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

- 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.

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.

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

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

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.

- 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.

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.

- 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

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.

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.

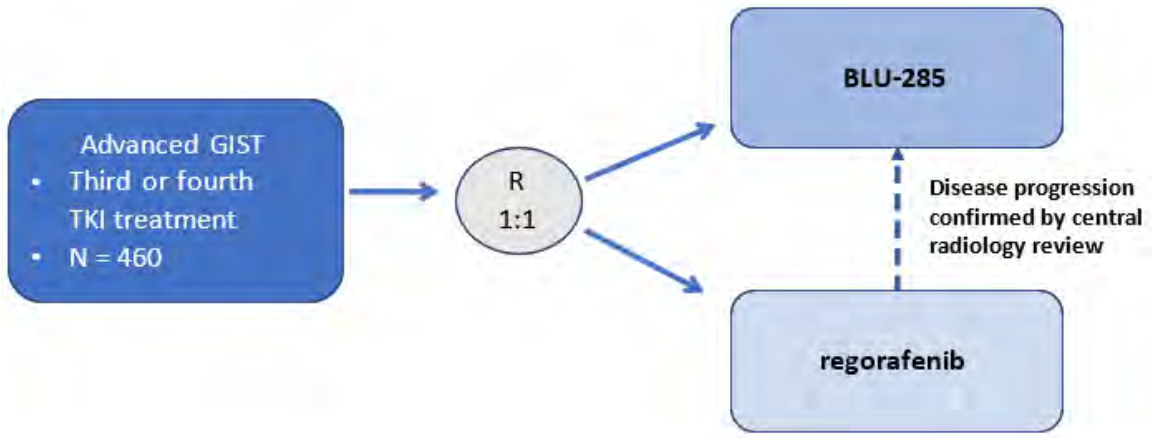
- deciding whether to recommend that the study continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups.

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

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

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

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

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

	• 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.

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.

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.

- 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

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)

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.

10.5.6 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.

- 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).