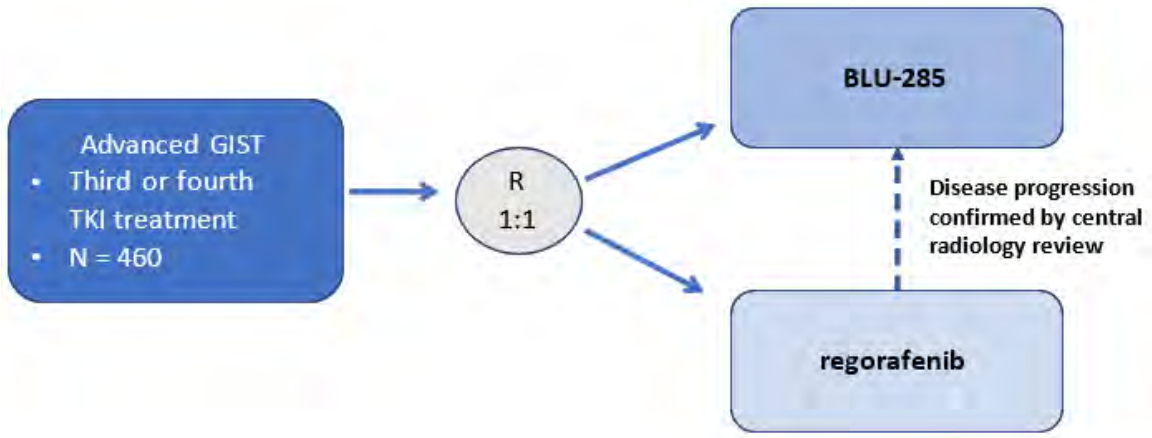
Tumor assessments will be performed at Baseline and then every 8 weeks (± 1 week) counting from C1D1, regardless of the scheduled treatment cycles, ie, if study treatment is interrupted or discontinued for any reason, tumor imaging should continue according to an 8-week schedule until tumor progression is confirmed by central radiology review. Computed tomography with intravenous (IV) contrast is the preferred imaging modality, unless a site of disease is better evaluated by MRI.

It is anticipated that patients will receive at least 1 cycle of avapritinib if randomized to Arm A and regorafenib if randomized to Arm B; no maximum treatment duration has been set. After C1, patients may continue to receive study drug until precluded by toxicity, noncompliance, pregnancy, withdrawal of consent, physician decision, PD, death, or closure of the study by the Sponsor.

All patients will attend an End-of-Treatment (EOT) visit within 14 (±7) days after the last dose of study drug. A safety Follow-up visit for resolution of any ongoing AE will be made on Day 30 (±7 days) after the last dose of study drug, or at the time the patient initiates another antineoplastic therapy. Patients who discontinue study treatment before disease progression will undergo tumor assessments every 8 weeks until disease progression, death, or patient withdrawal of consent. After documentation of disease progression by central radiology review, patients are to be followed for subsequent antineoplastic therapy and survival approximately every 2 months until death, withdrawal of consent or closure of the study by the Sponsor.

The expected enrollment period is approximately 18 months, and the expected duration of the study to reach the primary analysis timepoint is approximately 24 months until a total number of 264 PFS events are reached. The study will be completed when all patients are no longer receiving study drug and follow-up for OS has been concluded.

Study Schematic



Abbreviations: GIST = gastrointestinal stromal tumor; N = number of patients; R = randomized; TKI = tyrosine kinase inhibitor.

4.2 Justification of the Study Design

The study is designed as a randomized, open-label, efficacy and safety study. Patients who meet all study eligibility criteria will be randomly assigned in a 1:1 ratio to receive avapritinib or regorafenib. Random assignment of patients minimizes bias and helps ensure that both known and unknown risk factors are distributed evenly between treatment groups. Eligible patients will continue to receive BSC throughout the duration of the study.

The study is not blinded because the distinct AE profiles of regorafenib and avapritinib make effective blinding impossible. In particular, regorafenib treatment is associated with palmar-planar erythrodysesthesia (PPE) in 67% of patients, rash in 30% of patients and hypertension in 59% of patients (Stivarga, 2017). In addition, the adverse events requiring dose modification are very different between regorafenib and avapritinib; therefore, appropriate patient care requires that the treating physician and patient know which drug is being used. In order to prevent bias in assessing efficacy endpoints, PFS and response will be determined by independent, central radiology reviewers blinded to treatment group, and the sponsor team responsible for analysis of the study will not have access to efficacy and safety data identified by treatment group.

Demonstration of the efficacy of avapritinib as assessed by PFS is the primary objective of the study. Response assessments used to determine PFS for the primary endpoint will be based on standard response criteria (mRECIST, version 1.1) evaluated by blinded central radiology review to ensure consistent tumor assessments between the 2 randomized treatment arms.

Key secondary endpoints including ORR and OS and additional secondary endpoints including safety, DCR, DOR, disease response by Choi criteria, EORTC-QLQ-C30 scores, plasma drug concentration and an abdominal pain assessment will provide

important supportive data to help determine whether avapritinib provides a clinically relevant improvement in outcome compared to regorafenib.

An Independent Data Monitoring Committee (IDMC) will be in place to review study progress including final primary efficacy outcomes, safety data, adherence to protocol, and follow-up assessments.

4.3 Rationale for the Dose Selected

Dose selection for the treatment of unresectable or metastatic GIST patients with avapritinib was based on a 3+3 dose escalation study design with a starting dose of 30 mg QD (BLU-285-1101). Forty-six patients were enrolled in Part 1 (dose escalation) of the study, 23 patients with PDGFRα-mutated GIST and 23 patients with KIT-mutated GIST, treated with avapritinib at doses of 30 to 600 mg.

Preliminary data showed avapritinib to be well tolerated at QD doses of 30 mg to 400 mg. No DLTs were reported at doses ranging from 30 mg to 400 mg; 2 DLTs were observed at 600 mg, including Grade 2 hypertension, Grade 2 rash, and Grade 2 memory impairment in 1 patient and Grade 2 hyperbilirubinemia in the other patient in Study BLU-285-1101.

After a single dose and repeat dosing of avapritinib, systemic exposure was dose proportional over the dose range of 30 to 400 mg QD. The steady state (C1D15) geometric mean C_{max} (%CV) of avapritinib at doses of 300 and 400 mg QD was 774 ng/mL (49.4%) and 1009 ng/mL (50.9%), respectively, and the corresponding $AUC_{0-\tau}$ was 14074 h•ng/mL (45.1%) and 20298 h•ng/mL (41.5%). The mean accumulation ratio after repeat dosing of avapritinib (dose range: 30 – 400 mg QD) was 3.4 – 5.2.

On 14 February 2017, the maximum tolerated dose for the BLU-285-1101 study was determined to be 400 mg QD and the dose expansion (Part 2) phase of the study started to enroll patients at this dose. Subsequently, based on a joint Investigator and Sponsor review of the available safety, PK/pharmacodynamics, and clinical activity data observed across all cycles of treatment during Part 1 (dose escalation) and Part 2 (dose expansion), 300 mg QD was selected as the avapritinib starting dose for the remainder of Part 2.

Exposures in humans who have received avapritinib at 300 mg and 400 mg QD doses are active against resistance mutations in patient-derived xenograft models showing an overlap covering a broad range of KIT mutations, including exon 11/13 and exon 17/18. Hence, 300 mg PO QD is expected to be clinically active and well tolerated.

As of this 11 October 2017 data cut, 43 patients had initiated treatment in the dose expansion part (Part 2) of the study at 400 mg QD and 27 patients initiated at 300 mg QD.

5 POPULATION

5.1 Number of Patients

Approximately 460 patients will be enrolled and randomized in a 1:1 ratio, stratified by TKI treatment (third vs. fourth), geographic region (Asia vs. rest of the world), and mutation status (PDGFRα D842V mutation present vs. absent) including:

- Approximately 230 patients randomized to receive avapritinib (Arm A).
- Approximately 230 patients randomized to receive regorafenib (Arm B).

At least 70% of the patients enrolled should be receiving their third distinct TKI treatment for GIST, ie, no more than 30% of patients should be receiving their fourth distinct TKI treatment for GIST. Enrollment will be restricted to include only patients receiving their third distinct TKI once 30% of the targeted 460 patients who are receiving their fourth distinct TKI treatment have been enrolled.

5.2 Inclusion Criteria

Patients meeting the following criteria will be eligible for participation in the study:

1. Patients who are ≥ 18 years of age.
2. Patients who have histologically confirmed metastatic or unresectable GIST. Unresectable GIST must be confirmed to be unresectable by a qualified surgeon.
3. Patients who have received imatinib and 1 or 2 other TKIs for the treatment of GIST, including TKIs used for adjuvant therapy. Each different TKI is counted once regardless of how often it was used, and if 2 different TKIs are used in combination, both TKIs are counted. Patients must have disease progression prior to enrollment. Prior use of other systemic and local therapies is not restricted.
4. Patients who have an ECOG PS of 0 to 1.
5. Patient, or legal guardian if permitted by local regulatory authorities, who provides informed consent to participate in the study.

5.3 Exclusion Criteria

Patients meeting any of the following criteria will not be eligible for participation in the study:

1. Patients who have received prior treatment with avapritinib or regorafenib.
2. Patients who have previously received more than 3 different TKIs for the treatment of GIST, including TKIs used for adjuvant therapy. Each different TKI is counted once

regardless of how often it was used, and if 2 different TKIs are used in combination, both TKIs are counted.

3. Patients who are known to be both KIT and PDGRFα wild type.

4. Patients who received any systemic anticancer therapy within 1 week before the first dose of study drug. Prior radiotherapy (including stereotactic radiotherapy) to major organs within 2 weeks of the first dose of study drug, or focal radiotherapy (including stereotactic radiotherapy), such as to bones, limbs, or other areas not involving major organs, within 3 days.

5. Patients who have clinically significant, uncontrolled, cardiovascular disease, including congestive heart failure Grades II, III or IV according to the New York Heart Association classification, myocardial infarction or unstable angina within the previous 6 months, or uncontrolled hypertension.

6. Patients who have experienced arterial thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks) within 6 months before the first dose of study drug, or venous thrombotic events such as pulmonary embolism or deep vein thrombosis within 14 days before the first dose of study drug. Patients with venous thrombotic events such as pulmonary embolism or deep vein thrombosis ≥ 14 days before the first dose of study drug are not excluded provided they are on stable doses of anti-coagulation, or have completed the planned anti-coagulation regimen.

7. Patients who have experienced any hemorrhage or bleeding event NCI CTCAE version 5.0 Grade 3 or higher within 4 weeks before the first dose of study drug.

8. Patients who have a known risk of intracranial bleeding, such as a brain aneurysm that has not been removed or repaired, or a history of intracranial bleeding within 1 year prior to the first dose of study drug.

9. Patients who have a symptomatic non-healing wound, ulcer, gastrointestinal perforation, or bone fracture.

10. Patients who have poor organ function as defined by one or more of the following laboratory parameters:

    - Persistent proteinuria of NCI CTCAE version 5.0 Grade 3 or higher

    - Alanine aminotransferase and AST > 3 × upper limit of normal (ULN) if no hepatic metastases are present; > 5 × ULN if hepatic metastases are present.

    - Total bilirubin >1.5 × ULN; and in presence of Gilbert's syndrome, total bilirubin > 3 × ULN or direct bilirubin > 1.5 × ULN.

    - Estimated (per institutional standard; eg, Cockcroft-Gault formula or Modification of Diet in Renal Disease equation) or measured creatinine clearance

< 40 mL/min (if the estimated or measured creatinine clearance is ≥ 40 mL/min using any of these methods the patient is not excluded).

- Platelet count < 90×10^9/L and absolute neutrophil count (ANC) < 1.0×10^9/L.
- Hemoglobin < 9 g/dL. Transfusion and erythropoietin may be used to reach at least 9 g/dL, but must have been administered at least 2 weeks before the first dose of study drug.

11. Patients who have received neutrophil growth factor support within 14 days of the first dose of study drug.

12. Patients who require therapy with a concomitant medication that is a strong inhibitor or strong or moderate inducer of CYP3A4.

13. Patients who have had a major surgical procedure (minor surgical procedures such as central venous catheter placement, tumor needle biopsy, and feeding tube placement are not considered major surgical procedures) within 14 days of the first dose of study drug. Patient has significant traumatic injury within 28 days before the first dose of study drug.

14. Patients who have a history of another primary malignancy that has been diagnosed or required therapy within 3 years before the first dose of study drug. The following prior malignancies are not exclusionary: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ of any site. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational agent may be included after approval by medical monitor.

15. Patients who have a history of a seizure disorder requiring anti-seizure medication.

16. Patients who have metastases to the brain.

17. Patients who are unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures and study restrictions.

18. Patients who have a QT interval corrected using Fridericia's formula (QTcF) of > 450 msec.

19. Women who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception from the time of the first dose of study drug and for at least 60 days after the last dose of study drug. Men who are unwilling, if not surgically sterile, to abstain from sexual intercourse or employ highly effective contraception from the time of the first dose of study drug and for at least 90 days after the last dose of study drug. Refer to Section 6.6.2 for acceptable methods of contraception.

20. Women who are pregnant, as documented by a serum beta human chorionic gonadotropin (β-hCG) pregnancy test consistent with pregnancy, obtained within 7 days before the the first dose of study drug. Females with β-hCG values that are within the range for pregnancy but are not pregnant (false-positives) may be enrolled with written consent of the Sponsor, after pregnancy has been ruled out. Females of non-childbearing potential (postmenopausal for more than 1 year; bilateral tubal ligation; bilateral oophorectomy; hysterectomy) do not require a serum β-hCG test.

21. Women who are breastfeeding.

22. Patients who have prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the Investigator's opinion, could put the patient at an unacceptably high risk for toxicities, or alter the absorption, distribution, metabolism, or excretion of the study drug; or impair the assessment of study results.

23. Patients with a known hypersensitivity to avapritinib, regorafenib, or the excipients in either study drug.

5.4 Patient Identification and Registration

Patients who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria (see Section 5.2 and Section 5.3) have been satisfied.

Upon identification of an eligible patient, study centers will submit a request to the Sponsor or designee to register each patient for enrollment. Further instructions will be provided in the study manual.

The Medical Monitor or designee will confirm eligibility for all patients before randomization and administration of the first dose of study drug.

5.5 Randomization

Patients who meet all study eligibility criteria will be randomly assigned in a 1:1 ratio to receive avapritinib PO QD or regorafenib PO QD, stratified by TKI treatment (third vs. fourth), geographic region (Asia vs. rest of the world), and mutation status measured in ctDNA or a tumor sample (PDGFRα D842V mutation present vs. absent).

At least 70% of the patients enrolled in this study should be receiving study treatment as their third distinct TKI treatment for GIST, ie, no more than 30% of patients should be receiving their fourth distinct TKI treatment for GIST. Enrollment will be restricted to include only patients receiving their third distinct TKI treatment once 30% of the enrolled targeted 460 patients who are receiving their fourth distinct TKI treatment have been enrolled.

The randomization assignment will be implemented by an interactive web response system (IWRS).

5.6 Study Completion

It is anticipated that patients will receive at least 1 cycle of avapritinib or regorafenib; no maximum treatment duration has been set. After C1, patients may continue to receive study drug until precluded by toxicity, or until disease progression, noncompliance, pregnancy, withdrawal of consent, death, physician decision, or closure of the study by the Sponsor. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.

Patients will be considered to have completed the study if they withdraw from the study for any of the criteria listed in Section 5.7.

5.7 Patient Withdrawal Criteria

Patients have the right to withdraw from the study at any time for any reason.

Patients must withdraw or be withdrawn from study treatment for any of the following reasons:

- Withdrawal of consent
- Pregnancy
- Death

Patients may withdraw or be withdrawn from study treatment for any of the following reasons:

- AE
- Disease progression
- Protocol deviation
- Investigator decision
- Loss to follow-up

When a patient discontinues study drug or withdraws from the survival follow-up part of the study, the primary reason(s) for discontinuation or withdrawal must be recorded in the appropriate sections of the electronic case report form (eCRF) and all efforts will be made to complete and report final study observations as thoroughly as possible.

All related AEs should be monitored until they are resolved, have stabilized, have returned to pre-exposure baseline, are determined to be due to another illness, or until a subsequent therapy is initiated. For AEs considered not related to study drug, similar monitoring guidelines will only be required through 30 days after the last dose of study drug. If the patient withdraws from treatment because of an AE, every effort must be

made to perform protocol-specified safety follow-up procedures, as outlined in Section 7.6.

In the event a patient is withdrawn from study drug or the follow-up part of the study, the Medical Monitor must be informed. If there is a medical reason for withdrawal, the patient will remain under the supervision of the Investigator or designee until the condition has returned to baseline or stabilized.

6 STUDY CONDUCT

6.1 General Conduct

The study will be conducted at multiple centers in North America, Europe, Australia, and Asia.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Patients may be randomized in the system at any time but must be dosed within 28 days of signing of informed consent.

The schedule of assessments for the study is provided in Table 2.

The minimum duration of patient participation is expected to be approximately 3 months, including a screening period to assess study eligibility up to 4 weeks (28 days); a treatment period of at least 1 cycle (28 days); an EOT visit at least 14 ± 7 days after the last dose of study drug; and a Safety Follow-up visit in the clinic for physical examination and resolution of any AEs 30 days (± 7 days) after the last dose of study drug. Thereafter, patients are to be followed for tumor imaging every 8 weeks (± 7 days) until disease progression, death, initiation of new anti-GIST therapy, withdrawal of consent, or closure of the study by the Sponsor and then survival approximately every 2 months until death, withdrawal of consent or closure of the study by the Sponsor.

The end of the study is defined as the time that the last patient completes his/her last visit (LPLV), including assessments performed as part of PFS follow-up, if the patient enters the PFS follow-up part of the study. See Section 7 for details of all study assessments.

The expected enrollment period is approximately 18 months and the expected duration of the study to reach the primary analysis timepoint is approximately 24 months until a total number of 264 PFS events are reached. The study will be completed when all patients are no longer receiving study drug and follow-up for OS has been concluded.

6.2 Early Termination

The study may be terminated early at the discretion of the Sponsor, if there is sufficiently reasonable cause. In the event of such action, written notification documenting the reason for study termination will be provided to each Investigator.

Circumstances that may warrant early termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients.
- Insufficient adherence to protocol requirements.
- Plans to modify, suspend, or discontinue the development of study drug.
- Other administrative reasons.

Should the study be terminated prematurely, all study materials must be returned to the Sponsor or Sponsor's designee.

6.3 Dose and Administration

Avapritinib will be administered PO at a starting dose of 300 mg QD in continuous 28-day cycles.

Prespecified dose modifications guidance for AEs related to avapritinib including cognitive effects, are described in Section 6.3.1.

Regorafenib will be administered at 160 mg PO QD for 21 days in 28-day cycles with 1 week off therapy. Doses of avapritinib or regorafenib may be modified or discontinued for toxicity as described in Section 6.3.1.

Patients receiving regorafenib who experience disease progression may be offered the opportunity to cross over to the avapritinib treatment arm after evaluation and confirmation of disease progression by central radiology review and a washout period of 7 to 28 days after their last dose of regorafenib; see Section 7.6 for additional details. Prespecified dose modifications guidance for AEs related to regorafenib including hand-foot skin reaction, hypertension, and AST, ALT, or bilirubin increases are described in Section 6.3.1.

Patients will be dispensed the appropriate number of Sponsor-packaged, labeled bottles on D1 of each cycle to allow dosing until D1 of the next cycle, which is expected to be within 28 or 56 days. Patients must return all unused tablets (or the empty bottles) at each scheduled visit.

Avapritinib doses should be administered with a glass of water (at least 8 ounces or 250 mL) in a fasted state, with no food intake from 2 hours before until 1 hour after study drug administration. Patients should be instructed to swallow tablets whole and to not chew the tablets. Antacids should not be taken within 3 hours before or after study drug administration.

Regorafenib will be provided as 40 mg strength tablets and it should be administered after a low-fat meal. See Appendix 1 for additional details.

Avapritinib or regorafenib should be administered QD at approximately the same time each day. If a patient forgets to take his/her daily dose in the morning, he/she should take that dose by 4 pm that day. If the dose has not been taken by 4 pm, then that dose should be omitted, and the patient should resume treatment with the next scheduled dose.

If the patient forgets to take his/her daily dose in the evening, he/she should take the study drug dose by 12 am (midnight) that day, and at least 8 hours before the next dose. If the dose has not been taken by the specified times, that dose should be omitted, and the patient should resume treatment with the next scheduled dose.

If a patient vomits during or after taking avapritinib or regorafenib, re-dosing is not permitted until the next scheduled dose.

A temporary discontinuation, up to 56 days (8 weeks) in avapritinib or regorafenib dosing is allowed for patients who require an interruption (eg, for surgery or another interventional procedure) during the treatment period. Avapritinib should be discontinued 48 hours before the procedure (unless the procedure is required more urgently) and resumed at least 48 hours after the procedure is completed. For regorafenib, a vascular endothelial growth factor receptor inhibitor that can impair wound healing, treatment should be stopped at least 2 weeks before the procedure, if possible, and at least 1 week before the procedure, unless the procedure is required more urgently. The decision to resume regorafenib after surgery should be based on clinical judgment of adequate wound healing.

6.3.1 Dose Modification Recommendations for Adverse Events

Dose modification guidelines are summarized for avapritinib in Table 1, and for regorafenib in Appendix 2. These guidelines should be followed by clinical Investigators; however, for an individual patient, dose interruptions, reductions, and treatment discontinuation should also be based on the clinical circumstance. Deviation from these guidelines must be documented and communicated with the sponsor.

Adverse events are to be graded according to NCI CTCAE version 5.0. When the observed toxicity has resolved to ≤ Grade 2 or returned to baseline, the investigator may resume dosing if clinically indicated. Guidance for re-escalation after resolution of adverse drug reactions is provided in Section 6.3.2.

Avapritinib dose reductions to below 100 mg QD are not permitted (see Table 1), and regorafenib dose reductions to below 80 mg QD are not permitted (See Appendix 2). If a patient requires dose reduction below these dose levels, study treatment should be discontinued.

Doses may be interrupted for study-drug related toxicities for up to 56 days (8 weeks). In general, if a study drug-related toxicity does not resolve to ≤ Grade 2 or has not returned to baseline after dose interruption for more than 56 days, the patient must be discontinued from study treatment unless after discussion with the medical monitor, resumption of treatment is considered to be in the best medical interest of the patient, and this is documented in writing. Additionally, the Sponsor's medical monitor must be contacted if

an AE deemed unrelated to treatment requires a dose interruption for more 56 days; a longer recovery period is permitted with written approval by the Sponsor.

During dose interruptions, study sites should continue to observe the study schedule as planned.

Once adverse drug reactions have resolved after the guidelines below are followed, Investigators are encouraged to re-escalate the dose of study drug as described in Section 6.3.2.

Table 1: Dose Modification and Re-escalation Guidelines for Avapritinib-Related Toxicity

Toxicity	Modification
General	
Grade 1 or Grade 2	• No dose modification required
Grade 3 - 4	• Occurrence: Hold until event is ≤ Grade 2, or has returned to baseline, and then resume by reducing the dose by 100 mg less than the current dose ○ • Occurrence at 100 mg: Discontinue avapritinib ○
Cognitive or Mood Effects[1, 2]	
Grade 1 with only minor impairment	No dose modification required
Grade 1, other than minor impairment	• Interrupt dosing for 7 days, and resume dosing without dose reduction • The dosing interruption may be repeated if the impairment continues to worsen after resuming dosing; however, repeated dosing interruption is at the discretion of the investigator, and should be balanced with the need to treat the underlying GIST
Grade 2	• Interrupt dosing for a minimum of 7 days • Resume dosing with a dose reduction of 100 mg when the cognitive effect has improved to Grade 1 or less, or still at Grade 2, if continued treatment is considered in the best medical interest of the patient due to the underlying GIST • If the patient is already receiving a dose of 100 mg QD, and continued treatment is considered in the best medical interest of the patient due to the underlying GIST, treatment may be resumed at 100 mg
Grade 3-4	• Interrupt dosing for a minimum of 14 days • Resume dosing with a dose reduction of 100 mg when the cognitive effect has improved to Grade 1 or less, or when it has improved to Grade 2, if continued treatment is considered in the best medical interest of the patient due to the underlying GIST • Occurrence at 100 mg: Discontinue avapritinib
Intracranial Bleeding[2]	
Grade 1	• Interrupt dosing for a minimum of 7 days, and re-image the brain

	• Resume dosing without dose reduction, if the bleed is stable or improving, and continued treatment is considered in the best medical interest of the patient due to the underlying GIST
Grade 2	• Interrupt dosing for a minimum of 14 days and re-image the brain • Resume dosing with a dose reduction of 100 mg when the intracranial bleeding has improved to Grade 1 or less, or still at Grade 2, if continued treatment is considered in the best medical interest of the patient due to the underlying GIST • Occurrence at 100 mg: Discontinue avapritinib
Grade 3-4	• Discontinue avapritinib

Abbreviations: CNS = central nervous system; GIST = gastrointestinal stromal tumor; QD = once daily.
[1] Changes in cognition, memory, attention, mood, or speech (thought to originate in the CNS).
[2] If avapritinib treatment is resumed after interruption for a cognitive or mood effect, or for an intracranial bleeding event, the investigator must document in writing that resuming avapritinib treatment was considered to be in the best medical interest of the patient.

For regorafenib, dose modification is described in Appendix 2.

6.3.2 Dose Re-escalation After Resolution of Adverse Drug Reactions

Avapritinib and regorafenib doses may be re-escalated from the reduced dose level to the immediate previously administered dose level if any of the following criteria are met:

- All ≥ Grade 2 non-hematologic (other than CNS toxicities) have recovered to < Grade 2 for at least 2 weeks.
- All ≥ Grade 3 hematologic toxicities have recovered to ≤ Grade 2 and are manageable with supportive therapy.
- All ≥ Grade 2 CNS toxicities have recovered to ≤ Grade 1 and are manageable with supportive therapy.

Patients may receive step-wise avapritinib dose re-escalations up to 300 mg QD (eg, 100 mg QD to 200 mg QD to 300 mg QD) if the above criteria continue to be met.

Patients may receive step-wise regorafenib dose escalations up to 160 mg QD (eg, 80 mg QD to 120 mg QD to 160 mg QD) if the above criteria continue to be met.

A patient should be treated and tolerate therapy well for at least 1 cycle at each higher dose level before the dose is escalated again. In no circumstances should a patient receive a dose higher than 300 mg QD.

6.4 Prior and Concomitant Therapy

All medications administered and procedures conducted within 28 days before C1D1 should be recorded on the eCRF. In addition, all prior treatments for the underlying malignancy should be recorded.

6.4.1 Prohibited Concomitant Therapy

The following medications and procedures are prohibited during the study:

- In vitro studies with recombinant human CYP enzymes demonstrated that avapritinib phase I metabolism is predominantly mediated by CYP3A4, with CYP2C9 playing a minor role. Concomitant treatment with drugs that are strong CYP3A4 inhibitors or strong or moderate CYP3A4 inducers are prohibited for patients receiving avapritinib. Please refer to Appendix 3 for a list of prohibited medications and foods.

- Regorafenib is metabolized by CYP3A4 and UGT1A9. Concomitant treatment with drugs that are strong inhibitors of CYP3A4, strong inducers of CYP3A4, and strong inhibitors of UGT1A9 are prohibited for patients receiving regorafenib. Please refer to Appendix 3 for a list of prohibited medications and foods.

- Any investigational agent or device other than avapritinib or regorafenib, including commercially available agents that are investigational for the treatment of the patient's underlying malignancy.

- Any antineoplastic treatment (including kinase inhibitors, chemotherapy, and radiotherapy) other than avapritinib and regorafenib. Patients who experience centrally confirmed disease progression but subsequently undergo radiation therapy or surgery may continue to receive study treatment with avapritinib, if the treating investigator considers it to be in the patient's best medical interest.

6.4.2 Concomitant Therapy to be used with Caution

Avapritinib

In vitro, avapritinib is a reversible inhibitor of CYP2C9, and CYP3A4/5 at clinically relevant concentrations. Avapritinib also demonstrated time-dependent inhibition of CYP3A4/5 in vitro with an estimated K_{inact} and K_I of 0.0301 min^{-1} and 12.3 μM, respectively. Therefore, avapritinib treatment may increase the plasma concentration of other medications for which CYP2C9 or CYP3A-mediated metabolism constitutes the primary mechanism of clearance.

In vitro, avapritinib, at concentrations of 0.3 to 3 μM, induced CYP3A4 mRNA expression with a maximal 3.25-fold induction observed at 3 μM. In vitro, avapritinib is an inhibitor of P-gp, BCRP, BSEP, and MATE1 and MATE2K. Therefore, avapritinib may increase the plasma concentration of other medications that are substrates of these transporters. Medications that are CYP2C9, CYP3A4 or BCRP substrates, with a narrow therapeutic index and moderate inhibitors of CYP3A4 should be used with caution (Refer to Appendix 4 for a list of these medications).

Investigators should ensure patients avoid proton pump inhibitors and H_2-receptor antagonists during the study. Furthermore, antacids should be taken at a time point that is not proximal to study drug administration (at least 3-4 hours before or after study drug administration).

In addition, medications that are known to increase the risk of seizures should be used with caution.

Regorafenib

Investigators should ensure patients exercise caution while using concomitant therapies with regorafenib as listed in Appendix 4.

6.4.3 Permitted Concomitant Therapy

Medications and treatments other than those specified in Section 6.4.1 and Section 6.4.2, including palliative and supportive care for disease-related symptoms are permitted during the study.

Patients should be closely monitored, and treatment is to be instituted for disease-related symptoms as appropriate. Supportive care measures for treating AEs should be instituted as soon as they are recognized.

Anti-emetic treatments may be used at the Investigator's discretion and in accordance with the American Society of Clinical Oncology guidelines or equivalent after documented nausea or vomiting has occurred without medications having been used. The choice of anti-emetic treatment, if required, will be made at the Investigator's discretion. Anti-diarrhea medications may also be used after documented diarrhea has occurred, at the Investigator's discretion.

6.5 Schedule of Assessments

Table 2: Schedule of Assessments

Study Activities[a]	**Screening**	**Study Treatment**						**EOT[e] ± 7 days**	**Safety Follow-Up[f] ± 7 days**	**PFS Follow-up[g] ± 7 days**	**Survival Follow-up[h] ± 30 days**
Cycle		**C1**		**C2 ± 2 days**		**C3, C4, C5[b,c] ± 3 days**	**C7-EOT[b,d] ± 7 days**				
Study Day	**-28 to -1**	**D1**	**D15**	**D1**	**D15**	**D1**	**D1**	**14 days after last dose**	**30 days after last dose**	**Every 8 weeks after Safety F/U**	**Every 2 months**
Window (Days)						**±3**	**±7**	**±7**	**±7**	**±7**	**±1 month**
Informed consent[i]	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Medical history[j]	X										
Physical examination[k]	X	X		X		X	X	X			
Vital signs[l]	X	X	X	X	X	X	X	X			
Serum or urine pregnancy[m] (β-hCG) test	X	X		X		X	X	X	X[m]		
ECOG PS	X	X		X		X	X	X			
12-lead ECG	X	X		X		X	X	X			
Hematology[n]	X	X[o]		X		X	X	X			
Coagulation[p]	X	X[o]						X			
Serum chemistry[q]	X	X[o]	X[r]	X	X[r]	X	X[s]	X			

Study Activities[a]	**Screening**	**Study Treatment**						**EOT[e] ± 7 days**	**Safety Follow-Up[f] ± 7 days**	**PFS Follow-up[g] ± 7 days**	**Survival Follow-up[h] ± 30 days**
Cycle		**C1**		**C2 ± 2 days**		**C3, C4, C5 [b,c] ± 3 days**	**C7-EOT [b,d] ± 7 days**				
Study Day	**-28 to -1**	**D1**	**D15**	**D1**	**D15**	**D1**	**D1**	**14 days after last dose**	**30 days after last dose**	**Every 8 weeks after Safety F/U**	**Every 2 months**
Window (Days)						**±3**	**±7**	**±7**	**±7**	**±7**	**±1 month**
Urinalysis	X	X[o]						X			
Study drug administration		X									
PK blood samples[c] (Arm A: avapritinib patients only)		X		X		X[c]					
Mutation screening (ctDNA sample)	X										
Plasma sample for biomarkers		X[o]		X		X	X	X			
Tumor imaging[t]	X					X[t]	X	X		X	
Brain imaging (MRI or CT)[u]	X					X	X				
EORTC-QLQ-C30, [redacted]		X		X		X[v]	X[v]				
AE monitoring[w]		X									
SAE monitoring[x]	X										
Concomitant medications[x]	X										
Survival assessment											X
New antineoplastic therapy											X

Abbreviations: AE = adverse event; C = cycle; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT = End-of-Treatment; EQ-5D-5L = EuroQol 5 Dimension Questionnaire; F/U = follow-up; FACT-Cog = Functional Assessment of Cancer Therapy-Cognitive Function; GIST = gastrointestinal stromal tumor; IV = intravenous; MRI = magnetic resonance imaging; PD = progressive disease; PFS = progression-free survival; MRI = magnetic resonance imaging; PGI-C = Patients' Global Impression of Change; PGI-S = Patients' Global Impression of Severity; PK = pharmacokinetics; SAE = serious adverse event; ULN = upper limit of normal.

a On days when study drug is to be administered in the clinic, all tests or procedures must be completed pre-dose at each study visit unless otherwise indicated. Additional safety tests (eg, hematology, ECG) may be performed whenever clinically indicated, at the Investigator's discretion. Whenever a test result is questionable, it should be repeated immediately.

b Patients receiving regorafenib who experience disease progression documented by central radiology review may be permitted to cross over to receive treatment with avapritinib after disease progression confirmed by central radiology review (see Section 7.6) and a washout period of 7 to 28 days after their last dose of regorafenib. At the first study visit after the washout period, the patient will complete the C1D1 assessment schedule except for the following tests, which are not required: PK blood sample and biomarker plasma sample. After patients cross over to treatment with avapritinib, ECGs will be performed following the same schedule as prior to cross over and AEs will only be assessed for their relationship to avapritinib.

c Pharmacokinetics samples will be collected before dosing (ie, predose) on Day 1 of Cycles 1, 2, 3, and 5 only from patients in Arm A of the study (those receiving avapritinib). There will be no PK samples collected from patients in Arm B of the study (those receiving regorafenib). On C3D1 and C5D1, in addition to the predose sample in all patients, samples will be collected at any 1 time point between 1-8 hours postdose. On C2D1, additional samples will be collected predose and at 1 hour (±10 minutes), 4 hours (±15 minutes), and 6-8 hours (±15 minutes) postdose in a total of 25 patients at selected centers. Note: The predose samples for all patients are to be collected before the day's dose of avapritinib and should be taken as close as possible to 24 hours after the prior dose was taken.

d Every odd Cycle D1, eg, C7D1, C9D1, etc., moving forward through EOT. Visits may be performed more frequently, if dictated by the local standard of care or if needed to adequately monitor individual patients.

e If an alternative antineoplastic treatment is to be started within 14 days after the last dose of study drug, the EOT visit should be conducted before the dose of alternative antineoplastic therapy. Tumor assessment for EOT procedures do not need to be repeated if they were conducted within 7 days (or within 28 days for disease response assessments).

f The Safety Follow-up visit may be performed by clinic visit or a phone call for resolution of any ongoing AEs.

g After completing the Safety Follow-up assessments, patients are to be followed for tumor imaging every 8 weeks (±7 days) until disease progression, death, initiation of new anti-GIST therapy, withdrawal of consent, or closure of the study by the Sponsor.

h After documentation of disease progression by central radiology review, patients or their designated care giver will be contacted by phone every 2 months until withdrawal of consent, death, or closure of the study by the Sponsor to collect the drug name of any new systemic antineoplastic therapy or the date of death.

i Patients randomized to Arm A must consent to continue avapritinib treatment after disease progression and patients randomized to Arm B must consent to cross over to avapritinib after disease progression; see Section 7.7 for additional details.

j A complete medical history will be obtained at the Screening visit, including a history of GIST and/or other malignancies, prior treatments, response to each treatment (if available), and concurrent illnesses.

k A complete physical examination and a basic neurological assessment will be performed at the Screening visit. Subsequent physical examinations will focus on symptoms and signs of GIST, changes from previous physical examinations, and AEs.

l Vital signs include weight, temperature, pulse, and systolic/diastolic blood pressure. Height will also be measured at Screening.

m To be performed for women of childbearing potential. A serum pregnancy test is to be performed at Screening and at C1D1. A serum or urine pregnancy test should be performed every 4 weeks, even if a study visit is not specified, through 8 weeks after the last dose of study drug. Pregnancy tests may be performed locally during even cycles after C5D1 ± 5 days from expected CXD1 (ie, C6D1, C8D1, etc).
n Hematology parameters to be measured include hemoglobin, red blood cell count, white blood cell count with differential count (including absolute neutrophil count), and platelet count.
o Baseline (C1D1) safety laboratory tests and samples for pharmacodynamic markers are to be obtained within 7 days before the first study drug dose (prior to dosing on the first day of dosing permitted). If Screening tests occur within 7 days of C1D1, they do not need to be repeated.
p Coagulation studies include prothrombin time, international normalized ratio and activated partial thromboplastin time.
q The comprehensive serum chemistry panel includes sodium, potassium, blood urea nitrogen or urea, bicarbonate (venous), creatinine, calcium, chloride, magnesium, phosphorus, albumin, AST, ALT, alkaline phosphatase, and total bilirubin (direct bilirubin if total bilirubin is > ULN).
r Only liver function tests (ALT, AST, alkaline phosphatase, total bilirubin (direct bilirubin if total is > ULN) are required. These should be performed locally and any clinically significant abnormalities should be reported as an Adverse Event, and the laboratory values supporting Adverse Event should be entered into unscheduled visit laboratory page on eCRF.
s Liver function tests (ALT, AST, alkaline phosphatase, total bilirubin (direct bilirubin if total is > ULN) should be measured every 4 weeks. On even-numbered cycles, when a study visit is not required, these tests should be done locally, and any clinically significant abnormalities should be entered as adverse events, and laboratory values should be entered in unscheduled laboratory eCRF.
t Tumor imaging will be done at Screening and then every 8 weeks (± 1 week) from Cycle 1 Day 1 until disease progression and will be assessed by central radiology review. Disease response assessments using the Choi criteria will be performed centrally. Note that tumor imaging should occur every 8 weeks regardless of the scheduled treatment cycles ie, if study treatment is interrupted or discontinued for any reason, tumor imaging should continue according to an 8-week schedule until disease progression or death. Computed tomography (CT) with IV contrast of the chest and CT or MRI with IV contrast of the abdomen and pelvis will be performed. CT of the chest is not required after screening unless there were sites of disease in the chest. CT with IV contrast is the preferred imaging modality, unless a site of disease is better evaluated by MRI. If a patient is not tolerant of IV contrast, non-contrast scans may be performed. For each patient, the same method of tumor imaging used at baseline should be used throughout the study.
u Brain imaging should be performed at Screening, Week 12 (±1 week), and Week 24 (±1 week), and should be repeated as clinically indicated, ie, for unexpected neurologic AE. Patients who have been on study for more than 12 weeks should have imaging performed at the next scheduled visit and 12 weeks later (±1 week).
v The EORTC-QLQ-C30, [redacted] will be completed at scheduled clinical site visits up to EOT. The questionnaires are not required at the EOT visit or after cross-over.
w Adverse events are to be recorded from the start of study drug administration through the Safety Follow-up Assessment.
x Serious AEs and concomitant medications are to be recorded from the date of the informed consent signature through the Safety Follow-up Assessment.

6.6 Additional Considerations

6.6.1 Precautions

An in vitro phototoxicity study in 3T3 mouse fibroblasts as well as a phototoxicity study in pigmented rats demonstrated that avapritinib has a slight potential for phototoxicity. Therefore, prolonged exposure to sunlight should be avoided during treatment. In addition, patients should take other measures to avoid ultraviolet (UV) exposure such as wearing sunscreen and sunglasses, wearing protective clothing, and avoiding tanning beds. Refer to the avapritinib IB for details.

Hypospermatogenesis was observed in the testis and epididymis of rats and dogs and did not recover after 2-week recovery. Patients should be informed of the possibility of gamete and embryo banking.

Refer to the avapritinib Investigator Brochure for details.

6.6.2 Contraception Requirements

Women of childbearing potential must agree to use a highly effective method of contraception (CTFG, 2014) from the time of randomization until at least 8 weeks after the last dose of study drug. Women are considered to be of childbearing potential after menarche until becoming postmenopausal (defined as no menses for at least 12 months without an alternative medical cause) unless permanently sterile. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy (CTFG, 2014). Because avapritinib and regorafenib are potential CYP3A4 inducers, women should use hormonal contraception with caution and supplement with other highly effective methods.

Males with partners who are female of reproductive potential must agree that they will use condoms, and their partners will use a highly effective contraceptive method throughout the study, and for 90 days after the last dose of study treatment.

Highly effective forms of contraception are defined as the following (CTFG, 2014):

- Combined (estrogen and progestogen containing) hormonal contraceptives that inhibit ovulation, including oral, intravaginal and transdermal products.
- Progestogen-only hormonal contraceptives that inhibit ovulation, including oral, injectable, and implantable products.
- Intrauterine devices (IUD) and intrauterine hormone-releasing system (IUS).

- Bilateral tubal occlusion (women).
- Male partner vasectomy or other method of surgical sterilization provided that the partner is the sole sexual partner of the trial participant and the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence (men and women), when this is the preferred and usual lifestyle of the patient. Periodic abstinence (such as calendar, symptothermal and postovulation methods), withdrawal (coitus interruptus), and the lactational amenorrhea method are not acceptable methods of contraception.

The following methods of contraception are not considered highly effective (CTFG, 2014):

- Progesterone-only oral hormonal contraception that do not inhibit ovulation.
- Barrier methods with or without spermicide, or spermicide alone.

7 DESCRIPTION OF STUDY PROCEDURES

7.1 Screening

After informed consent, all patients will undergo screening procedures within 28 days before dosing on C1D1 to determine eligibility. Patients may be randomized in the system at any time but must be dosed within 28 days of signing of informed consent.

The following procedures will be performed at the Screening visit:

- Obtain demographic data, including sex, date of birth/age, race, and ethnicity;
- Complete medical history, including a history of GIST and/or other malignancies, prior treatments, the response to each treatment if available, and concurrent illnesses;
- Complete physical examination and a basic neurological assessment, including ECOG PS;
- Vital signs including weight, temperature, pulse, and systolic/diastolic blood pressure. Height will also be measured at Screening;
- 12-lead ECG;
- Obtain plasma sample for exploratory biomarkers and ctDNA mutation testing;
- Clinical laboratory assessment (hematology, coagulation, serum chemistry, and urinalysis);
- Serum pregnancy test (women of childbearing potential only);

- Tumor imaging by CT with IV contrast or MRI (CT is required for the chest and preferred for all body regions unless a site of disease is better imaged by MRI). If a patient is intolerant of IV contrast, CTs may be performed without IV contrast.

- Brain imaging by MRI or CT (MRI is preferred, if available);

- Recording of concomitant medications and SAEs. Concomitant medications and SAEs are to be collected from the date of the informed consent signature through the Safety Follow-up Assessment, while AEs are to be collected from start of study drug administration through the Safety Follow-up Assessment.

7.2 Safety Assessments

The schedule of safety assessments is described in Table 2. All clinical and laboratory safety assessments will be assessed by the Investigator for clinical significance and clinically significant findings will be reported as AEs. Additional safety assessments may be performed if dictated by the local standard of care and when clinically indicated, at the Investigator's discretion.

7.2.1 Physical Examination

A complete physical examination including a basic neurological assessment will be performed at the Screening visit. Subsequent physical examinations will be performed as outlined in Table 2, and will focus on symptoms and signs of GIST, changes from previous physical examinations, and AEs.

7.2.2 Eastern Cooperative Oncology Group Performance Status

Determination of ECOG PS will be performed at the time points outlined in Table 2. Refer to Appendix 5 for ECOG PS scoring.

7.2.3 Brain Imaging

Brain imaging by MRI or CT (MRI is preferred) will be performed at the visits outlined in Table 2, and should be repeated as clinically indicated, ie, for unexpected neurologic AEs. Patients who have been on study for more than 12 weeks should have imaging performed at the next scheduled visit and 12 weeks later (±1 week).

7.2.4 Vital Signs

Vital sign measurements will include temperature, systolic/diastolic blood pressure, pulse, and weight, and will be performed at the time points outlined in Table 2. Height will be measured at the Screening visit only.

Blood pressure and pulse assessments should be conducted while the patient is seated or supine.

7.2.5 ECGs

Twelve-lead ECGs will be obtained for all patients at the time points outlined in Table 2.

Twelve-lead ECGs are to be conducted after 5 minutes in recumbence or semi-recumbency.

7.2.6 Clinical Laboratory Tests

Clinical laboratory evaluations for safety will be performed at a central laboratory. Before starting the study, the Investigator will provide the Sponsor (or its designee) copies of all laboratory certifications and normal ranges for all laboratory assessments to be performed by that laboratory. Local laboratory assessments may be used to make treatment-related decisions.

Clinical laboratory evaluations will be conducted at the time points outlined in Table 2. In addition, all clinically significant laboratory abnormalities noted on testing will be followed by repeat testing and further investigated according to the judgment of the Investigator.

The following safety laboratory tests are to be evaluated by the Investigator:

Hematology:	Hemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential (including ANC), and platelet count
Coagulation:	Prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT)
Serum chemistry:	Sodium, potassium, blood urea nitrogen (BUN) or urea, bicarbonate (venous), creatinine, calcium, chloride, magnesium, phosphorus, albumin, AST, ALT, alkaline phosphatase (ALP), total bilirubin (direct bilirubin if total > ULN)
Urinalysis (dipstick):	pH, specific gravity, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, protein, and urobilinogen
Serum or urine pregnancy[a]:	β-hCG

[a] A serum pregnancy test should be performed for women of childbearing potential at Screening and at C1D1. A serum or urine pregnancy test should be performed every 4 weeks through 8 weeks after the last dose of study drug.

7.2.7 Adverse Events and Concomitant Medications

Each patient must be carefully monitored for the development of any AEs throughout the study from C1D1 (or from the time of signing informed consent, for SAEs) to 30 days

after the last dose. In addition, SAEs that are assessed as related to study treatment that occur > 30 days after the last dose also are to be reported.

Complete details on AE and SAE monitoring are provided in Section 9.

Concomitant medications will be recorded from the time of signing informed consent to 30 days after the last dose.

7.3 Pharmacokinetic Assessment

Blood samples will be collected from patients in Arm A of the study (those receiving avapritinib) before and after study drug dosing to determine circulating plasma concentrations of avapritinib (including any relevant metabolites). There will be no PK samples collected from patients in Arm B of the study (those receiving regorafenib).

Pharmacokinetic samples will be collected before dosing (ie, predose) on Day 1 of Cycles 1, 2, 3, and 5. On C2D1, additional samples will be collected predose and at 1 hour (±10 minutes), 4 hours (±15 minutes), and 6-8 hours (±15 minutes) postdose in a total of 25 patients at selected centers. On C3D1 and C5D1, in addition to the predose sample, samples will be collected at any 1 time point between 1-8 hours postdose. Note: The predose sample is to be collected before the day's dose of avapritinib and should be taken as close as possible to 24 hours after the prior dose was taken.

Additionally, Investigators may obtain blood samples for PK analysis at the time(s) that significant drug-related AEs and SAEs occur.

7.4 Blood Samples for Biomarker Assessment

Blood samples will be collected for patients at the time points outlined in Table 2 to characterize the mutant allele fraction in plasma ctDNA at Baseline, each visit thereafter, and at end of treatment to measure changes from Baseline in the levels of KIT, PDGFRα, and other cancer-relevant mutant allele fractions.

7.5 Efficacy Assessments

7.5.1 Disease Response Assessment

Blinded central radiology review of disease response or disease progression (per Choi criteria and per mRECIST, version 1.1) will be based on local imaging scans performed at the time points outlined in Table 2. Note that tumor imaging should occur every 8 weeks (± 1 week) from Cycle 1 Day 1 regardless of the scheduled treatment cycles ie, if study treatment is interrupted or discontinued for any reason, tumor imaging should continue according to an 8-week schedule until disease progression or death.

Computed tomography with IV contrast of the chest, CT or MRI with IV contrast of the abdomen and pelvis will be performed at Screening. At subsequent timepoints, the abdomen, pelvis, and all other body regions that contained sites of disease (target or non-target) at Screening will be imaged. Computed tomography of the chest is not required if

there were no sites of disease in the chest at Screening. Computed tomography with IV contrast is the preferred imaging modality, unless a site of disease is better evaluated by MRI. If a patient is not tolerant of IV contrast, non-contrast scans may be performed. For each patient, the same method of tumor imaging used at Baseline should be used throughout the study.

Computed tomography and MRI scans will be reviewed locally at the study center, ideally by the same individual for each patient at each time point, and disease response and progression will be assessed per mRECIST, version 1.1. Computed tomography and MRI scans will also be collected and reviewed centrally to provide a central assessment of response and progression, both per mRECIST, version 1.1 and per Choi criteria.

Patients on either treatment arm considered by local assessment to have disease progression shall not discontinue treatment until progression (per mRECIST, version 1.1) has been confirmed by central radiology review. Patients may only cross over from regorafenib treatment to avapritinib treatment if disease progression has been confirmed by central radiology review.

7.5.2 Central Radiology Review

A blinded central radiology review will be performed according to a prospectively established central imaging charter and conducted by an external imaging contract research organization. The central radiology review will be chartered to evaluate response assessment independently per mRECIST, version 1.1. (Appendix 6) and per Choi criteria (Appendix 7).

A detailed study-specific Imaging Core Manual will be made available to sites regarding scan acquisition requirements. All radiological scans acquired at all scheduled time points and any additional (unscheduled) radiological scans must be sent to the external imaging contract research organization.

7.5.3 Quality-of-Life Instruments

Patients will complete the EORTC-QLQ-C30 at scheduled clinical site visits up to the EOT visit, as outlined in Table 2. These assessments are provided in Appendix 8 (EORTC-QLQ-C30).

7.5.4 [redacted]

[redacted]

7.6 Crossover From Regorafenib to Avapritinib

Patients who experience disease progression while receiving regorafenib (Arm B), as confirmed by central radiology review, may be offered the opportunity to cross over to the avapritinib treatment arm (Arm A).

Patients who cross over to avapritinib must complete a washout period of 7 to 28 days after their last dose of regorafenib and consent to cross over before starting treatment with avapritinib. At the first study visit after the washout period, cross over patients will complete the C1D1 assessment schedule except for the following tests, which are not required: PK blood sample and biomarker plasma sample. Otherwise patients who crossed over will follow the same schedule of assessments as on the main portion of the Protocol (except C1D15 or C2D15 visits, which are not required). After patients cross over to treatment with avapritinib, ECGs will be performed following the same schedule as prior to cross over and AEs will only be assessed for their relationship to avapritinib.

7.7 Continuing Avapritinib After Disease Progression

Patients who experience disease progression while receiving avapritinib (Arm A), as confirmed by central radiology review, may be offered the opportunity to continue treatment with avapritinib if the following criteria are met:

- There are no symptoms or signs indicating clinical disease progression (including worsening of laboratory values).
- The patient is not experiencing rapid progression of disease or a progressive tumor requiring urgent alternative medical intervention at critical anatomical sites (eg, spinal cord compression).
- There has been no decline in ECOG PS

Patients randomized to Arm A must consent to continue avapritinib treatment after disease progression. This consent must be obtained after disease progression has occurred.

7.8 End-of-Treatment, Safety Follow-up and Progression-Free Survival Follow-up

All patients will attend an EOT visit approximately 14 days (± 7 days) after the last dose of study drug (see Table 2 for a description of EOT assessments). If an alternative antineoplastic treatment is started within 14 days of the last dose of study drug, the EOT visit should be conducted before the first dose of the alternative antineoplastic therapy. Tumor assessment for EOT procedures do not need to be repeated if they were performed within 7 days (or within 28 days for disease response assessments).

A Safety Follow-up visit (clinic visit or a phone call) for resolution of any ongoing AE will be made 30 days (± 7 days) after the last dose of study drug, or at the time the patient initiates another antineoplastic therapy.

Thereafter, patients without documented PD will be followed approximately every 8 weeks (±7 days) until disease progression, death, initiation of new anti-GIST therapy, withdrawal of consent, or closure of the study by the Sponsor.

7.9 Survival Follow-up

After documentation of disease progression by central radiology review, patients or their designated care giver will be contacted by phone every 2 months until withdrawal of consent, death, or closure of the study by the Sponsor to collect the drug name of any new systemic antineoplastic therapy or the date of death.

7.10 Sample Processing, Storage, and Shipment

Instructions for the processing, storage, and shipment of all study samples for central analysis will be provided in a separate study manual.

Samples will be stored until analysis and remaining samples will be retained until 10 years after completion of the study, or until the research is discontinued, whichever occurs first.

8 STUDY DRUG MANAGEMENT

8.1 Description

Both the investigational drug, avapritinib and the control drug, regorafenib, will be administered during this study.

8.1.1 Avapritinib

Avapritinib immediate release tablets will be supplied as 100 mg strength, round tablets composed of roller-compacted, aesthetically film-coated pharmacopeial excipients.

Avapritinib is for investigational use only and should only be used within the context of this study.

8.1.1.1 Storage

Avapritinib tablets must be stored at room temperature in their original container, according to the package label. Refer to the label or certificate of analysis for expiry.

All study drug products must be stored in a secure, limited-access location and may be dispensed only by the Investigator or by a member of the staff specifically authorized by the Investigator.

8.1.1.2 Packaging and Shipment

Avapritinib tablets will be supplied to the study center, packaged in 60 cc Wide Mouth Round high-density polyethylene bottles. Each bottle will be induction-sealed and capped with a 33 mm child-resistant closure.

Packaging will meet all regulatory requirements. See the pharmacy manual for additional details.

8.1.2 Regorafenib

Regorafenib will be provided to the study center as 40 mg strength tablets, packaged in bottles, and will be labeled according to local regulations. In the US, locally obtained commercial supplies of regorafenib may be used and reimbursed by the Sponsor. Regorafenib is to be stored in the original bottle at 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F). See Appendix 1 for additional details.

8.2 Accountability

Accountability for the study drug at the study center is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the study center, use by each patient, and return to the Sponsor or its designee (or disposal of the drug, if approved by the Sponsor). These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from the Sponsor. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The Sponsor or its designee will review drug accountability at the study center on an ongoing basis during monitoring visits.

Study drug must not be used for any purpose other than the present study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

Patients will receive instructions for home administration of avapritinib or regorafenib.

All used, unused, or expired study drug will be returned to the Sponsor or its designee, or if authorized, disposed of at the study center per the center's Standard Operating Procedures and documented. All material containing avapritinib or regorafenib will be treated and disposed of as hazardous waste in accordance with governing regulations.

8.3 Compliance

Patients will be dispensed the appropriate number of study drug bottles to allow for dosing for a full cycle, or until the next scheduled visit. Patients are to return all unused

tablets (or the empty bottles) on D1 of each treatment cycle or at the next scheduled visit. Compliance with the dosing regimen will be assessed based on return of unused drug (or empty bottles).

8.4 Overdose

Overdose includes any dose higher than the intended dose. Any instance of overdose (suspected or confirmed), irrespective of whether or not it involves any signs or symptoms, must be reported to the Sponsor within 24 hours of awareness of the incident. Details of dose taken, any signs or symptoms and their management should be recorded, including details of any antidote(s) administered.

If the overdose incident resulted in AEs, these must be reported in accordance with the instructions in Section 9 of this protocol.

The highest dose of avapritinib studied clinically is 600 mg QD; there is no known antidote for avapritinib overdose. In the event of suspected overdose, hold avapritinib dosing, institute supportive care, and observe until clinical stabilization.

The highest dose of regorafenib studied clinically is 220 mg QD. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue. There is no known antidote for regorafenib overdose. In the event of suspected overdose, interrupt regorafenib, institute supportive care, and observe until clinical stabilization.

9 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a study patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease (new, or exacerbated pre-existing condition).

Adverse events include the following:

- All AEs, whether or not considered related to the use of study drug;
- All AEs occurring in association to any medication overdose, medication error, drug-drug interaction, abuse, withdrawal, sensitivity, or toxicity;

- Any new illness, whether or not considered related to study drug, and any worsening/exacerbation of chronic or intermittent pre-existing conditions, including either an increase in frequency and/or intensity of the condition;

- Any injuries or accidents;

- Clinically significant abnormal results (new occurrence or worsening of previously known) from laboratory and physiological tests or physical examinations.

9.1.2 Adverse Event due to Protocol Procedures

An untoward medical occurrence in a study patient which is associated by the Investigator with protocol procedures (nondrug study drugs) is considered an AE, even if the patient was not exposed to study drug.

9.1.3 Serious Adverse Event

An AE is assessed as SAE if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes (seriousness criteria):

- **Death:** An AE that results in death.

  NOTE: For AEs that result in ‘death’ the adverse event term describing the medical occurrence causing death should be reported with the outcome and seriousness criteria recorded as ‘death’. Only if the cause of death is unknown and no other medical occurrence is suspected to have caused or contributed to ‘death’, ‘death’ should be used as adverse event term.

- **Life-threatening:** An AE is life-threatening.

  NOTE: The term ‘life-threatening’ refers to an event in which the study patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- **Inpatient hospitalization or prolongation of existing hospitalization:** All AEs requiring hospitalization (in-patient or emergency department treatment) for more than 24 hours should be considered SAEs.

  NOTE: Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (eg, elective surgery for a pre-existing condition that has not worsened) should not be reported as AE or SAE. Any untoward medical occurrence in temporal relationship to the procedure, however, must be reported as an AE, either 'serious' or ‘nonserious’ according to protocol definitions.

- **Persistent or significant disability/incapacity:** An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

- **Congenital anomaly/birth defect:** A fixed, permanent impairment in the offspring of a patient (or patient's partner) who received study treatment.

- **Medically important events**: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are:

    - Intracranial bleeding events. All events of intracranial bleeding should be reported as SAEs.

    - Intensive treatment in an emergency room or at home for allergic bronchospasm.

    - Blood abnormalities or convulsions that do not result in inpatient hospitalization.

- **Development of drug dependency or drug abuse**

9.2 Grading of Severity Using NCI CTCAE

Intensity of all AEs, including clinically significant laboratory abnormalities, will be graded according to the NCI CTCAE, version 5.0. Adverse events not specifically defined will be graded as follows:

- Grade 1: Mild, the event is noticeable to the patient but does not interfere with routine activity.

- Grade 2: Moderate, the event interferes with routine activity but responds to symptomatic therapy or rest.

- Grade 3: Severe, the event significantly limits the patient's ability to perform routine activities despite symptomatic therapy.

- Grade 4: Life-threatening, an event in which the patient was at risk of death at the time of the event.

- Grade 5: Fatal, an event that results in the death of the patient.

9.3 Relationship to Study Drug (Causality Assessment)

All AEs must have their causal relationship to study drug (study drug and/or protocol procedures) assessed by the Investigator using a binary system. Causality is either assessed as 'related' or 'not related':

- Related: The AE is known to occur with the study drug, there is a reasonable possibility that the study drug caused the AE, or there is a temporal relationship between the study drug and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.

- Not Related: Exposure to the study drug did not occur, or AE does not follow a reasonable temporal sequence from administration of the product and/or there is no reasonable possibility that the drug caused the AE. This assessment includes situations where an alternative etiology has been established (eg, the AE is related to other factors such as the patient's clinical state, other therapeutic interventions, or concomitant drugs administered to the patient).

9.4 Adverse Event Monitoring Period

Adverse events will be recorded in the eCRF from the first dose of a study drug dose through 30 days after the last dose of any study drug. Serious AEs and serious pretreatment events (see Section 9.9) will be recorded in the eCRF from the time of signing informed consent through 30 days after the last study drug dose. In addition, SAEs that are assessed as related to study treatment that occur > 30 days post-treatment will also be reported. All related AEs and AEs relating to cognitive function and intracranial bleeding should be monitored until they are resolved, are stabilized, have returned to pre-exposure baseline, are determined to be due to another illness, or until a subsequent antineoplastic therapy is initiated, even if > 30 days post last dose of study drug. For AEs considered not related to study drug, similar monitoring guidelines will only be required through 30 days after the last dose of study drug.

9.5 Eliciting Adverse Event Information

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care (or, when appropriate, be reported by a caregiver, surrogate, or the patient's legally authorized representative), or upon review by a study monitor.

The Investigator is responsible to report all directly observed AEs/SAEs, including all those spontaneously reported by the patient which came to the attention of site personnel.

In addition, each study patient will be questioned about adverse events at each visit following the initiation of treatment.

9.6 Adverse Event Reporting Conventions and Principles

9.6.1 Laboratory Values

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or interruption of treatment, dose modification, therapeutic intervention, or is considered by the Investigator to be clinically significant. A laboratory value may also be considered a SAE when it meets any of the seriousness criteria (see Section 9.1.3).

9.6.2 Preexisting Conditions

A pre-existing condition (ie, a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical examination form) should not be

reported as an AE unless the condition worsens, or episodes increase in frequency or severity during the AE reporting period.

9.6.3 Pre-Planned Therapeutic Procedures

Pre-planned therapeutic procedures not associated with a new medical condition or worsening pre-existing condition should not be reported as AEs.

9.6.4 Disease Progression

In general, disease progression should not be reported as an AE (or an SAE), or cause of death in this study. Instead the AEs (or SAEs) considered as complications of disease progression should be reported. However, if no specific complications of disease progression can be identified that explain the clinical observations, "disease progression" may be reported as an AE, SAE, or cause of death.

9.6.5 Lack of Efficacy

Lack of efficacy per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

9.6.6 Adverse Events NCI CTCAE Grade 5

All AEs with NCI CTCAE Grades 5 should be reported as SAE.

9.6.7 Second Malignancies

The occurrence of a second malignancy should be reported as SAE.

9.6.8 Special Situations

Certain safety events, called 'Special Situations', that occur in association with study drug(s) may require reporting. These Special Situations include, but are not limited to, the following:

- Overdose of the study drug
- Suspected abuse/misuse of the study drug
- Inadvertent or accidental exposure to the study drug by anyone other than the patient
- Medication error involving the study drug (with or without patient exposure to the Sponsor study drug, eg, name confusion)
- Drug-drug interaction.

Special situations should be reported on the Special Situations CRF whether they result in an AE/SAE or not. Special situations with associated AE/SAE should also be reported on the corresponding AE/SAE forms, following applicable AE or SAE process.

9.6.9 Exposure in Utero and Pregnancy

- A pregnancy in a female patient must be confirmed by a positive serum β human chorionic gonadotropin (β-HCG) test.

- The study medication should be immediately discontinued once the pregnancy of a female study patient has been confirmed.

- If any study patient or female partner of a male patient becomes or is found to be pregnant while receiving study drug or within 30 days of discontinuing the study medication, the pregnancy must be recorded on the Pregnancy Report Form/Exposure in Utero Form in the electronic data capture within 24 hours of awareness of the pregnancy.

- If a female partner of a male patient becomes pregnant, the male patient should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

- The Investigator must follow up and document the course and outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished. The female patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. Monitoring should continue until conclusion of the pregnancy.

- All outcomes of pregnancy must be reported by the Investigator to the Sponsor or Medical Monitor on a Pregnancy Outcome Report form within 24 hours after he/she has gained knowledge of the delivery or elective abortion.

- All neonatal deaths that occur within 1 month after birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the Investigator assesses as related to the in-utero exposure to the study medication should also be reported.

- Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (eg, spontaneous abortion, which may qualify as an SAE).

- Any SAE that occurs during the pregnancy of a study patient must be recorded on the SAE report form (eg, maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported **within 24 hours** in accordance with the procedure for reporting SAEs.

9.7 Adverse Event Collection and Reporting

The Investigator or qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the patient to discontinue study drug.

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- All AEs/SAEs must be assessed by the Investigator for seriousness (see Section 9.1.3) and causality (see Section 9.3).
- The Investigator will then record all relevant AE/SAE information in the CRF. Any laboratory assessments or other clinical findings considered an AE must be recorded on the AE page as well as the appropriate assessment page of the eCRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records in lieu of completion of the respective AE/SAE CRF pages.
- There may be instances when copies of medical records for certain cases are requested. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the requestor.
- For SAEs, additional conventions apply as outlined in Section 9.9.

9.8 Adverse Event Electronic Data Capture

All AEs, including SAEs, are to be accurately recorded on the AE page of the eCRF. Information to be recorded in the description of each AE (serious and non-serious) includes:

- A medical diagnosis of the event (If a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded.)
- The date of onset of the event
- The date of resolution of the event
- Whether the event is serious or not
- Intensity of the event (see Section 9.2)
- Relationship of the event to study drug (see Section 9.3)

- Action taken: none; change in the study drug administration (eg, temporary interruption in intervention); drug treatment required; nondrug treatment required; hospitalization or prolongation of hospitalization required (complete SAE page); diagnostic procedure performed; patient discontinued from the study (complete End of Study visit)

- Outcome: patient recovered without sequelae; patient recovered with sequelae; event ongoing; patient died. If this occurs, notify the Medical Monitor immediately. and complete the SAE form.

9.8.1 Follow-Up of Unresolved Events

All related AEs and AEs relating to cognitive function and intracranial bleeding should be monitored until they are resolved, have stabilized, have returned to pre-exposure baseline, are determined to be due to another illness, or until a subsequent therapy is initiated even if > 30 days from last dose of study drug. For AEs considered not related to study drug, similar monitoring guidelines will only be required through 30 days after the last dose of study drug. If the patient withdraws from treatment because of an AE, every effort must be made to perform protocol-specified safety follow-up procedures, as outlined in Section 7.8.

In the event a patient is withdrawn from study drug or the follow-up part of the study, the Medical Monitor must be informed. If there is a medical reason for withdrawal, the patient will remain under the supervision of the Investigator or designee until the condition has returned to baseline or stabilized.

9.9 Reporting Serious Adverse Events

All SAEs or serious pretreatment events that occur during the AE monitoring period (see Section 9.4) must be reported by the Investigator to the Sponsor or its designee within 24 hours from the point in time when the Investigator becomes aware of the SAE. In parallel, the eCRF pages for the AE should also be completed. The same 24-hour timeline applies for any follow-up information received by the Investigator.

NOTE: Compliance with this time requirement is essential so that the Sponsor may comply with its regulatory obligations.

All SAEs must be reported whether or not they are considered causally related to study treatment.

SAE forms will be completed in English language and should contain, at a minimum:

- Patient number/ID, sex, and age/year of birth

- The date of the report

- Name of the Investigator

- Name of the suspected study drug
- Assessment of event severity/intensity (and/or NCI CTCAE Grade)
- Investigator causality assessment
- A description of the event, including event term(s), seriousness criteria, and a clinical summary of the event
- SAEs with outcome 'death': cause of death, autopsy or death certificate, as applicable and available

Refer to the study manual for reporting instructions.

9.10 Regulatory and Institutional Reporting Responsibilities

The Sponsor and/or its designee are responsible for reporting SAEs to all applicable regulatory agencies and the central ethics committees within the required timeline.

The Investigators are responsible for submitting required safety information to their local Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as per local regulations. This information includes, but is not limited to, any safety alert letter received from the Sponsor and any SAEs occurring at their investigative site.

For patients who are screen failures (ie, sign informed consent, did not meet eligibility criteria, and therefore did not receive study drug), SAEs should be collected up to 30 days after signing informed consent.

10 STATISTICS

10.1 General Procedures

All tabular summaries will be presented by treatment arm. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage (n, %) of patients within each category. Appropriate CIs will also be presented. All data will be provided in by-patient listings.

Efficacy, safety, and PK will be assessed in the appropriate populations.

10.2 Sample Size Estimation

A total of approximately 460 patients will be needed for the study. Patients will be recruited from approximately 90 sites and it is expected that each site will enroll about 3-10 patients.

The sample size calculation was based upon the assumption that the median PFS for regorafenib is approximately 5 months (Stivarga, 2017). Assuming avapritinib can reduce

the risk of PFS by 33%, ie, assuming the HR of 0.67 (avapritinib compared to regorafenib), a minimum of 264 PFS events are needed to provide 90% power at a 2-sided alpha of 0.05 for the study. With an 18-month accrual period and a 6-month follow-up period, the total sample size needed for the study is approximately 460 patients (230 patients per arm) in order to achieve 264 total PFS events. The sample size calculation has taken a 2% dropout rate into consideration and assumes accrual will follow a truncated exponential distribution with a scaled power parameter -9.

The sample size calculated for the primary endpoint, PFS, is also sufficient for detecting a difference in ORR between the two arms. Assuming a null ORR of 5% and an alternative ORR of 15%, approximately 95% power is obtained using a test of two-proportions.

We assume the same effect size for OS as for PFS, hence the same number of events (264) is required to power the analysis. The timing of the OS analysis, however shall be later than the PFS analysis as it will be at such time that 264 deaths occur.

Gate keeping sequential testing will be implemented to test PFS, then ORR, and then OS.

10.3 Analysis Populations

The following analysis populations will be used for presentation of the data:

- Intent-to-treat (ITT) Population: The ITT population includes all randomized patients, independent of whether they received the study medication or not. All primary efficacy analyses will be based on the ITT population. All patients in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

- Per-Protocol (PP) Population: The PP population includes all patients in the ITT population who have no major violations of the inclusion/exclusion criteria. Patients in this population will be analyzed according to the treatment to which they are randomized. The analyses using data from the PP population are considered supportive and sensitivity analyses.

- Response-Evaluable (RE) Population: The response-evaluable population is defined as all patients in the ITT population who received at least 1 dose of avapritinib or regorafenib, have at least 1 target lesion per mRECIST, version 1.1, at Baseline and have at least 1 postbaseline disease assessment by central radiology per mRECIST, version 1.1. Selected efficacy analysis may be performed using the RE population.

- Safety Population: The safety population is defined as all patients who received at least 1 dose of study medication. The safety population will be analyzed according to the treatment the patient actually received.

- PK Population: The PK population is defined as all patients who have adequate PK samples collected so that the PK parameters can be assessed and calculated.

10.4 Randomization and Stratification

Eligible patients will be randomized in a 1:1 ratio to receive avapritinib or regorafenib, stratified by line of therapy (third vs. fourth), geographic region (Asia vs. rest of the world), and mutation status measured in ctDNA or a tumor sample (PDGFRα D842V mutation present vs. absent). The randomization scheme will be generated by an independent statistical group. The randomization assignment will be implemented by an IWRS.

10.5 Statistical Methods

10.5.1 Disposition

A tabulation of the disposition of patients will be presented by treatment arm, including the number of patients randomized, patient distribution for each stratification factor, the number treated, the reasons for treatment discontinuation, and the reasons for study discontinuation. Entry criteria and protocol deviations will be listed.

10.5.2 Demographic and Baseline Characteristics

Demographic and baseline disease characteristic data will be presented by treatment arm. Data to be tabulated will include sex, age, and race and ethnicity, as well as disease-specific information.

10.5.3 Efficacy Analysis

10.5.3.1 Analysis of the Primary Efficacy Endpoint

The primary endpoint of PFS is defined as the time from randomization to disease progression or death due to any cause, whichever occurs first. The primary analysis for PFS is based on the central radiological assessment of PD per mRECIST, version 1.1 in the ITT population.

Patients without disease progression or death at the time of analysis will be censored at their last date of tumor evaluation. Patients who withdraw from the study and receive subsequent antineoplastic therapy without documented PD will be censored at the time of the last adequate (CT or MRI scan available) disease assessment. For PD documented between scheduled evaluations, the actual date of PD will be used, not the date of the next scheduled evaluation. For death or PD after no more than 1 missed evaluation, the date of the event will be the date of PD or death, whichever occurs first. For death or PD after more than 1 missed evaluation, the date of the event will be censored at the last adequate disease assessment. Detailed censoring methods will be described in the statistical analysis plan (SAP).

The Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. The primary treatment comparison is based on a stratified log-rank test in the ITT population. The HR, and its 95% CI, are to be estimated based on a stratified Cox's model with treatment as the explanatory variable. Stratification factors include TKI

treatment (third vs. fourth), geographic region (Asia vs. rest of the world), and mutation status measured in ctDNA or a tumor sample (PDGFRα D842V mutation present vs. absent).

Progression-free survival derived from the Investigator assessment per mRECIST, version 1.1 in the ITT population, and from central radiological assessment per Choi criteria in the ITT population will be evaluated and used as supportive evidence. The analysis of PFS based on the PP population will also be included as a sensitivity analysis.

10.5.3.2 Analyses of Secondary Efficacy Endpoints

10.5.3.2.1 Objective Response Rate

Objective response rate is defined as the percentage of patients whose best response is CR or PR as assessed by central radiological assessment according to mRECIST, version 1.1. The ORR will be evaluated and analyzed for the ITT population.

Objective response rate will be summarized for each treatment group. A stratified Cochran-Mantel-Haenszel (CMH) test will be performed to test treatment difference. A logistic regression model will be used to estimate the treatment effect measured in terms of odds ratios. The odds ratio and its 95% CI will be presented.

A gate-keeping method will be implemented to control Type I error. The ORR will be analyzed when superiority is demonstrated for PFS.

Additionally, response as assessed by investigator per mRECIST, version 1.1 and response based on central radiology per Choi criteria will be evaluated and analyzed for the ITT population as supportive analysis. All the proposed response assessments will be examined based on the response-evaluable population and/or per protocol population, as sensitivity analyses.

10.5.3.2.2 Overall Survival

Overall survival is defined as the time from date of randomization to death due to any cause. The primary treatment comparison will be based on a rank preserving structural failure time (RPSFT) model to account for treatment crossover effects from regorafenib to avapritinib. The survival time gained/lost by receiving avapritinib after crossover in the regorafenib group will be estimated. Rank preserving structural failure time reconstructs the survival duration of patients as if they had never received avapritinib, assuming treatment is acting by multiplying survival time by a given factor once a patient starts receiving avapritinib (Korhonen et al, 2012).

If the patient is alive or the vital status is unknown at the time of analysis, OS will be censored at the date the patient is last known to be alive. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. The HR and its 95% CI will be estimated based on Cox's regression model with stratification factors as covariates.

In addition, the probability of survival by time after randomization based on Kaplan-Meier estimates will be tabulated for each treatment group along with the standard errors estimated by the Greenwood formula.

A gate-keeping method will be implemented to control Type I error. The OS will be analyzed when superiority is demonstrated for both PFS and ORR. The OS will also be analyzed at the follow-up when 264 events (deaths) occur.

A sensitivity analysis will be conducted in the ITT population where treatment crossover is ignored. Other sensitivity analyses may be considered as appropriate.

10.5.3.2.3 Analyses of Health-Related Quality-of-Life

The EORTC-QLQ-C30 questionnaire will be used to collect data on the patient's functioning, disease-related symptoms, and health-related QoL. For all individual scores, eg, physical functioning, pain, role functioning, and appetite loss, etc, mean changes from baseline to Week 12 will be compared between treatment groups by a t-test. Post hoc analyses to explore thresholds for meaningful change using cumulative distribution function to determine clinical benefit will be outlined in the SAP.

10.5.3.2.4 Disease Control Rate

Disease control is defined as rate of CR or PR of any duration, or SD lasting for at least 16 weeks per mRECIST version 1.1 from the beginning of treatment. Disease control rate will be analyzed similarly as the ORR.

10.5.3.2.5 Duration of Response

Duration of response (CR or PR) is calculated from the date of initial documentation of a response to the date of first documentation of PD or death due to any cause. Censoring rules for DOR will be similar to those for PFS.

The Kaplan-Meier method will be used to descriptively summarize DOR. No inferential statistics will be performed.

10.5.4 Exposure and Safety Analyses

A summary of study drug exposure, including total dose, duration of treatment, dose intensity, and the proportion of patients with dose modifications will be summarized by treatment arm. Reasons for dose modifications will be listed by patient and summarized.

Safety will be evaluated by the incidence of AEs, causality, intensity, seriousness, and type of AEs, and by the patient's vital signs, ECOG PS scores, clinical laboratory test results, and ECG data.

Concomitant medications will be listed by patient and will be summarized by treatment arm.

All safety data will be summarized by treatment arm for the safety population.

10.5.4.1 Adverse Events

Summary tables and listings for AEs will include TEAEs, where an AE is defined as any TEAE that occurred between the first dose of a study drug through 30 days after the last dose of any study drug. The incidence of TEAEs (new or worsening from Baseline) will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and/or preferred term, intensity (based on NCI CTCAE version 5.0 grading as assessed by the Investigator), seriousness, and relation to study treatment. The following summaries will be produced:

- All AEs
- AEs leading to dose modifications
- Treatment-related AEs
- Grade 3 or higher AEs
- Grade 3 or higher treatment-related AEs
- Most commonly reported AEs (ie, those events reported by ≥ 10% of patients in either treatment group)
- SAEs
- Treatment-related SAEs
- Discontinuations due to AEs

By-patient listings will be provided for on-treatment deaths (on-treatment is defined as the period starting from the first dose to 30 days after the last dose), AEs, SAEs, and AEs leading to discontinuation of treatment.

10.5.4.2 Laboratory Abnormalities

For laboratory tests included in the NCI CTCAE version 5.0, laboratory data will be graded accordingly; a Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

The following summaries will be generated separately for hematology, serum chemistry and coagulation studies, and urinalysis laboratory tests:

- Descriptive statistics for the actual values and/or change from Baseline of clinical laboratory parameters over time.
- Shift tables using NCI CTCAE grades to compare baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the corresponding NCI CTCAE grades.

In addition to the above-mentioned tables and listings, graphical displays of key safety parameters, such as scatter plots of actual values or change in laboratory test results over time or box plots may be specified in the SAP.

10.5.4.3 Other Safety Data

Descriptive statistics for the actual values and/or the changes from Baseline of vital signs (including systolic and diastolic blood pressure, heart rate, and temperature) over time will be summarized.

Descriptive statistics of ECOG PS over time will be summarized by frequency.

Descriptive statistics for the actual values and changes from Baseline in ECG data over time will be summarized. In addition, a categorical analysis of QTcF intervals may be performed for each time point. Maximum QTcF intervals and maximum changes from Baseline may also be summarized similarly in a separate display. ECG abnormalities will be presented in a data listing.

Additional safety analyses may be performed if deemed necessary.

10.5.5 Pharmacokinetics Analyses

Avapritinib plasma concentration-time data for individual subjects in each cycle along with descriptive statistics will be summarized.

Mean and individual subject predicted avapritinib exposure parameters (C_{max}, AUC_{0-24}, and C_{trough}) from the PopPK model will be summarized, as appropriate.

10.5.6 Analyses of the Exploratory Endpoints

Baseline KIT, PDGFRα, and other cancer-relevant mutation status will be correlated with antineoplastic activity (PFS, ORR, DCR, OS) by analysis of ctDNA.

Changes in KIT, PDGFRα and other cancer-relevant mutant allele fractions in ctDNA will be correlated with measures of antineoplastic activity (PFS, ORR, DCR, OS).

For all other biomarker data, summary statistics and graphs will be provided as appropriate. Relationships between biomarker data and efficacy measures will be descriptively analyzed, as appropriate.

11 ETHICS AND RESPONSIBILITIES

11.1 Good Clinical Practice

The study will be conducted in accordance with the International Council for Harmonisation (ICH) GCP guidelines and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and IB. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

11.2 Independent Data Monitoring Committee

A formal IDMC will be used for this study. The roles and responsibilities of the IDMC are listed below. Further details will be described separately in the IDMC charter.

The IDMC is composed of 3 members, 2 oncologists with expertise in the treatment of patients with GIST, and a statistician with expertise in clinical trials. The members of the IDMC and their academic affiliation are the following:

The aim of the committee is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

The IDMC will receive and review information on the progress and accumulating data of this study and provide advice on the conduct of the study.

The IDMC will make recommendations to the Blueprint Study Management Group and the Study Steering Committee regarding the following aspects of the study; as is relevant in regard to the study design:

- whether it is ethical to continue randomizing patients when there is compelling evidence that the risk/benefit ratio favors one of the arms over the other or conversely, where there is compelling evidence of futility (ie, that the study will never lead to concluding against the null hypothesis) following protocol-defined stopping rules.

- whether the results of all or some of the study endpoints should be published or presented publicly earlier than anticipated, ie, before study maturity.

- whether a modification should be made to the study for safety reasons, for example, a modification of the eligibility criteria when the risk/benefit ratio seems unfavorable in specific subgroups of patients.

- on early termination of a trial when the scientific value of the trial is insufficient, either because of compelling external evidence regarding the hypothesis being tested or because the trial will not be able to produce scientifically valid results due to lack of accrual or lack of quality.

- on modifications to the study sample size.

- on actions needed to manage identified issues related to patient compliance or study feasibility and/or quality.

The role of the IDMC is to perform interim reviews of the study's progress including adherence to protocol, follow-up assessments, primary efficacy outcomes, and safety data.

Specifically, this role includes:

- monitoring evidence for treatment harm (eg, toxicity, SAEs, deaths).

- assessing the impact and relevance of external evidence.

- deciding whether to recommend that the study continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups.

- deciding whether study follow-up should be stopped earlier.

- maintaining confidentiality of all study information that is not in the public domain.

- considering the ethical implications of any recommendations made by the IDMC.
- monitoring planned sample size assumptions, preferably with regards to (i) a priori assumptions about the control arm outcome and/or (ii) emerging differences in clinically relevant subgroups, rather than on emerging, un-blinded differences between treatment groups, overall.
- suggesting additional data analyses if necessary.
- advising on protocol modifications proposed by the Investigators or the Sponsor (eg, to inclusion criteria, study endpoints, or sample size).
- monitoring compliance with previous IDMC recommendations

11.3 Institutional Review Board/Independent Ethics Committee

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki.

The Investigator must obtain IRB/IEC approval for the investigation and must submit written documentation of the approval to the Sponsor before he or she can enroll any patient into the study. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at study centers where IRB/IEC approval has been obtained. The protocol, IB, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC. The IRB/IEC is to be notified of any amendment to the protocol in accordance with local requirements. Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

11.4 Informed Consent

The Investigator at each study center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study-related procedures. The Investigator must maintain the original, signed consent form. A copy of the signed form must be given to the patient.

The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP and all applicable regulatory requirement(s).

11.5 Records Management

All data for the patients recruited for the trial will be entered onto the eCRFs via an Electronic Data Capture system provided by the Sponsor or designee. Only authorized staff may enter data into the eCRFs. If an entry error is made, the corrections to the eCRFs will be made according to eCRF guidelines by an authorized member of the center staff.

Electronic case report forms will be checked for correctness against source document data by the Sponsor's monitor. If any entries into the eCRF are incorrect or incomplete, the monitor will ask the Investigator or the study center staff to make appropriate corrections, and the corrected eCRF will again be reviewed for completeness and consistency. Any discrepancies will be noted in the eCRF system by means of electronic data queries. Authorized study center staff will be asked to respond to all electronic queries according to the eCRF guidelines.

11.6 Source Documentation

Source documents/eCRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's source document/eCRF. The source document/eCRF should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The Investigator, or designated representative, should complete the source document/eCRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the source document/eCRF to endorse the recorded data.

The Investigator will retain all completed source documents.

11.7 Study Files and Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained by the sponsor for at least 25 years after the last marketing application approval in major markets (ie, US, EU, Japan, Canada) or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

11.8 Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

12 AUDITING AND MONITORING

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) and will include on-site review of the source documents/eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications.

All unused study drug and other study materials should be destroyed or returned to the Sponsor or designee after the study has been completed, as directed by the Sponsor.

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, eCRFs, and other study documentation for an on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

13 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by Blueprint Medicines. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. Blueprint Medicines will submit protocol amendments to the appropriate regulatory authorities for approval.

If, in the judgment of the IRB/IEC, the Investigator, and/or Blueprint Medicines, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

14 STUDY REPORT AND PUBLICATIONS

Blueprint Medicines is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of Blueprint Medicines is discussed in the Investigator's Clinical Research Agreement.

15 STUDY DISCONTINUATION

Both Blueprint Medicines and the Investigator reserve the right to terminate the study at the Investigator’s site at any time. Should this be necessary, Blueprint Medicines or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Investigator will inform the IRB/IEC of the same. In terminating the study, Blueprint Medicines and the Principal Investigator will assure that adequate consideration is given to the protection of the patients’ interests.

16 CONFIDENTIALITY

All information generated in this study is considered confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Blueprint Medicines. However, authorized regulatory officials, IRB/IEC personnel and Blueprint Medicines and its authorized representatives are allowed full access to the records.

Identification of patients and eCRFs shall be by initials (when permitted) and screening and treatment numbers only.

17 REFERENCES

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18 APPENDICES

18.1 Appendix 1

REGORAFENIB LABELING INFORMATION

US prescribing information for regorafenib is available at: http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf.

The Summary of Product Characteristics for regorafenib is available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002573/WC500149164.pdf

Canadian prescribing information for regorafenib is available at: https://omr.bayer.ca/omr/online/stivarga-pm-en.pdf.

18.2 Appendix 2

PRESPECIFIED DOSE MODIFICATIONS FOR ADVERSE EVENTS RELATED TO REGORAFENIB

Prespecified dose modifications for adverse events related to study drug excluding hand–foot skin reaction, hypertension, and aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin increases

National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE v5.0) Grade	Dose Interruption	Dose Modification[a]	Dose for Subsequent Cycles
Grade 0–2	Treat on time	No change	No change
Grade 3	Delay until ≤ Grade 2[b]	Reduce by 1 dose level[c]	If toxicity remains ≤ Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction
Grade 4	Delay until ≤ Grade 2[b]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion	

[a] Not for alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity, and asymptomatic laboratory abnormalities.
[b] Patients requiring a delay of > 56 days should discontinue protocol therapy.
[c] Dose level 0 = 160 mg, dose level –1 = 120 mg, dose level –2 = 80 mg.
Source: (Demetri et al, 2013b)

Prespecified Dose Modifications for Treatment-related Hand–foot Skin Reaction

Skin Toxicity Grade (according to NCI-CTCAE v5.0 "Palmar–plantar erythrodysesthesia syndrome")	Occurrence	Suggested dose modification (more liberal management is allowed if judged medically appropriate by the Investigator)
Grade 1: Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2: Skin changes (e.g., peeling,blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental activities of daily living	1st occurrence	Consider decreasing dose by 1 dose level[a] and immediately institute supportive measures. If there is no improvement, interrupt therapy for ≥ 7 days, until toxicity resolves to Grade 0–1[b]
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0–1. Resume treatment at reduced dose level[b]
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0–1. On resuming treatment, decrease dose by one additional dose level[a,c]
	4th occurrence	Discontinue treatment
Grade 3: Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, orhyperkeratosis) with pain; limiting self-care activities of daily living	1st occurrence	Institute support measures immediately. Interrupt therapy for ≥ 7 days until toxicity resolves to Grade 0–1. On resuming treatment, decrease dose by one dose level[a]
	2nd occurrence	Institute support measures immediately. Interrupt therapy for ≥ 7 days until toxicity resolves to Grade 0–1. On resuming treatment, decrease dose by one additional dose level[a,c]
	3rd occurrence	Discontinue treatment permanently

[a] Dose level 0 = 160 mg, dose level –1 = 120 mg, dose level –2 = 80 mg.
[b] If toxicity returns to Grade 0–1 after dose reduction, re-escalation is permitted at the discretion of the investigator.
[c] Patients requiring >2 dose level reductions (ie, a reduction that would result in a dose <80 mg) should discontinue protocol therapy.

Prespecified Dose Modifications for Treatment-related Hypertension

NCI-CTCAE v5.0 Grade	Definition	Antihypertensive therapy	Study drug dosing
Grade 1	Systolic blood pressure (BP) 120– 139 mmHg or diastolic BP 80-89 mmHg	None	Continue study drug Consider increased blood pressure monitoring
Grade 2	Systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg if previously within normal limits; change in baseline medical intervention indicated; recurrent or persistent (≥ 24 h); or Symptomatic increase by > 20 mmHg (diastolic) or to > 140/90 mmHg; monotherapy indicated initiated	Treat to achieve diastolic BP ≤ 90 mmHg If BP previously within normal limits, start antihypertensive monotherapy If patient already on antihypertensive medication, titrate dose up	Continue study drug If symptomatic, hold study drug until symptoms resolve and diastolic BP ≤ 90 mmHg[a] On resuming study drug, continue at same dose level
Grade 3	Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg; Medical intervention indicated; More than one drug or more intensive therapy than previously used indicated	Treat to achieve diastolic BP ≤ 90 mmHg — Start antihypertensive medication and/or — Increase current antihypertensive medication and/or — Add additional antihypertensive medications	Hold study drug until diastolic BP ≤ 90 mmHg and, if symptomatic, symptoms resolvea On resuming study drug, continue at same dose level If BP is not controlled with addition of new or more intensive therapy, reduce study drug by one dose level[b,c] If Grade 3 hypertension recurs despite study drug dose reduction and antihypertensive therapy, reduce study drug by one additional dose level[b,d]
Grade 4	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurological deficit, hypertensive crisis) Urgent intervention indicated		Discontinue treatment

[a] Patients requiring a delay of > 4 weeks should discontinue protocol therapy.
[b] Dose level 0 = 160 mg, dose level –1 = 120 mg, dose level –2 = 80 mg.
[c] If blood pressure remains controlled for at least one full cycle, study drug dose re-escalation is permitted at the investigator's discretion.
[d] Patients requiring >2 study drug dose level reductions (ie, a reduction that would result in a study drug dose < 80 mg) should discontinue protocol therapy

Prespecified Dose Modifications for Treatment-related Increases in ALT and/or AST and/or Bilirubin

NCI-CTCAE v5.0 Grade	1st occurrence	Restart	Reoccurrence
Baseline Grade 0→Grade 1 or Baseline Grade 1→Grade 2	Give study drug on time Check AST, ALT and bilirubin twice weekly for 2 weeks then weekly for at least 4 weeks		Give study drug on time Check AST, ALT and bilirubin twice weekly for 2 weeks then weekly for at least 4 weeks
Baseline Grade 0→Grade 2	Delay study drug until ≤ Grade 1 Check AST, ALT, and bilirubin twice weekly	Reduce study drug by 1 dose level[a] Check AST, ALT, and bilirubin twice weekly for 2 weeks then weekly for at least 4 weeks[b]	Discontinue study drug[c]
Baseline any Grade→Grade 3	Delay study drug until ≤ Grade 1 if baseline was Grade 0 or 1 or until Grade 2 if baseline was Grade 2 Check AST, ALT, and bilirubin twice weekly If ALT or AST >8× upper limit of normal, with concomitant rise in bilirubin (of any degree) versus previous bilirubin values, consider permanent discontinuation of study drug at first occurrence[c]	Reduce study drug by 1 dose level[a] Check AST, ALT, and bilirubin twice weekly for 2 weeks then weekly for at least 4 weeks[b]	Discontinue treatment[c]
Baseline any Grade→Grade 4	Discontinue treatment[c]		

[a] Dose level 0 = 160 mg, dose level –1 = 120 mg, dose level –2 = 80 mg.
[b] If all values remain stable for two full cycles, study drug dose re-escalation may be considered at the discretion of the investigator. After re-escalation AST, ALT, bilirubin should be checked twice weekly for 2 weeks then weekly for at least 4 weeks.
[c] In case of discontinuation, check AST, ALT, and bilirubin twice weekly for 2 weeks then weekly until recovery to baseline.

18.3 Appendix 3

EXCLUDED MEDICATIONS AND FOODS FOR PATIENTS RECEIVING AVAPRITINIB

Strong CYP3A4 Inhibitors	Strong CYP3A4 Inducers	Moderate CYP3A4 Inducers
Boceprevir	Carbamazepine	Bosentan
Clarithromycin	Phenytoin	Efavirenz
Cobicistat	Rifampin	Etravirine
Conivaptan	St. John's Wort	Modafinil
Grapefruit, grapefruit juice	Phenobarbital	Dabrafenib
Indinavir		
Itraconazole		
Ketoconazole		
Lopinavir		
Nefazodone		
Nelfinavir		
Posaconazole		
Ritonavir		
Saquinavir		
Telaprevir		
Telithromycin		
Voriconazole		

Abbreviations: CYP3A4 = cytochrome P450 3A4.
CBD Oil is not considered to be a CYP3A4 inhibitor or inducer and is therefore permitted while on treatment.
This list is not intended to be exhaustive. A similar restriction will apply to other drugs that are known to strongly modulate CYP3A4 via inhibition or induction or are moderate CYP3A4 inducers; appropriate medical judgement is required. Please contact Blueprint Medicines with any queries you have on this issue.

EXCLUDED MEDICATIONS AND FOODS FOR PATIENTS RECEIVING REGORAFENIB

Strong CYP3A4 Inhibitors	Strong CYP3A4 Inducers	Strong UGT1A9 Inhibitors
Boceprevir	Carbamazepine	Mefenamic acid
Clarithromycin	Phenytoin	diflunisal
Cobicistat	Rifampin	Niflumic acid
Conivaptan	St. John's Wort	
Grapefruit, grapefruit juice	Phenobarbital	
Indinavir		
Itraconazole		
Ketoconazole		
Lopinavir		
Nefazodone		
Nelfinavir		
Posaconazole		
Ritonavir		
Saquinavir		
Telaprevir		
Telithromycin		
Voriconazole		

Abbreviations: CYP3A4 = cytochrome P450 3A4.
This list is not intended to be exhaustive. A similar restriction will apply to other drugs that are known to strongly modulate CYP3A4 via inhibition or induction or are strong inhibitors of UGT1A9; appropriate medical judgement is required. Please contact Blueprint Medicines with any queries you have on this issue.

18.4 Appendix 4

MEDICATIONS TO BE USED WITH CAUTION WITH AVAPRITINIB

CYP3A4 Substrates	CYP2C9 Substrates	BCRP Substrates	Moderate CYP3A4 Inhibitors
Alfentanil	Warfarin	Rosuvastatin	Erythromycin
Cyclosporine		Methotrexate	Fluconazole
Dihydroergotamine		Lapatinib	Crizotinib
Ergotamine			Dronedarone
Fentanyl			Imatinib
Midazolam			Diltiazem
Pimozide			
Quinidine			
Simvastatin			
Sirolimus			
Tacrolimus			
Terfenadine			

Abbreviations: BCRP = Breast Cancer Resistance Protein; CYP3A4 = Cytochrome P450 3A4; CYP2C9 = cytochrome P450 2C9

This list is not intended to be exhaustive. A similar restriction will apply to other drugs that are sensitive substrates of CYP3A4, CYP2C9, or BCRP, and moderate inhibitors of CYP3A4; appropriate medical judgement is required. Please contact Blueprint Medicines with any queries you have on this issue.

MEDICATIONS TO BE USED WITH CAUTION WITH REGORAFENIB

BCRP Substrates
Methotrexate
Fluvastatin
Atorvastatin

Abbreviations: BCRP = Breast Cancer Resistance Protein.

18.5 Appendix 5

EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: (Oken et al, 1982).

18.6 Appendix 6

MODIFICATIONS TO RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1 (MRECIST 1.1), FOR PATIENTS WITH GIST

1. No lymph nodes to be chosen as target lesions. Enlarged lymph nodes are to be followed up as non-target lesions.

2. No bone lesions to be chosen as target lesions.

3. ^{18}Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) is not acceptable for radiological assessment.

4. A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria in order to be regarded as unequivocal evidence of progressive disease:

    a. The lesion must be ≥ 2 cm in size and definitely be a new active GIST lesions (eg, enhanced with contrast or other criteria to rule out artifact); or

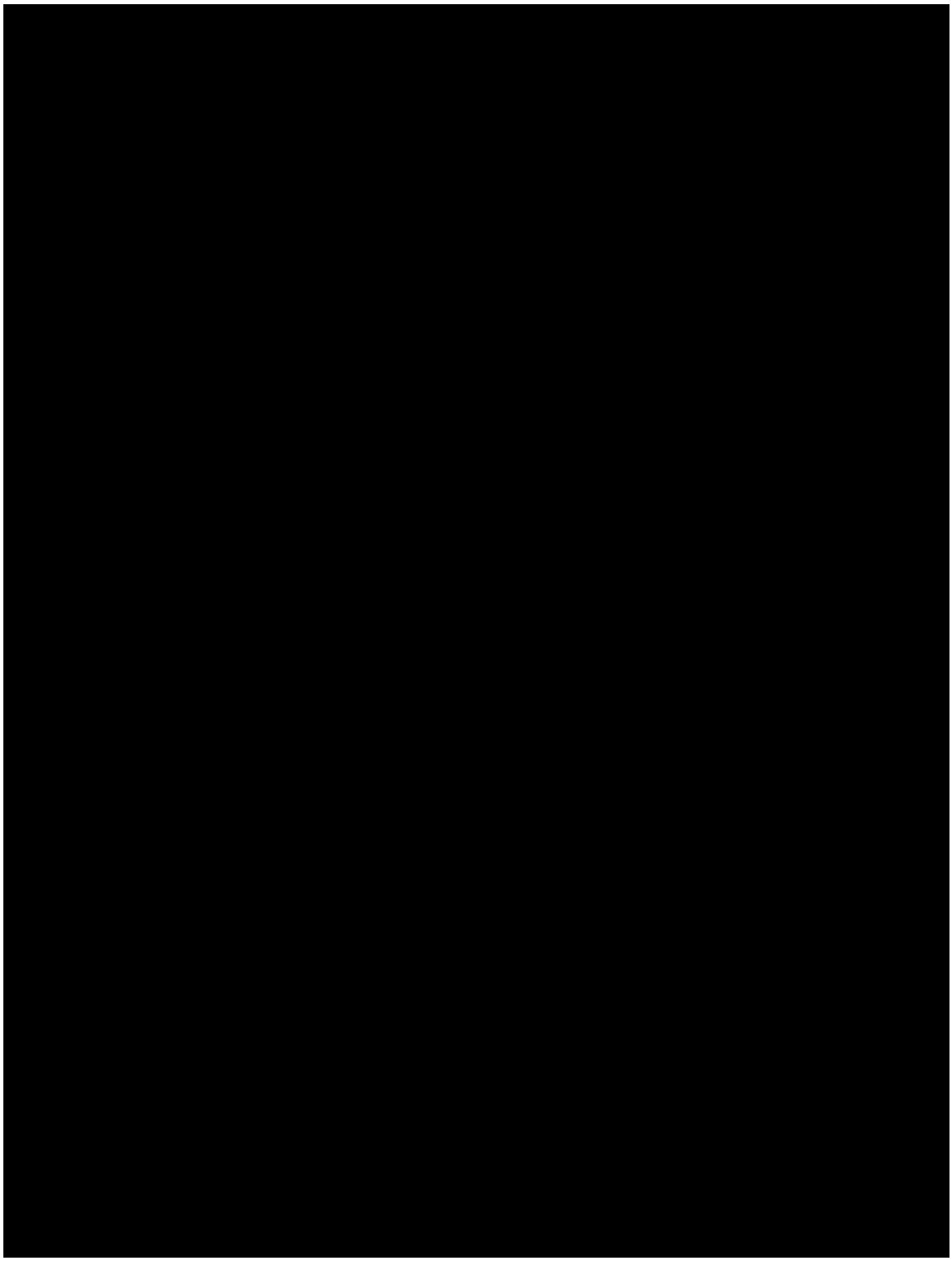
    b. The lesion must be expanding on at least 2 sequential imaging studies.

Source: (Demetri et al, 2013a)

18.7 Appendix 7

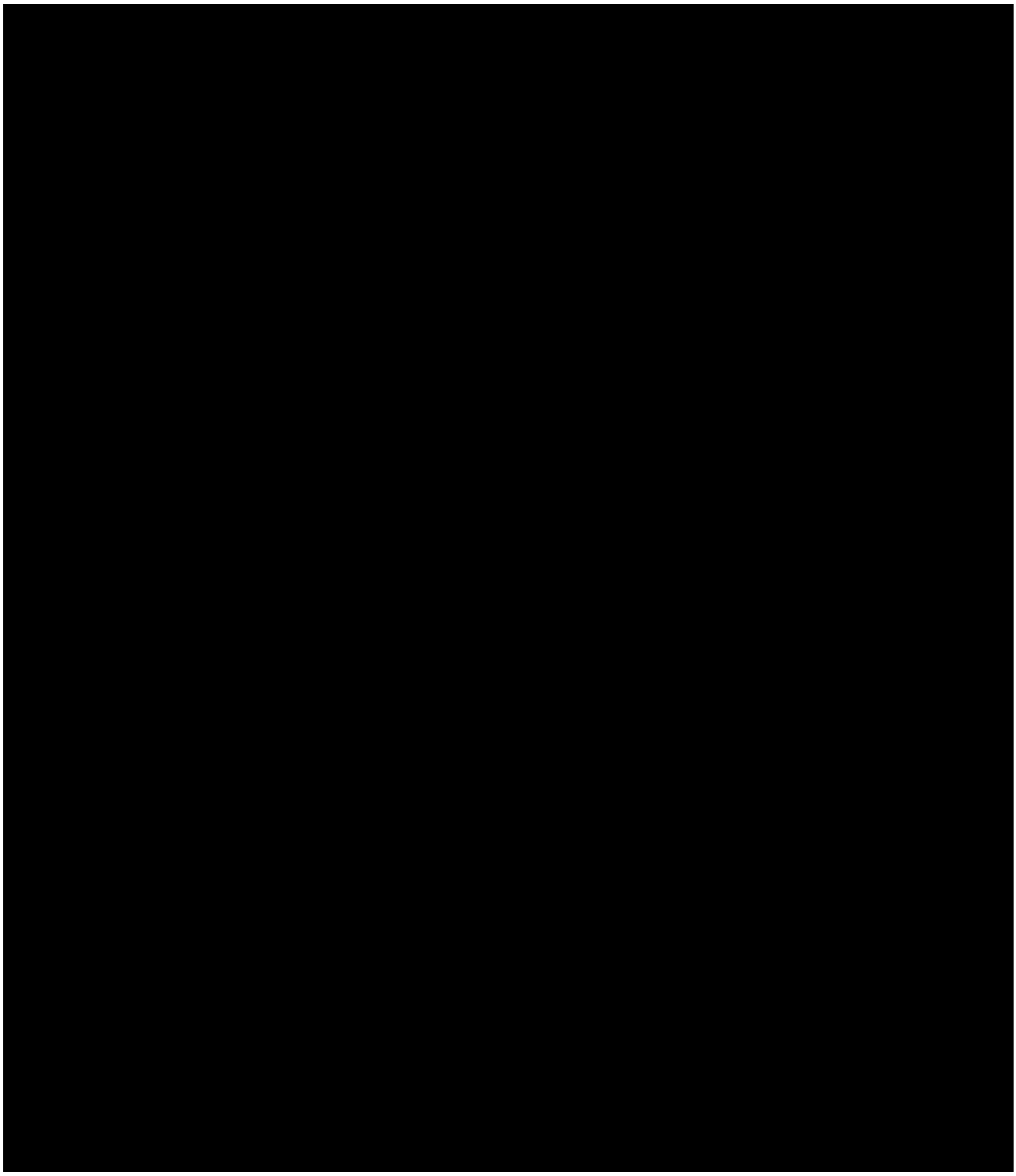
18.8 Appendix 8

[redacted]

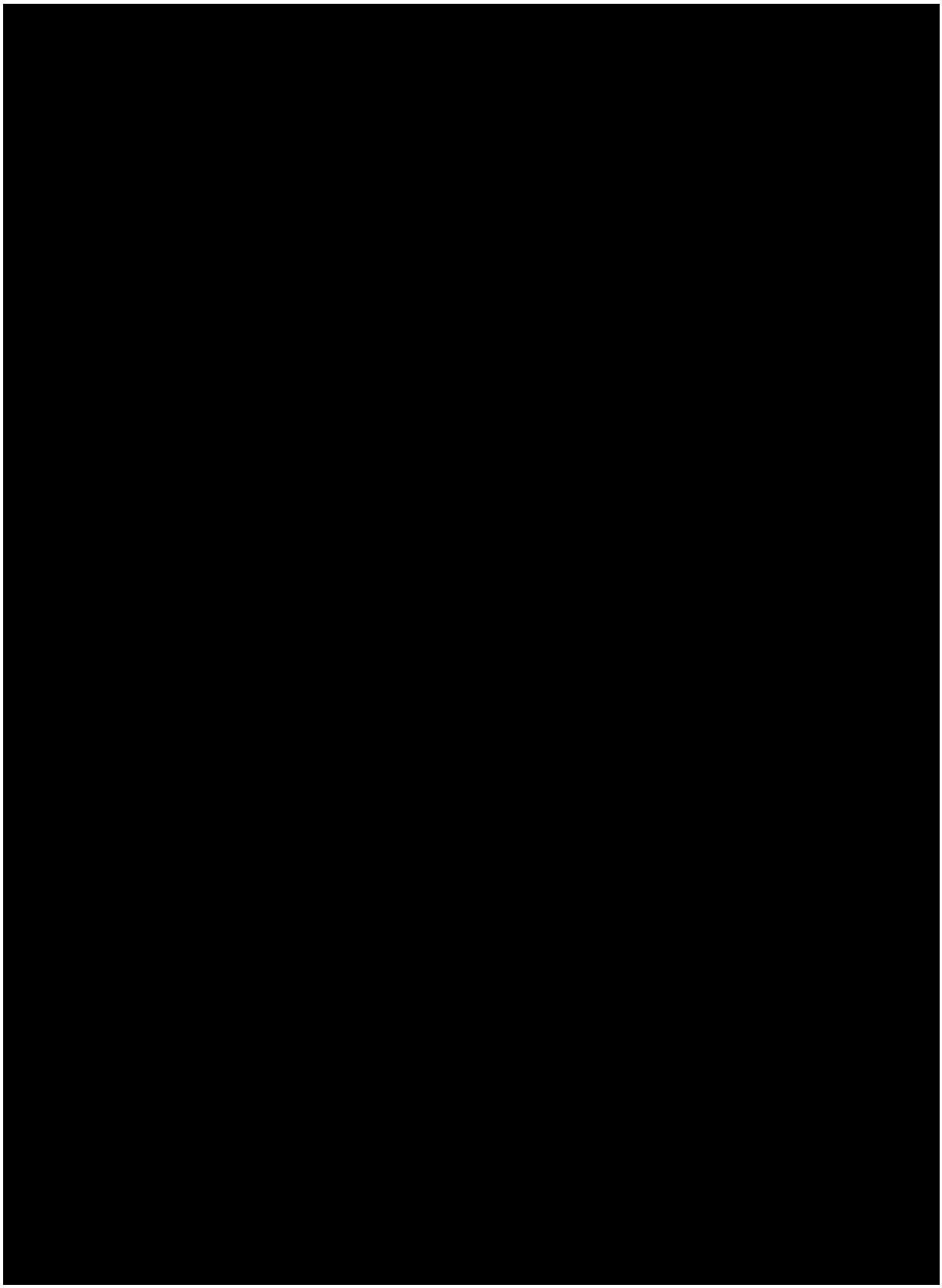


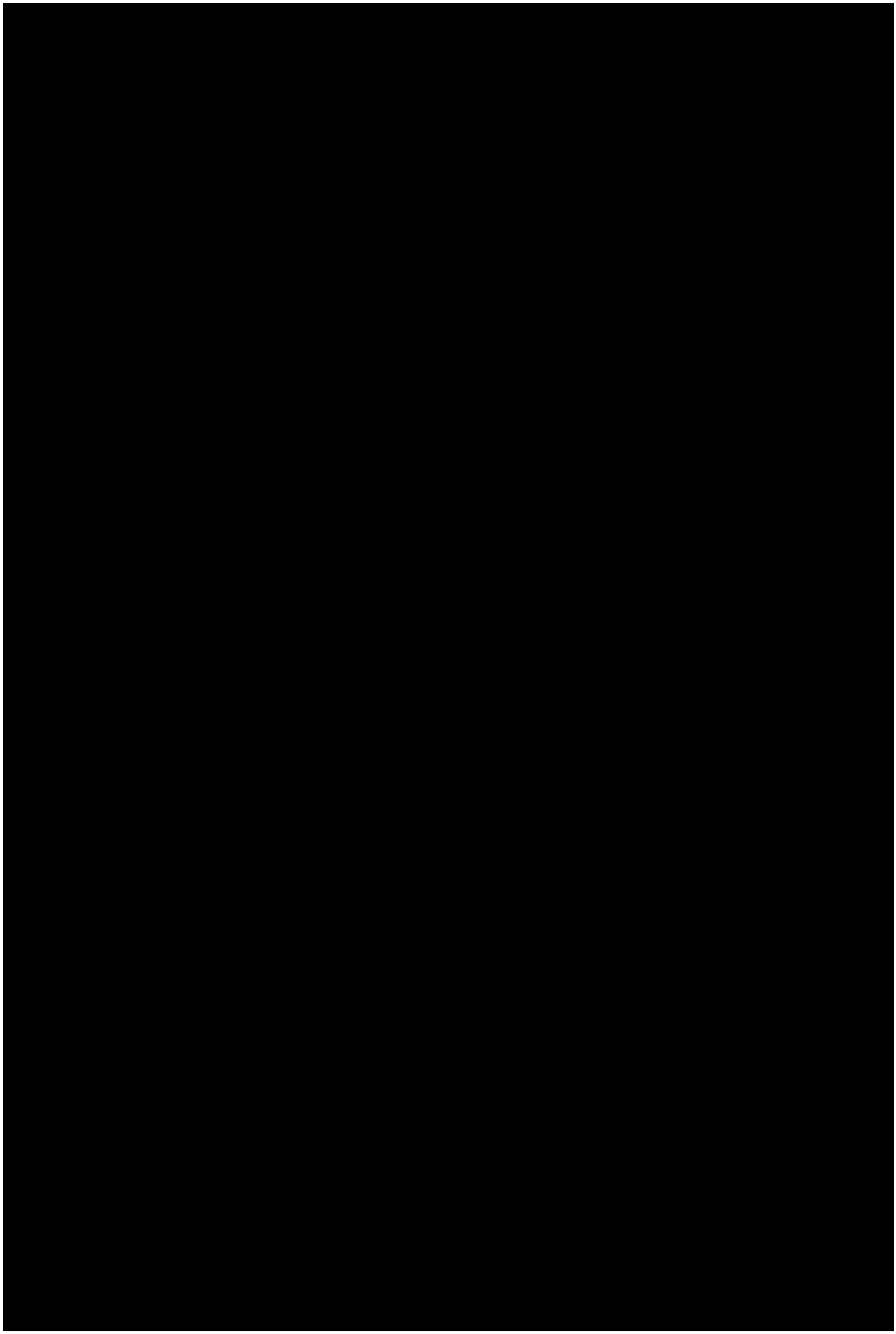
18.9 [redacted]

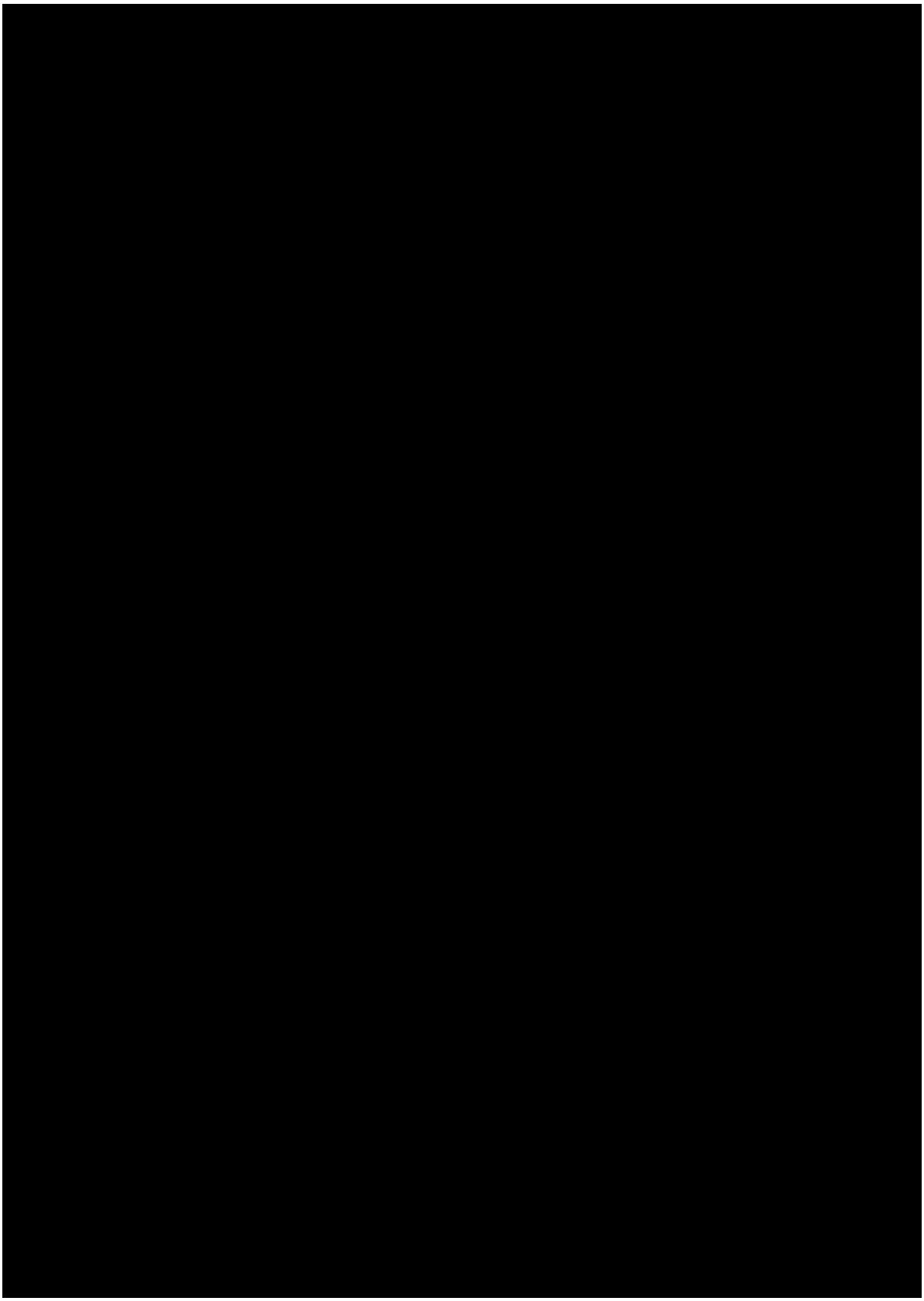
18.10 Appendix 10



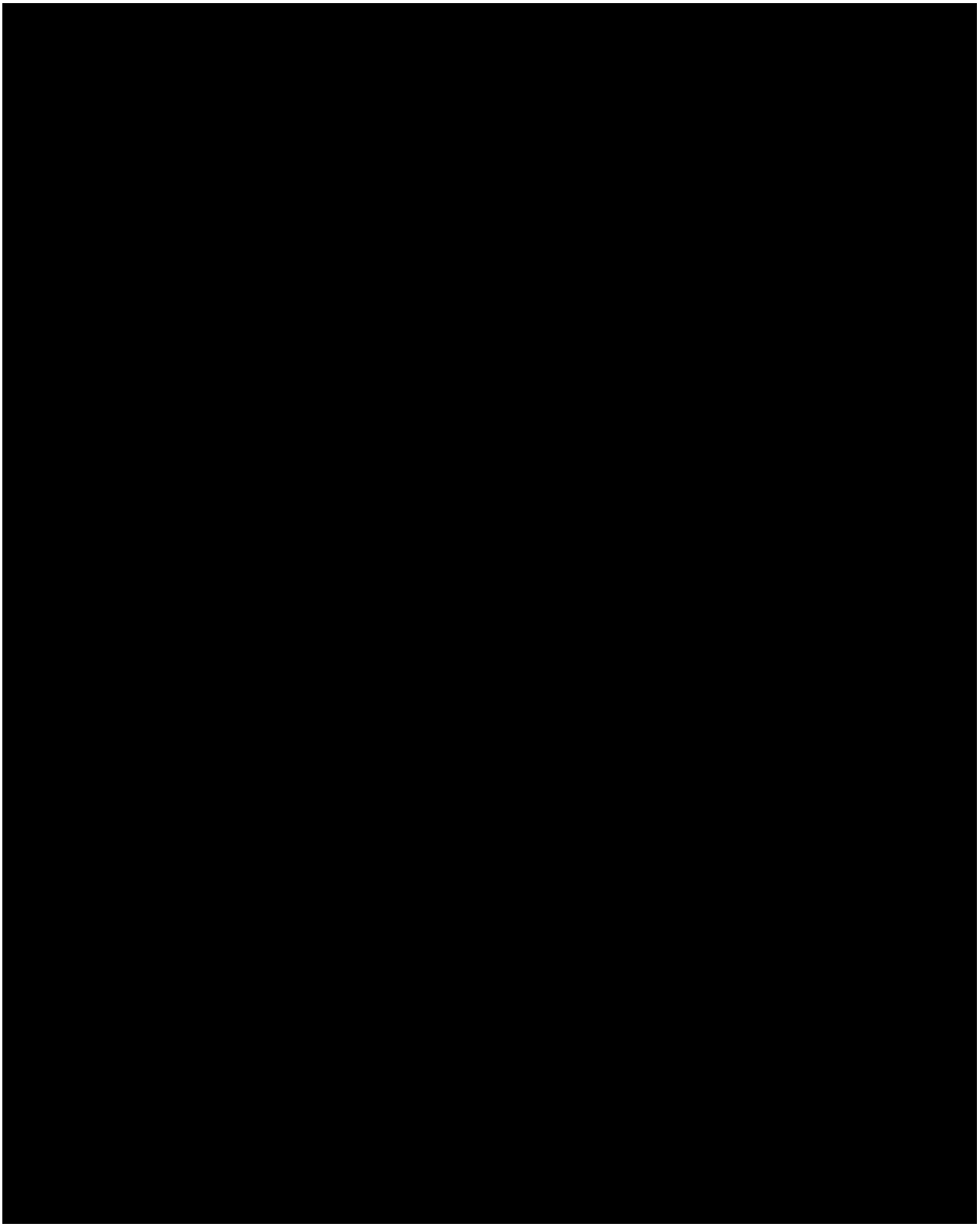
18.11 Appendix 11

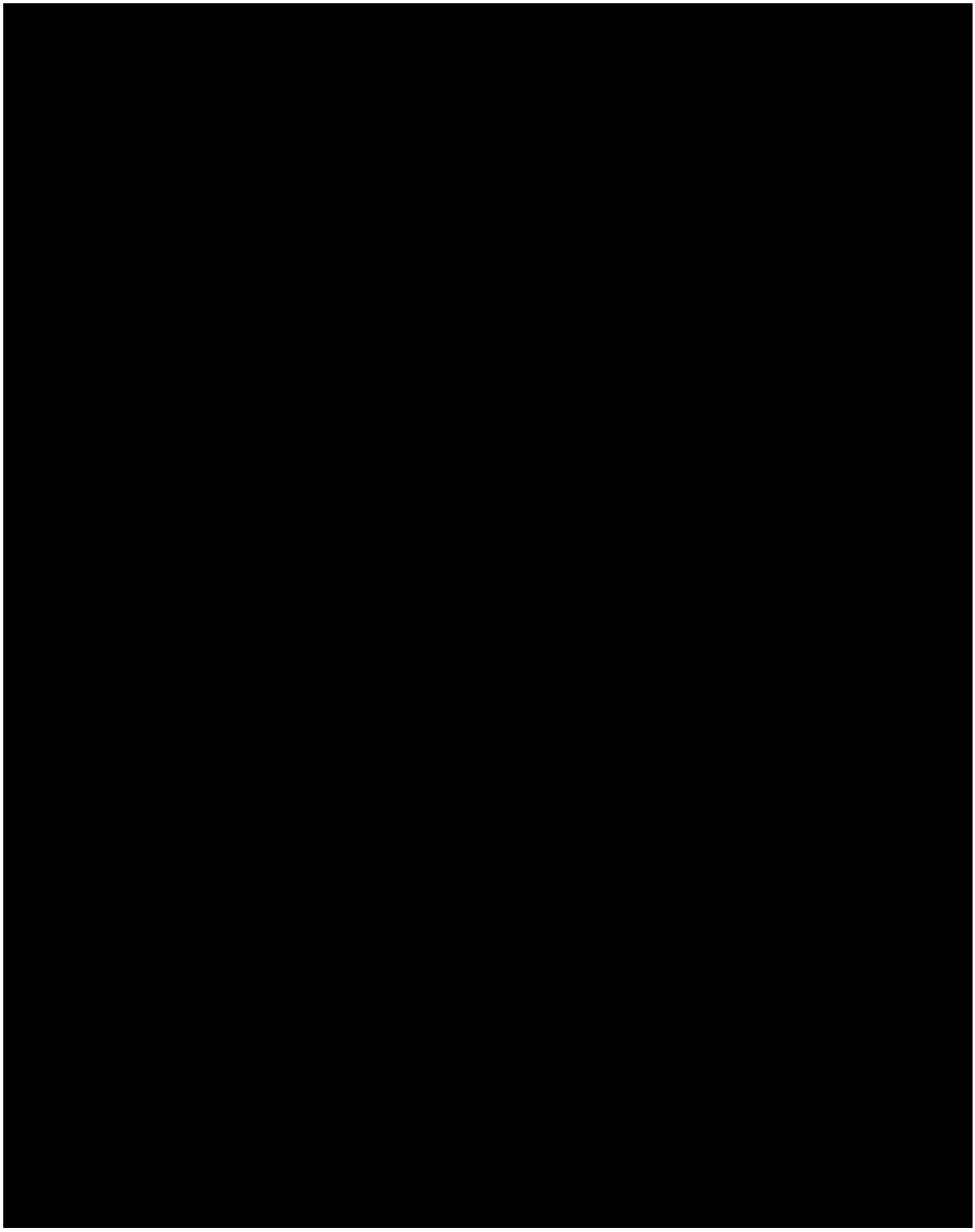


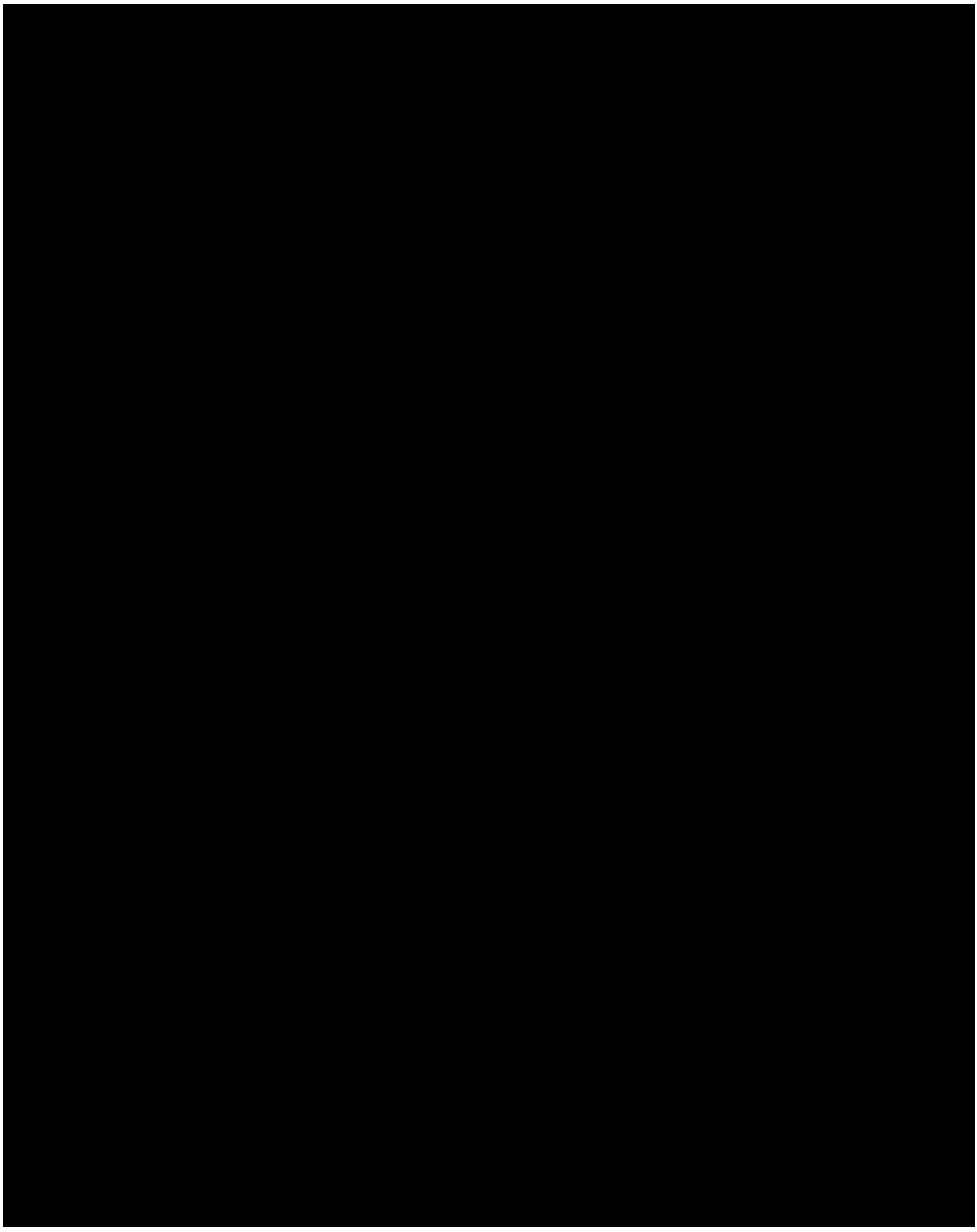




18.12 Appendix 12







18.13 Appendix 13

18.14 Appendix 14

BLU-285-1303

An International, Multicenter Open-label Randomized Phase 3 Study of BLU-285 vs Regorafenib in Patients with Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to avapritinib are the confidential and proprietary information of Blueprint Medicines, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Blueprint Medicines.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council for Harmonisation guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Blueprint Medicines or specified designees. I will discuss the material with them to ensure that they are fully informed about avapritinib and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____

Date