NCT #: NCT04825574

CLINICAL PROTOCOL

DRUG:	Avapritinib (also known as BLU-285)
PROTOCOL NUMBER:	BLU-285-1408
PROTOCOL TITLE:	Open-Label Extension Study to Evaluate the Safety of Long-Term Treatment with Avapritinib for Patients Previously Involved in an Avapritinib Study
EudraCT NUMBER	2020-005751-21
SPONSOR:	Blueprint Medicines 45 Sidney Street Cambridge, MA 02139
PROTOCOL DATE:	07 April 2021
VERSION NUMBER:	Amendment 1

APPROVAL PAGE

Protocol Title:	**Extension Protocol for Patients Previously Treated in Avapritinib Clinical Trials**
Protocol No.:	**BLU-285-1408**
Original Protocol Date:	**03 December 2020**
Protocol Version No.:	**Amendment 1**
Protocol Version Date:	**07 April 2021**

This study protocol was subject to critical review and has been approved by Blueprint Medicines. 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.

PPD

See eSignature

PPD

Date

PROTOCOL SUMMARY

Title:	Extension Protocol for Patients Previously Treated in Avapritinib Clinical Trials
Centers:	Multiple study centers worldwide that were previously active on avapritinib clinical trials.
Introduction and Rationale:	Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors occurring in the gastrointestinal (GI) tract, representing approximately 0.1–3.0% of all GI malignancies. 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 (PDGFRA) (10–15%), most commonly a substitution of valine for aspartic acid at amino acid 842 (D842V) in exon 18. On a molecular level, the most common sites for mutations in KIT at the time of diagnosis are exon 11 (60–70%) and exon 9 (5–15%) with exon 17 mutations being identified in approximately 1% of patients. Disease progression during treatment with a tyrosine kinase inhibitor (TKI) is associated with new mutations in KIT, with an increasing prevalence of mutations in exon 17. Avapritinib (also known as BLU-285) has demonstrated potent and selective activity against KIT exon 17 and PDGFRA exon 18 mutants in pre-clinical studies. Avapritinib has been shown to be tolerable at active doses in toxicology and safety pharmacology studies. In the ongoing Phase 1 GIST trial, clinical activity was also observed in a broad range disease driving mutations. Avapritinib is now approved in the US for the treatment of adult patients with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. Avapritinib is also approved in the EU for the treatment of adult patients with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) D842V mutations.
Number of Patients:	Approximately 5 patients may be treated in this extension study.

Objectives:	The objectives of the study are: • To provide long term safety data for GIST patients who are deriving clinical benefit from avapritinib on an existing avapritinib clinical trial To further characterize the rate of SAEs and AESIs of avapritinib.
Study Design:	This is an open-label extension study to provide long term safety data for GIST patients who are deriving clinical benefit from avapritinib upon the completion of avapritinib clinical trials.
Duration of Patient Participation:	The patient will remain on treatment and safety data will be collected as long as clinically appropriate according to the judgment of the Investigator.
Duration of Study:	The study is anticipated to last 24 months, or when the last patient discontinues from the study.
Target Population:	Patients who: • Have histologically confirmed metastatic or unresectable GIST • Have received prior treatment with avapritinib in a clinical trial and require continued therapy • Are free of disease progression since receiving avapritinib • Have adequate organ function
Dosage and Administration:	Avapritinib will be administered orally (PO) at the dose received by the patient on the prior avapritinib protocol in continuous 28-day cycles. Dosing modifications for avapritinib-related toxicity is recommended; modification guidelines are provided in the protocol.
Efficacy Evaluations:	Disease responses as assessed by Investigator according to local standard of care.
Safety Evaluations:	General safety will be assessed by the monitoring and recording of all serious adverse events (SAEs), and adverse events of special interest (AESI) including cognitive effects and intracranial bleeding; regular monitoring of hematology and blood chemistry, regular measurement of vital signs and the performance of physical examinations and other safety assessments in accordance with standard of care.
Safety Analysis:	Serious Adverse events (SAEs) will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria

	for Adverse Events (CTCAE) version 5. The proportion of patients who reported SAEs and AESIs will be collected and summarized for all patients who receive at least one dose of avapritinib. Summary of SAE and AESIs will also be provided by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Summary statistics will be provided for duration of avapritinib treatment. Dose discontinuation and reasons for dose discontinuation will also be reported.
Efficacy Analysis:	Investigators will monitor response to treatment according to local standard of care. Response to treatment will not be collected.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of Special Interest
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CRF	Case report form
CRO	Clinical Research Organization
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
IB	Investigator's Brochure
IEC	Independent Ethics Committee
KIT	V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
NCI	National Cancer Institute
ORR	Overall response rate
PDGFRα	Platelet-derived growth factor receptor alpha
PFS	Progression-free survival
PO	Orally
PRO	Patient reported outcome
QD	Once daily
SAE	Serious Adverse Event
TKI	Tyrosine kinase inhibitor

1 BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumors (GIST) is a rare sarcoma that arises 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% - 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).

Gastrointestinal stromal tumors 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.

Molecular Pathology of GIST

Approximately 90% of patients with newly diagnosed 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%) (Antonescu et al, 2005; Barnett and Heinrich, 2012; Corless et al, 2005). A majority of mutations in PDGFRα occur at amino acid 842, with the most common mutation at this site being a substitution of valine for aspartic acid (D842V). The remaining cases, denoted as KIT and PDGFRα wild-type, are due to other abnormalities such as succinate dehydrogenase deficiency (Nannini et al, 2013).

KIT-mutated GIST

On a molecular level, the most common sites for mutations in KIT at the time of diagnosis are exon 11 (60-70%) and exon 9 (5-15%) with exon 17 mutations being identified in approximately 1% of patients (Debiec-Rychter et al, 2006; Heinrich et al, 2008). Disease progression during treatment with a tyrosine kinase inhibitor (TKI) is most commonly due to the emergence of resistance mutations in KIT, including an increasing prevalence of those in exon 17, which are refractory to standard first and second line therapy, imatinib (Gleevec, 2016) and sunitinib (Sutent®, 2014). At the time

of progression on first-line TKI (imatinib) therapy, approximately 20-25% of patients had GIST harboring a mutation in exon 17 (Antonescu et al, 2005; Liegl et al, 2008; Wardelmann et al, 2006). No currently approved TKI selectively inhibits mutations in exon 17 of KIT.

Although imatinib is effective in many patients with GIST as first-line therapy, some patients do not respond and subsequent lines of therapy for those who respond are significantly less effective. Therapeutic failure appears linked to acquired resistance mutations, particularly those involving the ATP binding pocket (exons 13 and 14) and activation loop (exons 17 and 18) of KIT (Heinrich et al, 2008). Post-imatinib, ATP-binding pocket mutations and activation-loop mutations occur at a rate of ~30% and ~20%, respectively. Thirty-five percent of patients progress on imatinib without secondary mutations (mostly with KIT exon 9 mutations). The remainder of GIST patients who are unresponsive to imatinib harbor alterations in PDGFRα or succinate dehydrogenase (SDH). In KIT-mutant GIST, the response rate for patients with tumors bearing ATP-binding pocket mutations to sunitinib is low (ORR 11%) and responses rarely occur in the setting of activation-loop mutations (ORR 0%; Heinrich et al, 2008). Thus, patients failing imatinib due to either ATP-pocket or activation-loop mutations, represent an important medical need.

PDGFRα-mutated GIST

Gastrointestinal stromal tumors dependent on mutations in PDGFRα occur more frequently in the stomach, are more commonly resectable, have a somewhat more indolent clinical course than KIT-dependent GIST, and are less 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography (18FDG-PET) avid compared to GIST dependent on a mutation in KIT (Matro et al, 2014). Despite the more indolent course while localized, once metastatic, patients with GIST harboring the PDGFRα D842V mutation have an extremely poor prognosis and respond poorly to imatinib and other TKIs (Cassier et al, 2012; Goodman et al, 2007; Heinrich et al, 2008; Yoo et al, 2016).

In a retrospective study, Cassier et al identified 44 patients with PDGFRα-mutant GIST who had advanced disease from databases at 12 European institutions (N = 3,510 genotyped GIST patients) and an additional 16 patients with advanced,

PDGFRα-mutant GIST from the European Organisation for Research and Treatment of Cancer (EORTC) advanced GIST database (N = 465 genotyped GIST patients). Of 58 patients evaluable for efficacy post-imatinib, 32 patients (55%) had the

PDGFRα D842V mutation and the remainder had mutations in PDGFRα exon 4, 12, or 18 (non-D842V). The non-D842V patients had an overall response rate (ORR) of 36% with imatinib and median PFS >1 year. In contrast, patients with the D842V-mutation had no response (ORR = 0%). Median PFS with second-line treatment was short (2.1 months) and was not significantly different between imatinib, sunitinib, and other treatments. Similarly, in a small, retrospective Korean study (N=18) PDGFRα-mutant

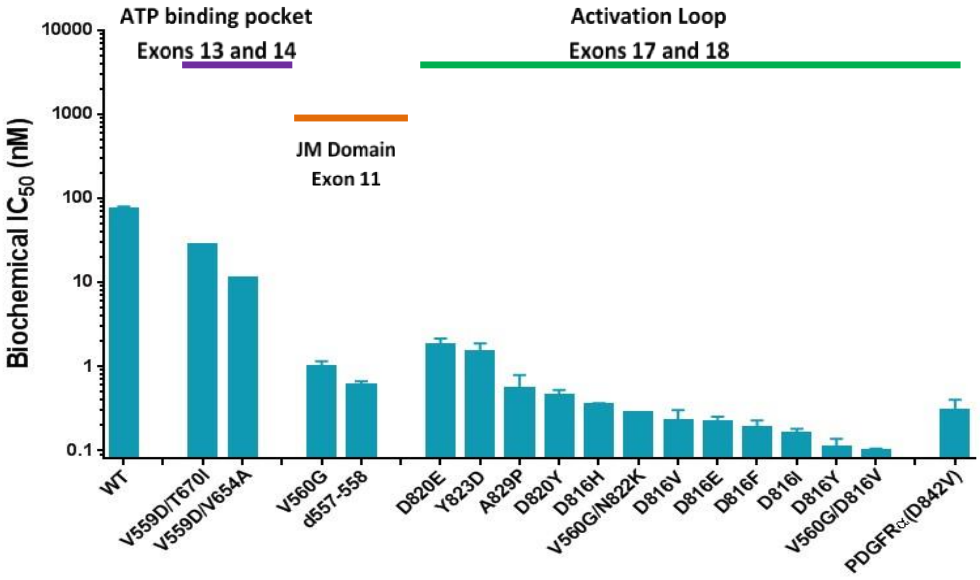
GIST patients treated with imatinib reported a similar PDGFRα D842V prevalence (9/18; 50%) and poor outcome (median PFS 3.8 months and ORR 0% [0/5 evaluable patients]). Patients with the D842V substitution treated with sunitinib as second-line therapy reported median PFS 1.9 months and ORR 0% (Yoo et al, 2016). A recent multicenter, retrospective study of adult patients with locally advanced, metastatic, or recurrent PDGFRα D842 mutant GIST diagnosed between Jan 2000 and Jul 2016 who were treated with at least one TKI showed a median PFS consistent with the findings of other studies that have shown a median PFS of 3–5 months. Twenty-two patients were identified at 3 US academic institutions. One patient had a complete response to first-line imatinib following partial resection of the primary tumor and completed 1 year of treatment. No complete or partial responses were reported in patients receiving TKI treatment in the second-line or third-line setting. Median PFS across the first-, second- and third-line treatment groups was 5.6, 2.6, and 5.6 months, respectively (von Mehren et al, 2018). Avapritinib was first approved in the US on January 2020 for the treatment of adults with metastatic GIST harboring a PDGFRA exon 18 mutation and then received conditional approval in the EU in September 2020 as monotherapy for adult patients with unresectable or metastatic GIST harboring the PDGF D842V mutation. Avapritinib currently has an orphan drug designation in both the US and EU.

1.1.2 Avapritinib

Avapritinib, 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.

Avapritinib has demonstrated clinically important activity against GIST following 3 or more prior lines of therapy, and regardless of line of therapy in the setting of an exon 18 mutation in PDGFRA in the ongoing NAVIGATOR clinical study (Heinrich et al, 2018). Please refer to the avapritinib Investigator's Brochure (IB) for additional information.

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



Source: Evans EK et al. Sci Transl Med. 2017;9(414):eaao1690

1.1.3 Extension Study

This extension study is designed to provide long term safety data for GIST patients who are deriving clinical benefit from avapritinib on an existing avapritinib trial. GIST is a serious or immediately life-threatening condition, for which there are no standard treatment options available and continued treatment with avapritinib remains an effective treatment option.

This study is sponsored by Blueprint Medicines.

1.1.4 Extension Study Rationale

This extension study is designed to provide long term safety data for GIST patients who have been deriving clinical benefit from avapritinib treatment on an avapritinib trial that is has met its primary endpoints.

This extension study is designed to provide ongoing safety data on patients previously enrolled on avapritinib safety and efficacy studies, that have completed their planned analyses.

1.1.5 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 regorafenib 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.

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.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of avapritinib may be found in the avapritinib IB.

2 STUDY OBJECTIVES

The objectives of the extension study are:

- To provide long term safety data for GIST patients who are deriving clinical benefit from avapritinib on an existing avapritinib clinical trial
- To further characterize the rate of SAEs and AESIs of avapritinib.

3 STUDY PLAN

3.1 Study Design

This is an open-label extension study to provide long term safety data for GIST patients who are deriving clinical benefit from avapritinib on an existing clinical trial. Avapritinib will be administered orally (PO) in adult patients with unresectable GIST until such time that avapritinib becomes available through other mechanisms or the Sponsor chooses to discontinue the Study. Avapritinib will be administered once daily (QD) at the dose received by the patient on the prior avapritinib protocol in continuous 28-day cycles, with a maximum dose of 300 mg QD.

All study visits are intended to be conducted on an outpatient basis but may be conducted on an inpatient basis as needed. After provision of written informed consent, patients will be evaluated for eligibility during the screening period before avapritinib administration on Cycle 1 Day 1 (C1D1). A treatment cycle is 28 days in duration.

No minimum or maximum treatment duration has been set. Patients will be monitored at regular intervals for safety and for response to treatment, as per investigator assessed response. Patients may continue to receive avapritinib until precluded by toxicity, noncompliance, patient decision, physician decision, progressive disease, death, or closure of the study by the Sponsor.

All patients will have an End of Study evaluation with reason for discontinuation recorded.

4 POPULATION

4.1 Number of Patients

Approximately 5 patients may be enrolled in this extension study.

4.2 Selection of Patients

Patients must meet the inclusion and exclusion criteria to be enrolled in the trial. The Sponsor will consider inclusion of patients who do not meet the inclusion and exclusion criteria on a case by case basis following receipt of supporting information and rationale from the Investigator. Such exceptions may also require approval by the Independent Ethics Committee (IEC), as appropriate.

4.3 Inclusion Criteria

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

1. Patient has histologically confirmed metastatic or unresectable GIST as established by entry in a previous avapritinib clinical trial and has been receiving treatment with avapritinib on one of these trials.

2. Patient continues to receive clinical benefit from avapritinib treatment, as assessed by the investigator.
3. Patient or legal guardian, if permitted by local regulatory authorities, provides informed consent.

4.4 Exclusion Criteria

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

1. Patient requires therapy with a concomitant medication that is a strong inhibitor or strong inducer of cytochrome P450 (CYP) 3A4 (see Section 5.4.1).

2. Patient has a history of intracranial bleeding either prior to or during avapritinib treatment

3. Patients who have poor organ function, defined as Adverse Events of NCI CTCAE version 5.0 Grade 3 or higher at the time of enrollment must delay start of treatment until symptoms return to Grade 2 or baseline, or the start of treatment has been approved by the Sponsor.

4. Patients who have ongoing cognitive or mood effects Adverse Events of NCI CTCAE version 5.0 higher than Grade 1 must delay start of treatment until symptoms return to Grade 1 or baseline.

5. Women who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception from the time of enrollment and for at least 30 days after the last dose of avapritinib. Men who are unwilling, if not surgically sterile, to abstain from sexual intercourse or employ highly effective contraception from the time of first dose and for at least 90 days after the last dose of avapritinib. Refer to Section 5.5.1 for acceptable methods of contraception.

6. 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 enrollment. 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.

7. Women who are breast feeding.

8. Patients with a known hypersensitivity to avapritinib or the excipients.

4.5 Patient Identification and Registration

Patients who are candidates for enrollment into this extension protocol will be evaluated for eligibility by the Investigator to ensure that the inclusion (see Section 4.3) and exclusion criteria (see Section 4.4) are met. Patients must be registered with the Sponsor (or Clinical Research Organization [CRO]) prior to approval for entry to the Study.

4.6 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, the primary reason(s) for discontinuation is to be recorded in the case report form (CRF). Following discontinuation of Study drug, all efforts will be made to complete and report the protocol-defined Study observations as completely as possible.

If a patient discontinues treatment because of an adverse event (AE), protocol-specified safety follow-up is to be performed, and the patient should remain under the supervision of the Investigator or designee until the condition has returned to baseline or stabilized.

5 STUDY CONDUCT

5.1 General Conduct

The schedule of assessments for the Study is provided in Table 1.

The end of the Study is defined as the time that the last patient completes his/her last visit.

Table 1: Schedule of Assessments

Study Activities[a]	**Screening**	**Treatment**		**EOT**[b]
Cycle		**C1**	**Every 3 months (+/- 15 days)**	
Program Day	**D0–28**	**D1**	**D1**	
Informed consent	X			
Inclusion/Exclusion criteria	X			
Demographics	X			
Physical examination[c]	X	X	X	X
Vital signs[d]	X	X	X	X
ECOG status[e]	X			
Pregnancy (β-hCG) test[f]	X		X	
Hematology[g]	X	X	X	X
Serum chemistry[h]	X	X	X	X
Efficacy assessment[i]			Per Investigator discretion	
Avapritinib administration[j]		X		
SAE and AESI monitoring[k]		X		

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; C = cycle, D = day, ECOG = Eastern Cooperative Oncology Group, EOT = end-of-treatment; GIST = gastrointestinal stromal tumor; Hgb = hemoglobin; INR = international normalized ratio; QD = once daily;SAE = serious adverse event; ULN = upper limit of normal.

a Additional safety tests may be performed whenever clinically indicated, at the Investigator's discretion. Whenever a test result is questionable, it should be repeated. Timing of procedures may be modified at Investigator discretion.
b At EOT, the reason for EAP discontinuation and last day of dosing should be recorded. This can be done by telephone if necessary.
c A complete physical examination including weight, evaluation of the skin, head and neck, lymph nodes, heart, lungs, breasts, abdomen, pelvis (if indicated based on symptoms), musculoskeletal system, neurologic system, and a basic assessment of mental status and mood will be performed at the Screening visit.

Subsequent physical examinations will focus on weight, signs of GIST, changes from previous physical examinations, neurologic, mental status, and mood examinations, and AEs.

d Vital signs include temperature, pulse, systolic/diastolic blood pressure, and weight.

e Refer to Appendix 3 for ECOG performance status scoring.

f To be performed for women of child-bearing potential. A serum pregnancy test should be performed at baseline (within 7 days before the first dose of avapritinib). Serum or urine pregnancy test should be performed on D1 of every study visit, or more frequently if required by local requirements.

g Hematology parameters to be measured include hemoglobin, white blood cell count with differential count, and platelet count.

h Serum chemistry panel includes sodium, potassium, BUN or urea, bicarbonate (venous), creatinine, calcium, chloride, magnesium, phosphorus, albumin, AST, ALT, ALP, and total bilirubin (direct bilirubin if total bilirubin is > ULN).

i Disease response assessments should be performed per standard of care.

j Avapritinib will be administered QD in the morning at least 2 hours after and 1 hour before eating.

k SAEs, AESIs and concomitant medications are to be collected from the date of the informed consent signature through end of treatment. See Section 9 for details of SAE/AESI.

5.2 Early Study 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;
- Other administrative reasons.

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

5.3 Dose and Administration

Avapritinib will be administered PO at the dose received by the patient on the prior avapritinib protocol in continuous 28-day cycles. Dosing will be continuous, with no inter-cycle rest periods unless warranted for individual safety reasons. Pre-specified dose modification recommendations for AEs related to avapritinib are described in Section 5.3.1.

Avapritinib should be administered with a glass of water (at least 8 ounces or 250 mL). The tablets should be taken on an empty stomach at least 1 hour before or least 2 hours after a meal. Each dose should be administered at approximately the same time each day. Do not make up for a missed dose within 8 hours of the next scheduled dose. If a patient vomits during or after taking avapritinib, the dose should not be replaced, and the next dose should be taken at the next scheduled dosing time.

Patients should be instructed to swallow tablets whole and to not chew the tablets. Interruption in avapritinib dosing may be required for surgery or other procedure during the treatment period. At a minimum, avapritinib should be discontinued 48 hours before the procedure and resumed 48 hours after the procedure is completed.

5.3.1 Dose Reduction for Adverse Events

Dosing modifications are recommended for patients experiencing avapritinib-related toxicity. Modification guidelines are summarized in Table 2.

If a patient experiences a Grade 3 or worse (based on NCI CTCAE criteria) AE thought to be caused by avapritinib, avapritinib treatment should be interrupted until the AE improves to Grade 2 or to the patient's baseline, or it is considered stable, and does not preclude continued therapy. At that time, avapritinib treatment may resume either at the same dose, or at reduced dose. Dose reductions should be in increments of 100 mg. If a Grade 3 or worse AE recurs, dosing should be interrupted as described above, and if dosing is resumed, the dose should be reduced by at least 100 mg.

Table 2: Dose Modification 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 1-4	• 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.

5.4 Prior and Concomitant Therapy

5.4.1 Prohibited Concomitant Therapy

Concomitant treatment with drugs that are strong CYP3A4 inhibitors are prohibited (refer to Appendix 1 for a list of strong CYP3A4 inhibitors).

Avapritinib should not be administered simultaneously with other antineoplastic therapy.

If radiotherapy is required to treat local sites of disease, avapritinib treatment should be interrupted for 2 days prior to the first fraction of radiotherapy through 2 days after the last fraction.

5.4.2 Concomitant Therapy to be used with Caution

Medications that are CYP2C9, CYP3A4, or BCRP substrates with a narrow therapeutic index should be used with caution (Refer to Appendix 2 for a list of these medications).

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

5.4.3 Permitted Concomitant Therapy

Medications and treatments other than those specified in Section 5.4.1 and Section 5.4.2, including pallative and supportive care for disease-related symptoms are permitted.

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. Prophylaxis for nausea, vomiting, and diarrhea may be given as needed.

5.5 Additional Precautions

The light absorption characteristics of avapritinib suggest the possibility the avapritinib treatment will be associated with phototoxicity. Therefore, patients should use clothing and sunscreen to avoid direct sun exposure.

Avapritinib treatment has been associated with seizures at high doses in toxicology studies in rats, and with intracranial bleeding in toxicology studies in dogs. There have been cases of intracranial bleeding in patients treated with avapritinib. Therefore, patients at increased risk of seizure, or increased risk of intracranial bleeding (such as those with a vascular aneurysm or a history of intracranial bleeding within the prior year) should only receive avapritinib if the potential benefits are anticipated to exceed the increased risk.

5.5.1 Contraception Requirements

Women of childbearing potential must agree to use a highly effective method of contraception (CTFG, 2014) from the time of enrollment until at least 30 days after the last dose of avapritinib. 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 their participation in the Study, and for 90 days after the last dose of avapritinib. 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.

5.5.2 Gamete and Embryo Banking

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

6 DESCRIPTION OF STUDY PROCEDURES

Upon entry into the Study, the following baseline procedures and laboratory tests are to be performed before treatment with avapritinib is initiated. Please refer to Table 1 for the Schedule of Assessments.

6.1 Assessment Prior to Initiating Treatment

The following procedures will be performed at the Screening visit:

- Obtain Informed Consent;
- Obtain demographic data, including gender, date of birth/age, race, and ethnicity;
- Complete physical examination, basic neurological assessment, and ECOG performance status;
- Vital signs including height, weight, temperature, pulse, and systolic/diastolic blood pressure;
- Clinical laboratory assessment (hematology, coagulation, serum chemistry);
- Serum pregnancy test (for women of childbearing potential only);

6.2 Safety Assessments

The schedule of safety assessments is detailed in Table 1. Additional safety assessments may be performed when clinically indicated, at the Investigator's discretion.

6.2.1 Physical Examination

A complete physical examination will be performed at the Screening visit. Subsequent physical examinations will be performed as outlined in Table 1, and will focus on symptoms and signs of GIST, changes from previous physical examinations, and AEs.

6.2.2 Eastern Cooperative Oncology Group Performance Status

Determination of ECOG performance status will be performed at the time points outlined in Table 1. Refer to Appendix 3 for ECOG performance status scoring.

6.2.3 Vital Signs

Vital sign measurement will include temperature, systolic/diastolic blood pressure, and pulse, and will be performed at the time points outlined in Table 1.

6.2.4 Clinical Laboratory Tests

Clinical laboratory evaluations will be performed at the local laboratory.

Clinical laboratory evaluations will be conducted at the time points outlined in Table 1. 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 parameters are to be evaluated by the Investigator:

Hematology:	Hemoglobin (Hgb), white blood cell with differential count, platelet count
Serum chemistry:	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)
Serum or Urine Pregnancy[a]:	β-hCG

a For women of childbearing potential only, as defined in Section 9.6. A serum pregnancy test should be performed at baseline (within 7 days before the first dose of avapritinib). Serum or urine pregnancy test should be performed as required per local regulations and as outlined in Table 1.

6.2.5 Adverse Events and Concomitant Medications

Each patient must be carefully monitored for the development of any AEs throughout the study from the start of avapritinib administration (or from the time of signing informed consent, for SAEs) to 30 days after the last administration. In addition, SAEs that are assessed to be at least possibly related to Study treatment that occur > 30 days posttreatment are to be reported.

Adverse events will be recorded locally, but only SAEs will be reported to the sponsor or its designee. Complete details on AE and SAE monitoring are provided in Section 8 and Section 9, respectively.

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

6.3 Assessment of Response

Investigator will perform assessment of response to treatment with avapritinib per local standard of care.

6.4 Patient Reported Outcome Instruments

No patient reported outcome instruments will be used in this study.

6.5 Data Collection and Reporting

Limited data will be collected from this study as the primary analysis has been completed for the initial clinical trials conducted in this setting. Nevertheless, adverse events will be reported and SAEs should be reported to the Sponsor, as required. Treatment records including record of drug dispensation shall be maintained to ensure appropriate drug accountability.

7 STUDY DRUG MANAGEMENT

7.1 Description

7.1.1 Avapritinib

7.1.1.1 Formulation

Avapritinib will be administered as an immediate release tablet for oral administration. The drug substance and drug product are manufactured and formulated following current Good Manufacturing Practices (GMP). Avapritinib tablets are prepared as 100 mg in strength.

7.1.1.2 Storage

Avapritinib tablets must be stored at 15°C to 30°C (59°F to 86°F), in their original container, according to the package label. If the product has been exposed to temperatures outside of this range, advice must be sought from the Sponsor as to whether the product is still suitable for patient use.

7.1.1.3 Packaging and Shipment

Avapritinib tablets will be supplied 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. Bottles will contain 30 tablets each.

7.2 Accountability

Accountability for avapritinib at the clinical site is the responsibility of the Investigator. The Investigator will ensure that avapritinib 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 site, 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 avapritinib 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 site on an ongoing basis during monitoring visits.

Avapritinib must not be used for any purpose other than this Study. Avapritinib 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.

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

7.3 Compliance

Patients will be dispensed the appropriate number of avapritinib bottles to allow for dosing until the next scheduled visit. Patients are to return all unused capsules and tablets (or the empty bottles) at the next scheduled visit. Compliance with the dosing regimen will be assessed based on return of unused drug (or empty bottles).

8 ADVERSE EVENTS

All patients will be monitored for adverse events throughout their participation in the Study. Serious AEs and adverse events of special interest (AESIs) will be recorded in the CRF from the time of first dose of avapritinib through 30 days after the last avapritinib dose. In addition, serious adverse events (SAEs) and AESIs that are assessed as related to avapritinib treatment and that occur > 30 days posttreatment will also be reported. All related SAEs and AESIs should be monitored until they are resolved, stabilized, have returned to pre-exposure baseline, determined to be due to another illness, or until a subsequent therapy is initiated.

8.1 Definitions

An **AE** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (eg, off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. Overdose includes only clinically symptomatic doses that are at least twice the intended dose.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the Investigator to be clinically significant.

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 SERIOUS ADVERSE EVENTS

9.1 Definition of Serious Adverse Event

A SAE is any event that meets any of the following criteria:

- Death
- Life-threatening

A serious adverse event is life threatening if the patient was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

- Inpatient hospitalization or prolongation of existing hospitalization

Adverse events requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything, untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

- Persistent or significant disability/incapacity

An SAE 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 in the offspring of a subject who received avapritinib.

- Other: 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 one of the outcomes listed in this definition. Examples of such events are:

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

  Blood abnormalities or convulsions that do not result in inpatient hospitalization o

  Development of drug dependency or drug abuse

9.2 Reporting Serious Adverse Events

All SAEs or serious pretreatment events 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, SAEs will be captured in the safety database only, they will not be captured in an CRF. 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.

9.3 Documenting Serious Adverse Events and Adverse Events of Special Interest

Each patient must be carefully monitored for the development of any SAEs and AESIs,

Adverse Events of Special Interest for avapritinib are, regardless of grade or causality:

- cognitive effects which include the following terms: memory impairment, cognitive disorder, confusional state and encephalopathy.

- intracranial bleeding including haemorrhage intracranial, cerebral haemorrhage , and subdural haematoma.

This information should be obtained in the form of non-leading questions (eg, "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

All SAEs and AESIs reported by the patient or revealed by observation, physical examination, laboratory testing or other diagnostic procedures will be recorded in the appropriate section of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

9.4 Assessment of Intensity

Intensity of all AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Adverse events not listed in the CTCAE 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.

9.5 Assessment of Causality

Relationship to avapritinib administration will be determined by the Investigator according to the following criteria:

- Not Related: Exposure to avapritinib did not occur, or the occurrence of the AE is not reasonably related in time, or the AE is clearly caused by something other than avapritinib.
- Related: The AE does not meet the criteria for "Not Related".

9.6 Pregnancy Reporting

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).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient or partner of a male patient occurring while the patient is being treated with avapritinib, or within 30 days of the patient's last dose of avapritinib, are considered immediately reportable events. If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking avapritinib should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. In pregnant female patients, avapritinibis to be discontinued immediately and the patient instructed to return any unused avapritinib to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately using the Pregnancy Report Form. 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 or partner of a male 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 30 days after he/she has gained knowledge of the delivery or elective abortion.

Any SAE that occurs during pregnancy 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 Overdose

Overdose includes only clinically symptomatic doses that are at least twice the intended dose. Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved avapritinib) must be communicated to Blueprint Medicines or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

10 STATISTICS

Sample size estimation is not based on any hypothesis testing, rather an estimation of how many patients might roll over to avapritinib treatment after participation in an avapritinib clinical trial. Safety assessments in these patients from this protocol will be considered as continuum of these same patients while on other avapritinib studies when assessments of avapritinib safety in target populations are performed.

The Safety Population is defined as all patients who enroll in and receive at least one dose of avapritinib on this Study. Reasons for treatment discontinuation will be reported. Duration of treatment will be summarized descriptively. SAE and AESIs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) in the Safety Population.

11 ETHICS AND RESPONSIBILITIES

11.1 Good Clinical Practice

The Study will be conducted in accordance with the International Conference on Harmonization (ICH) for GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of avapritinib 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 Ethics Committee

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

The Investigator must obtain 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 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 clinical centers where IEC approval has been obtained. The protocol, IB, informed consent form, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IEC. The 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 IEC according to local regulations and guidelines.

11.3 Informed Consent

Physicians are responsible for obtaining consent from each patient being treated with avapritinib as a part of the Study. The patient or the patient's legal representative must give written consent prior to receiving treatment.

11.4 Records Management

All data for the patients recruited for the Study will be entered onto the CRFs. Only authorized staff may enter data into the CRFs. If an entry error is made, the corrections to the CRFs will be made according to CRF guidelines by an authorized member of the site staff.

11.5 Source Documentation

Source documents/CRFs 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/CRF. The source document/CRF 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/CRF as soon as possible after information is collected, preferably on the same day that the 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/CRF to endorse the recorded data.

The Investigator will retain all completed source documents

11.6 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 for at least 2 years after the last marketing application approval 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.

11.7 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 phone or email routinely from a representative of the Sponsor (site monitor) and will

include questioning with regard to patient enrollment, status on treatment, data submission and clarification, drug disposition, and potential request for source documents, and clarification of administrative matters. All submitted documents should be redacted 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 avapritinib 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 IEC, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, CRFs, 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 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 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 IEC and the Investigator must await approval before implementing the changes.

If in the judgment of the IEC, the Investigator, and/or Blueprint Medicines, the amendment to the protocol substantially changes the design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a 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 appropriate 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

Blueprint Medicines has initiated this Study to provide long-term safety data for patients who are deriving clinical benefit from avapritinib on an existing avapritinib clinical trial. Patients must meet strict inclusion criteria to be eligible for treatment with avapritinib. Blueprint Medicines will provide the drug used in this Study free of charge whenever possible but is not obligated to do so in all cases or after drug is commercially available in any market.

Blueprint Medicines reserves the right to terminate the Study at any time; however, the intent is to continue until the drug is commercially available in any market, or other events dictate the need to close the Study and cease supply. In consideration of patients' best interests, Blueprint Medicines intends to provide physicians and patients reasonable advance notice of discontinuation.

Physicians and patients reserve the right to withdraw their consent to participate in the Study at any time for any reason.

16 CONFIDENTIALITY

All information and data generated from treatment with avapritinib is considered confidential and must not be used or disclosed to any person or entity not directly involved unless prior written consent is gained from Blueprint Medicines. This information and data is owned by Blueprint Medicines.

Authorized regulatory officials, IEC personnel, Blueprint Medicines and its authorized representatives are allowed access to the records.

17 REFERENCES

Antonescu CR, Besmer P, Guo T, Arkun K, Hom G, Koryotowski B, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res.* 2005;11(11):4182-90.

Barnett CM, and Heinrich MC. Management of tyrosine kinase inhibitor-resistant gastrointestinal stromal tumors. *Am Soc Clin Oncol Educ Book.* 2012:663-8.

Cassier PA, Fumagalli E, Rutkowski P, Schoffski P, Van Glabbeke M, Debiec-Rychter M, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. *Clin Cancer Res.* 2012;18(16):4458-64.

Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. *J Clin Oncol.* 2005;23(23):5357-64.

CTFG 2014 Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

Debiec-Rychter M, Sciot R, Le Cesne A, Schlemmer M, Hohenberger P, van Oosterom AT, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer.* 2006;42(8):1093-103.

Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):295-302.

FDA 2016 Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Gleevec. Package Insert. 2016. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation.

Goettsch WG, Bos SD, Breekveldt-Postma N, Casparie M, Herings RM, and Hogendoorn PC. Incidence of gastrointestinal stromal tumours is underestimated: results of a nationwide study. *Eur J Cancer.* 2005;41(18):2868-72.

Goodman VL, Rock EP, Dagher R, Ramchandani RP, Abraham S, Gobburu JV, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res.* 2007;13(5):1367-73.

Heinrich M, Mehren Mv, Jones R, and al e. Avapritinib is highly active and welltolerated in patients (PTS) with advanced GIST driven by diverse variety of oncogenic mutations in KIT and PDGFRA. *In* Annual Meeting of the Connective Tissue Oncology Society. 2018, Vol. 012 #3027631. Rome, Italy.

Heinrich MC, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol.* 2008;26(33):5352-9.

Kang YK, Ryu MH, Yoo C, Ryoo BY, Kim HJ, Lee JJ, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2013;14(12):1175-82.

Liegl B, Kepten I, Le C, Zhu M, Demetri GD, Heinrich MC, et al. Heterogeneity of kinase inhibitor resistance mechanisms in GIST. *J Pathol.* 2008;216(1):64-74.

Matro JM, Yu JQ, Heinrich MC, Ramachandran A, Ku N, and Mehren Mv. Correlation of PET/CT and CT RECIST response in GIST patients with PDGFRA D842V gene mutations treated with crenolanib. *Journal of Clinical Oncology.* 2014;32(15_suppl):10546-10546.

Miettinen M, and Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med.* 2006;130(10):1466-78.

Nannini M, Biasco G, Astolfi A, and Pantaleo MA. An overview on molecular biology of KIT/PDGFRA wild type (WT) gastrointestinal stromal tumours (GIST). *J Med Genet.* 2013;50(10):653-61.

NCCN. National Comprehensive Cancer Network. Soft Tissue Sarcoma (Version 1. 2015) [Online]. Available at: http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed 22 April 2015. 2015.

Nilsson B, Bumming P, Meis-Kindblom JM, Oden A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era--a population-based study in western Sweden. *Cancer.* 2005;103(4):821-9.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-55.

Rammohan A, Sathyanesan J, Rajendran K, Pitchaimuthu A, Perumal SK, Srinivasan U, et al. A gist of gastrointestinal stromal tumors: A review. *World J Gastrointest Oncol.* 2013;5(6):102-12.

Stivarga®. [Prescribing Information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2017 [Online]. Available at: http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf. Accessed 31 August 2017. 2017.

Sutent®. [Prescribing Information]. New York, NY: Pfizer Labs; 2014 [Online]. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=607. Accessed 09 March 2015. 2014.

von Mehren M, M H, H S, P M, K M, A B, et al. A retrospective natural history study of patients with PDGFRα D842V mutant advanced gastrointestinal stromal tumor previously treated with a tyrosine kinase inhibitor. *In* American Society of Clinical Oncology Annual Meeting. 2018. Chicago, IL.

Wardelmann E, Merkelbach-Bruse S, Pauls K, Thomas N, Schildhaus HU, Heinicke T, et al. Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. *Clin Cancer Res.* 2006;12(6):1743-9.

Yoo C, Ryu MH, Jo J, Park I, Ryoo BY, and Kang YK. Efficacy of Imatinib in Patients with Platelet-Derived Growth Factor Receptor Alpha-Mutated Gastrointestinal Stromal Tumors. *Cancer Res Treat.* 2016;48(2):546-52.

18 APPENDICES

18.1 Appendix 1: List of Prohibited Medications and Food

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.
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.
Source: (FDA, 2016)

18.2 Appendix 2: List of Medications and Food to be Used with Caution

MEDICATIONS TO BE USED WITH CAUTION WITH AVAPRITINIB

CYP3A4 Substrates	CYP2C9 Substrates	BCRP Substrates	Moderate CYP3A4 Inhibitors
Alfentanil	Warfarin	Rosuvastatin	Erythromycin
Cyclosporine	Phenytoin	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.

Source: (FDA, 2016)

18.3 Appendix 3: Eastern Cooperative Oncology Performance Group 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).

18.4 Appendix 4: Investigator Signature Page

Protocol BLU-285-1408

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 participate in the 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 Conference on Harmonization guidelines.

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