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Protocol

Study BLU-285-1101

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

Document Date: 28 February 2018

NCT Number: 02508532

CLINICAL RESEARCH PROTOCOL

DRUG:	Avapritinib (also known as BLU-285)
STUDY NUMBER(S):	BLU-285-1101
PROTOCOL(S) TITLE:	A Phase 1 Study of BLU-285 in Patients with Gastrointestinal Stromal Tumors (GIST) and other Relapsed and Refractory Solid Tumors
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This study protocol was subject to critical review and has been approved by the sponsor. The information contained in this protocol is consistent with the current risk-benefit evaluation of the investigational product.

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

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28-Feb-2018

Date

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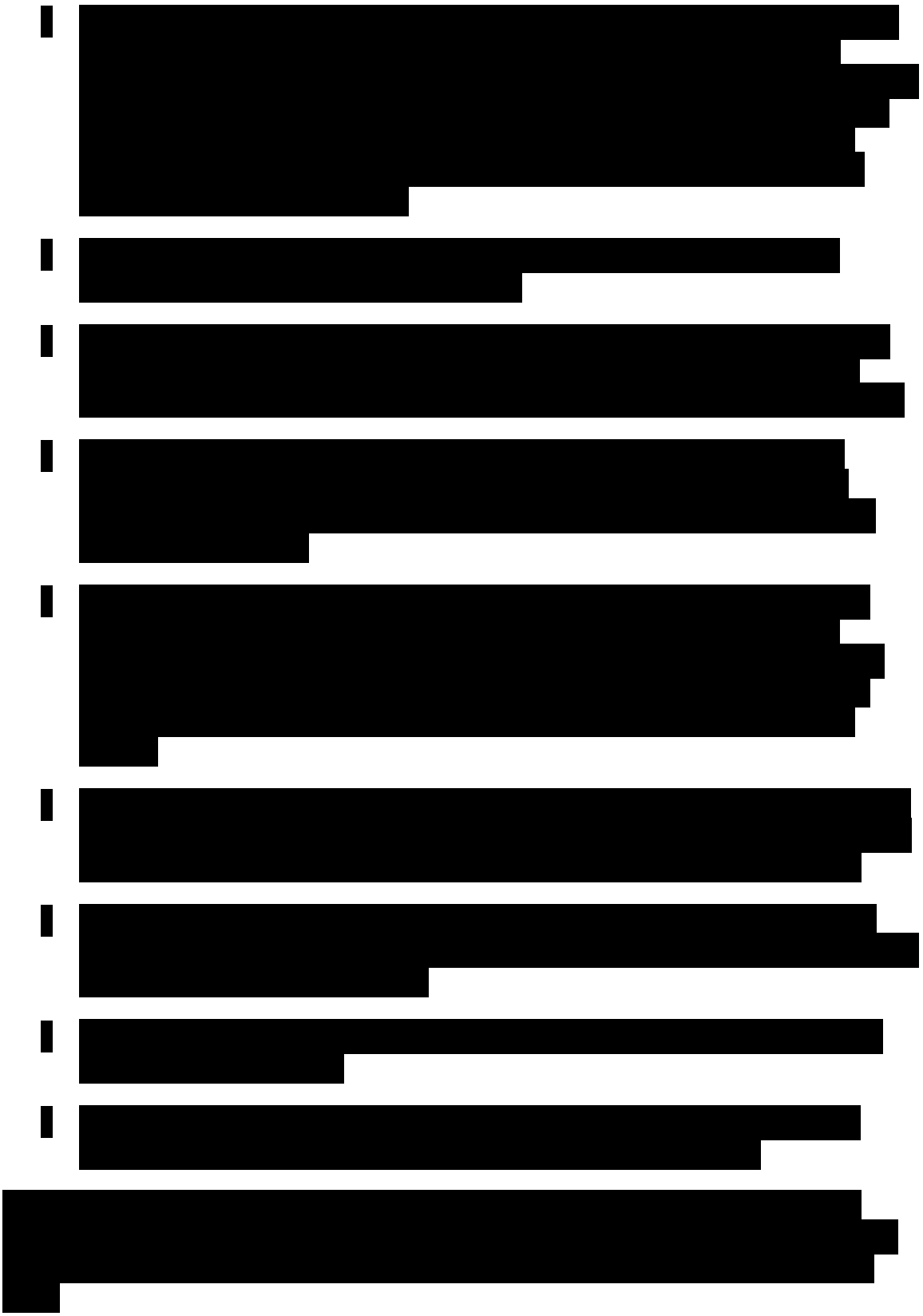

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STUDY SUMMARY

Title:	A Phase 1 Study of BLU-285 in Patients with Gastrointestinal Stromal Tumors (GIST) and other Relapsed and Refractory Solid Tumors
Study Centers	The study will be conducted at multiple study centers in the United States (US), European Union (EU), and Asia.
Introduction and Rationale:	Gastrointestinal stromal tumors 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 (PDGFRα) (10-15%), most commonly a substitution of valine for aspartic acid at amino acid 842 (D842V). 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%), though exon 17 mutations are 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 to approximately 95-99% following second-line TKI therapy. No currently approved TKI selectively inhibits mutations in exon 17 of KIT or at PDGFRα D842. Thus, GIST dependent on either of these mutations represents an unmet medical need. Avapritinib (also known as BLU-285) has demonstrated potent and selective activity against KIT exon 17 and PDGFRα D842 mutants *in vitro* and growth inhibition in TKI-resistant models *in vivo*. 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 of KIT mutations beyond exon 17, such as exons 9, 11, 13, and 18. Given the poor prognosis and potential risk/benefit of avapritinib for patients with advanced GIST, further development of this agent is warranted.
Number of Patients:	Approximately 235 patients will be enrolled in this study, including: • Approximately 50 patients in Part 1 (Dose Escalation) • Approximately 185 patients in Part 2 (Expansion) The total number of patients to be enrolled in Part 1 is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the maximum tolerated dose (MTD).

Objectives:

Primary Objectives:

Part 1

- To determine the MTD and recommended Phase 2 dose (RP2D) of avapritinib.
- To determine the safety and tolerability of avapritinib.

Part 2

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

Secondary Objectives:

- To characterize the pharmacokinetic (PK) profile of avapritinib, and correlate drug exposure with safety assessments, including changes in electrocardiogram (ECG) intervals.
- To assess evidence of antineoplastic activity of avapritinib as measured by duration of response (DOR), progression free survival (PFS), and clinical benefit rate (CBR).
- To assess antitumor activity as measured by Choi Criteria.
- To compare PFS on avapritinib with PFS on last prior anti-cancer therapy.
- To assess mutations in KIT, PDGFRα and other cancer-relevant genes in tumor tissue at baseline and at the end of treatment (EOT).

- To assess the KIT, PDGFRα and other cancer-relevant gene mutant allele fractions measured in circulating tumor deoxyribonucleic acid (ctDNA) at baseline, and changes in the mutant allele fractions measured in ctDNA after treatment with avapritinib.

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Study Design:

This is a Phase 1, open-label, first-in-human (FIH) dose-escalation study designed to evaluate the safety, tolerability, PK, PD and preliminary antineoplastic activity of avapritinib, administered orally (PO), in adult patients with unresectable GIST or other relapsed or refractory solid tumors.

The study consists of 2 parts: dose-escalation (Part 1) and expansion (Part 2).

After provision of written informed consent, patients will be evaluated for study eligibility during the Screening period within 56 days (weeks) before study drug administration on Day -3 for patients participating in the PK lead-in stage (Part 1) or Cycle 1 Day 1 (C1D1) for patients not participating in the PK lead-in stage (Part 2).

A treatment cycle is 28 days in duration. Patients in Part 1 (Dose-Escalation) will present to the study center on Day -3 for the first dose of study drug and serial PK sampling, PD sample collection, vital sign measurement, ECG monitoring, safety monitoring and adverse event (AE) recording. The dose received on D -3 will be the dose of the patient's assigned cohort. On Days -2, -1, and 1 (24, 48, and 72 hours after study drug administration) patients will return for PK sampling and safety monitoring. Immediately after the 72-hour PK sample is obtained, the C1D1 dose will be administered.

Patients in Part 2 will present to the study center on C1D1 for the first dose of study drug and serial PK sampling (Groups 1 and 2), PD sample collection, vital sign measurement, ECG monitoring, safety monitoring and AE recording. Approximately 20 patients in Groups 1 and 2, at selected sites will participate in continuous ECG (Holter) monitoring for extraction of ECGs at the times of PK sampling; Holter recordings will be collected in Cycle 1 on Days 1, 2, and 15.

During Cycle 1 (C1) following the PK Lead-in (Part 1), patients are to attend study center visits on C1D1 (Parts 1 and 2) Days 8, 15, and 22 (Part 1), and Days 2 (Part 2, Groups 1 and 2) and 15 (Part 2). On C1D8 and C1D22, patients will undergo safety monitoring, on C1D15, safety monitoring and dense PK sampling (Part 1), and on Day 15 (Part 2) patients will undergo simplified safety monitoring, dense PK sampling (Groups 1 and 2), and sparse PK sampling (Group 3).

During Cycle 2 (C2), all patients are to attend study center visits on Day 1 (D1) and Day 15 (Part 1), and on Day 1 only (Part 2) for safety monitoring and PK blood draws, and then on D1 of subsequent cycles. After C2, patients will return to the study center on Day 1 of each subsequent cycle to Cycle 13 for safety monitoring and (through Cycle 4 Day 1) PK blood draws. After C2 (C3D1) and every 2 cycles thereafter (e.g., C5D1, C7D1), patient's tumor status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) through Cycle 13. After 13 cycles have been completed on trial, patients are to attend study center visits every 3 cycles on Day 1 for safety monitoring and a tumor status assessment (e.g., C16D1, C19D1, C22D1). This decreases the visit frequency and radiation exposure to the patient.

It is anticipated that patients will receive at least 1 cycle of avapritinib; no maximum treatment duration has been set. After C1, patients may continue to receive avapritinib until precluded by toxicity, noncompliance, withdrawal of consent, physician decision, progressive disease, death, or closure of the study by the Sponsor.

All patients will attend an EOT visit within 14 (±7) days after the last dose of study drug. A Safety Follow-up that may be performed by telephone contact for resolution of any residual 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. Thereafter, patients are to be followed for disease assessment, subsequent antineoplastic therapy and survival approximately every 3 months until death, withdrawal of consent, or closure of the study by the Sponsor.

Part 1 (Dose Escalation)

The dose escalation part of the study will enroll patients with unresectable GIST or another advanced solid tumor. Patients with GIST must have disease that has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase-inhibitor, or disease with a D842 mutation in the PDGFRα gene. Patients with an advanced solid tumor other than GIST must have relapsed or refractory disease without an available effective therapy.

The first cohort of patients will receive avapritinib at a starting dose of 30 mg once daily (QD). The dose escalation increment for the first escalation step will be a maximum of 100%; however, if ≥ 1 patient treated at the starting dose level has a ≥ Grade 2 non-hematologic AE or a ≥ Grade 3 hematologic AE and the AE (non-hematologic or hematologic) is not clearly attributable to a cause other than avapritinib, then the maximum dose escalation increment for the first escalation step will be 50%. All subsequent dose escalation increments will be a maximum of 50%.

Three patients will be enrolled initially in each cohort and an additional 3 patients (for a total of 6) will be enrolled should the cohort require expansion due to dose-limiting toxicity (DLT). After the current escalation cohort is full, up to 3 additional patients, all of whom must have the diagnosis of GIST, may be enrolled into an enrichment cohort at a lower dose that included only 3 patients evaluable for DLT, was reviewed at a dose-escalation meeting, and did not exceed the MTD. Data from these patients will allow for further exploration of PK, PD, and safety in patients with GIST. Enrollment of patients into an enrichment cohort requires written approval from the Sponsor. In cohorts in which the administered dose is < 100 mg QD, enrolled patients may have the diagnosis of either GIST or a relapsed/refractory solid tumor. In cohorts in which the administered dose is ≥ 100 mg QD, at least 2 patients in each cohort (4 if the cohort is expanded to 6 patients) must have the diagnosis of GIST.

The specific dose for each subsequent cohort will be determined at a dose-escalation meeting that includes the Study Investigators and the Sponsor Clinical Study Team, and must be agreed to by the Study Investigator at each study center and the Sponsor Clinical Study Team. Dose-escalation meetings will occur after all patients in the current cohort have completed at least 28 days of observation after their first dose of avapritinib, or have experienced a DLT.

Dose escalation will continue until the MTD or a RP2D below the MTD has been determined. In addition, based on evaluation of the data, alternative dosing regimens (e.g., twice daily [BID]) or schedules (e.g., 3 weeks on, 1-week rest) may be explored.

Part 2 (Expansion)

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

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

	• Group 2: Patients with unresectable GIST harboring a D842V mutation in the PDGFRα gene (N~35) The PDGFRα mutation will be identified by local and central assessment, either in archival tissue or a new tumor biopsy obtained, prior to treatment with avapritinib. • Group 3: Patients with unresectable GIST that has progressed and/or those who have experienced intolerance following treatment with imatinib (including in the adjuvant setting) and who have not received additional kinase-inhibitor therapy and do not have a known D842V mutation in PDGFRα (N~50). Patients with GIST harboring a D842V mutation in the PDGFRα gene may be enrolled based on local mutation testing. However, during Part 2 of the study, Group 1 and 2 patients will be required to submit a formalin-fixed, paraffin-embedded tumor sample for PDGFRα mutational testing at a central laboratory prior to beginning treatment with avapritinib. During Part 2, patient safety will be reviewed on an ongoing basis at teleconferences (approximately every 1 - 2 months) that include the Study Investigators and the Sponsor Clinical Study Team. All safety data collected to date will be reviewed to confirm that no unexpected, significant, or unacceptable risk to patients enrolled in the study has been discovered. Available tumor response, PK, and PD data will also be reviewed.
Duration of Treatment	It is anticipated that patients will receive at least 1 cycle of avapritinib; no maximum treatment duration has been set. After C1, patients may continue to receive avapritinib until precluded by toxicity, noncompliance, withdrawal of consent, physician decision, progressive disease, death, or closure of the study by the Sponsor.
Duration of Patient Participation	The minimum duration of patient participation is approximately 3 months, including a screening period to assess study eligibility up to 8 weeks (56 days); a PK Lead-in stage (3 days) for all patients in Part 1; a treatment period of at least 1 cycle (28 days); an EOT visit at least 14 (± 7) days following the last dose of study drug; and a Follow-up telephone contact for resolution of any AEs 30 (+7) days following the last dose of study drug or at the time the patient initiates another antineoplastic therapy. Thereafter, patients are to be followed for disease assessment, subsequent antineoplastic therapy and survival approximately every 3 months until death, withdrawal of consent or closure of the study by the Sponsor.
Duration of Study	The expected enrollment period is approximately 45 months and the expected duration of the study is approximately 60 months.
Target Population	Main entry criteria:

- Patient is ≥ 18 years of age.
- For Part 1: Histologically- or cytologically-confirmed diagnosis of unresectable GIST or another advanced solid tumor. Patients with unresectable GIST must have disease that has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase-inhibitor agent, or disease with a D842 mutation in the PDGFRα gene. Patients with an advanced solid tumor other than GIST must have relapsed or refractory disease without an available effective therapy.
- For Part 2:
- Group 1: Patients must have a confirmed diagnosis of unresectable GIST that has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase-inhibitor agent and the patient does not have a D842V mutation in PDGFRα.
- Group 2: Patients must have a confirmed diagnosis of unresectable GIST with a D842V mutation in the PDGFRα gene. The PDGFRα mutation will be identified by local or central assessment, either in an archival tissue sample or a new tumor biopsy obtained prior to treatment with avapritinib.
- Group 3: Patients must have a confirmed diagnosis of unresectable GIST that has progressed and/or patients must have experienced intolerance to imatinib and not received additional kinase-inhibitor therapy. Patients must not have a known D842V mutation in PDGFRα.
- Groups 1, 2, and 3: At least 1 measurable lesion defined by mRECIST version 1.1 for patients with GIST.
- Groups 1 and 2: A tumor sample (archival tissue or a new tumor biopsy) has been submitted for mutational testing.

Primary Endpoints:

Part 1

- MTD and RP2D of avapritinib.
- Overall safety profile of BLU-285, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs, serious adverse events (SAEs), and changes in vital signs, ECGs, and safety laboratory tests.

Part 2

- ORR, defined as the rate of confirmed complete response (CR) or partial response (PR) by mRECIST version 1.1.

- Overall safety profile of avapritinib, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs, SAEs, and changes in vital signs, ECGs, and safety laboratory tests.

Secondary Endpoints:

- PK parameters of avapritinib: Maximum plasma drug concentration (C_{max}), time to maximum plasma drug concentration (T_{max}), time of last quantifiable plasma drug concentration (T_{last}), area under the plasma concentration versus time curve from time 0 to 24 hours postdose (AUC_{0-24}), plasma drug concentration at 24 hours postdose (C_{24}); apparent volume of distribution (V_z/F), terminal elimination half-life ($t_{½}$), apparent oral clearance (CL/F), accumulation ratio (R), and correlations between PK parameters and safety findings of interest, including ECG intervals.
- DOR, PFS, and CBR as per mRECIST version 1.1.
- Response rate as defined by Choi Criteria.
- PFS on last prior anti-cancer therapy.
- KIT, PDGFRα, and other cancer-relevant mutations present in tumor tissue at baseline and at EOT.
- Change from baseline in the levels of KIT, PDGFRα, and other cancer-relevant mutant allele fractions in peripheral blood.

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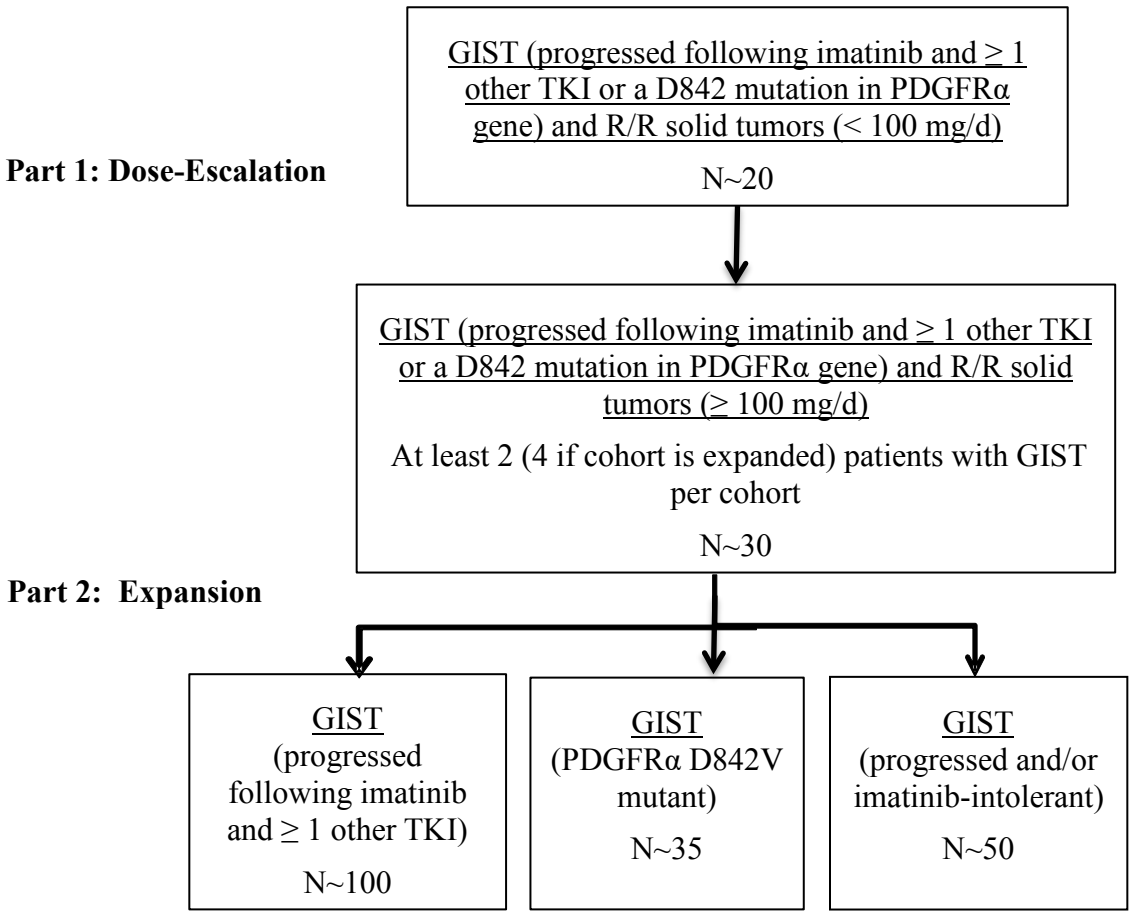
STUDY SCHEMATIC



Abbreviations: GIST = gastrointestinal stromal tumor; PDGFRα = platelet-derived growth factor receptor alpha; R/R = relapsed/refractory; TKI = tyrosine kinase inhibitor.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration versus time curve from time 0 to 24 hours postdose
β-hCG	Beta human chorionic gonadotropin
BCRP	Breast cancer resistance protein
BID	Twice daily
C_{24}	Plasma drug concentration at 24 hours postdose
C_{max}	Maximum plasma drug concentration
CBR	Clinical benefit rate
CL/F	Apparent oral clearance
cm	Centimeter
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CxDx	Cycle x Day x
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEG	Electroencephalogram
EOT	End-of-treatment
^{18}FDG-PET	^{18}Fluorodeoxyglucose positron emission tomography
FIH	First in human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor

GLP	Good Laboratory Practice
Hgb	Hemoglobin
HNSTD	Highest non-severely toxic dose
IB	Investigator's Brochure
IC_{50}	Half-maximal inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine/hormone-releasing system
IV	Intravenous
K_d	Dissociation constant
KIT	V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
mRECIST	Response Evaluation Criteria in Solid Tumors modified for patients with gastrointestinal stromal tumors.
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PDGFRα	Platelet-derived growth factor receptor alpha
PDX	Patient derived xenograft
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PO	Per os (by mouth; orally)
PR	Partial response
PR (ECG interval)	Time elapsed from the P wave to the R wave
PS	Performance status
QD	Once daily
QRS	time elapsed from the Q/R wave to the end of the S wave
QT	Interval between the Q/R wave and T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected using Fridericia's formula

R	Accumulation ratio
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STD_{10}	Severely toxic dose for 10% of animals
$t_{½}$	Terminal half-life
TKI	Tyrosine kinase inhibitor
T_{max}	Time to maximum plasma drug concentration
T_{last}	Time of last quantifiable plasma drug concentration
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution

1 INTRODUCTION AND RATIONALE

1.1 Background

Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumors (GIST) are thought to develop from the interstitial cells of Cajal or their stem cell precursors. They are the most common mesenchymal tumors occurring in the gastrointestinal (GI) tract, representing approximately 0.1% - 3.0% of all GI malignancies (Miettinen et al, 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).

GISTs 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 et al, 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%), though exon 17 mutations are identified in approximately 1% of patients (Heinrich et al, 2008; Debiec-Rychter et al, 2006). Disease progression during treatment with a tyrosine kinase inhibitor (TKI) is most commonly due to the emergency 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 and sunitinib. At the time of progression on first-line TKI

(imatinib) therapy approximately 20-25% of patients had GIST harboring a mutation in exon 17; this increased to 95-99% following second-line TKI therapy (Liegl et al, 2008; Wardelmann et al, 2006; Antonescu et al, 2005). No currently approved TKI selectively inhibits mutations in exon 17 of KIT.

There are no agents approved to treat GIST after failure of regorafenib as no currently approved TKI selectively inhibits mutations in exon 17 of KIT, though other options, including sorafenib, nilotinib, dasatinib (for patients with the PDGFRα D824V mutation), and pazopanib are included in the National Comprehensive Cancer Network (NCCN) guidelines based on limited data (NCCN Soft Tissue Sarcoma Guidelines, 2015).

Avapritinib (also known as BLU-285) has potent activity on the KIT activation loop mutants with biochemical half-maximal inhibitory concentration (IC_{50}) against all activation-loop mutants (exons 17 and 18) of less than 2 nM. In context of primary KIT exon 11 mutations, the avapritinib biochemical IC_{50} against the predominant resistance mutation in exon 13 (V654A) is 11-nM. In addition, considerable avapritinib activity below 30 nM is retained in combinations of exons 11 14 mutations. Due to its high selectivity, avapritinib is well tolerated. Therefore, avapritinib can be dosed to cover a wide array of disease-relevant KIT mutants found in GIST patients. It is projected that the achieved RP2D of 300 mg avapritinib described in Section 1.4 will cover primary exon 11 mutants observed in imatinib-naïve GIST as well as combinations of exon 11 with acquired resistance mutations in exons 13, 14, 17, or 18 in the post-imatinib setting. Pharmacokinetic data from the ongoing BLU-285-1101 Phase 1 dose escalation and expansion cohorts support these assumptions.

Although imatinib is effective in many patients with GIST as first-line therapy, many 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 MC 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 SDH. In KIT-mutant GIST, the response rate for patients with tumors bearing ATP-binding pocket mutations to sunitinib is rather low (ORR 11%) and absent in activation-loop mutations (ORR 0%; Heinrich MC et al, 2008). Thus, patients failing imatinib due to either ATP-pocket or activation-loop mutations, represent an important medical need. The results observed thus far in this ongoing Phase 1 trial with avapritinib demonstrate important antitumor activity, including radiographic response with a disease-control rate of 56% based on central review (PR+SD) and prolonged PFS of 9.3 months in patients with heavily pretreated, KIT-mutant GIST. In this heavily pretreated population, imatinib rechallenge has shown a median PFS of 1.8 months (Kang et al, 2013). Based on these findings, an investigation of avapritinib, a potent and highly selective inhibitor of the post-imatinib mutants found in GIST, is warranted.

In the second-line GIST setting, sunitinib is the only approved TKI. A statistically significant improvement in PFS was demonstrated among patients treated with sunitinib compared with patients who received placebo (6.4 months vs 1.5 months; hazard ratio 0.33). No patients in either group had a complete response (CR), while 14 of the 207 patients in the sunitinib group and none of the 105 patients in the placebo group had a partial response (PR), giving ORRs of 6.8% and 0%, respectively. (Goodman et al, 2007). The benefit of sunitinib in the second-line setting is considered modest post-imatinib progression, and treatment is associated with various severe toxicities. The most common adverse events (AEs) related to sunitinib included diarrhea, mucositis, skin abnormalities, and altered taste. Severe hypertension and reductions in left ventricular ejection fraction were also more common in sunitinib-treated patients. Even though sunitinib may be potent against the wild-type KIT kinase compared to first-line therapy, resistance to sunitinib usually evolves within 1 year of treatment.

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, 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; Yoo et al, 2015; Goodman et al, 2007; Heinrich et al, 2008).

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, 2015).

As there are no approved agents that target PDGFRα D842 mutations, unresectable PDGFRα-driven GIST represents a high, unmet medical need.

1.1.1 Preclinical Pharmacology

BLU-285 was designed as a potent, selective, small molecule inhibitor of the KIT containing mutations in exon 17, and PDGFRα containing mutations at D842V, which mediate ligand independence. It has demonstrated biochemical in vitro activity on the KIT exon 17 mutant enzyme, KIT D816V (half-maximal inhibitory concentration [IC_{50} = 0.27 nM]) and the homologous mutant PDGFRα D842V (IC_{50} = 0.24 nM). These mutations result in resistance to the TKI used to treat GIST: imatinib, sunitinib, and regorafenib (Table 1).

Table 1: Biochemical Activity of BLU-285 and GIST Agents against KIT Exon 17 D816V and PDGFRα D842V Mutants

Compound	PDGFRα D842V IC_{50} (nM)	KIT D816V IC_{50} (nM)
BLU-285	0.24	0.27
Sunitinib	118	191
Regorafenib	825	3619
Imatinib	656	8481

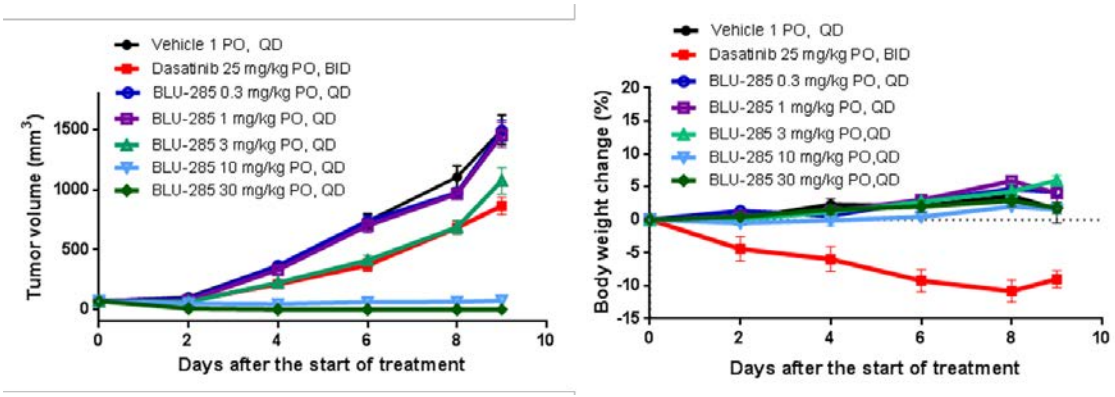
Abbreviations: GIST = gastrointestinal stromal tumors; IC_{50} = half-maximal inhibitory concentration of enzyme activity; KIT = V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog; PDGFRα = platelet-derived growth factor receptor alpha.

The selectivity of BLU-285 was characterized across a panel of over 450 human kinases and disease-relevant kinase mutants. BLU-285 demonstrated the highest affinity for KIT exon 17 mutants (KIT D816V dissociation constant [K_d] = 0.3 nM; KIT D816H K_d = 0.6 nM), and also bound a small group of highly related class III receptor tyrosine kinases: KIT wild type (K_d = 17 nM), PDGFRα wild type (K_d = 1 nM), platelet-derived growth factor receptor beta wild type (K_d = 1 nM), colony stimulating factor 1 receptor (K_d = 6 nM), and FMS-like tyrosine kinase 3 (K_d = 25 nM). All other kinases demonstrated K_d values greater than 50 nM. These data demonstrated that BLU-285 is selective for the KIT exon 17 mutant proteins specifically and has limited potential for activity outside of the related class III receptor tyrosine kinases (Report BPM-0002).

In vitro, BLU-285 was noted to inhibit the growth of the human mast cell leukemia cell line HMC1.2 (dependent on KIT D816V) and the mouse mastocytoma cell line P815 (dependent on the mouse homolog of the human KIT D816Y mutant). Additionally, BLU-285 inhibited signaling of the oncogenic and ligand-independent PDGFRα D842V when expressed in an engineered cell line, a model against which imatinib is inactive. In each of these model systems, BLU-285 demonstrated dose-dependent inhibition of KIT exon 17 or PDGFRα D842V as well as inhibition of key downstream effector pathways known to be involved in tumorigenesis.

In vivo, anti-tumor efficacy of BLU-285 was demonstrated in a P815 mastocytoma xenograft and an imatinib-resistant mutant GIST patient-derived xenograft (PDX) tumor model, both of which are driven by exon 17 mutant KIT (Figure 1). In the P815 model, robust antitumor activity was demonstrated in animals treated with doses (10 or 30 mg/kg) of BLU-285 that were well tolerated, as noted by a lack of impact on body weight.

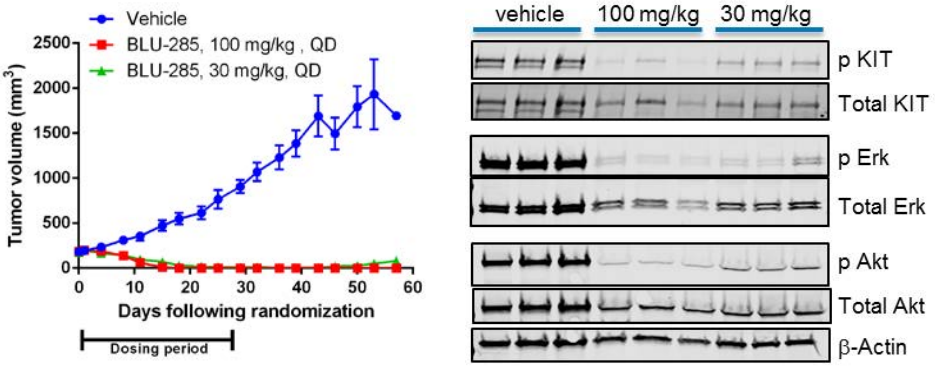
Figure 1: Efficacy of, and Body Weight Measurements for, BLU-285 in a KIT Exon 17 Mutant Driven P815 Xenograft Model



Abbreviations: BID = twice daily; KIT = v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PO = per os (orally); QD = once daily.
Mice bearing P815 xenograft tumors were dosed PO, QD with vehicle, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, or 30 mg/kg BLU-285 or 25 mg/kg dasatinib BID.
Left panel: A dose-dependent decrease in tumor growth was observed with PO, QD oral dosing of BLU-285. 10 mg/kg and 30 mg/kg BLU-285 PO, QD dosing produced complete tumor growth inhibition with several tumor regressions over the 10-day dosing period. Due to the aggressive disease course, all vehicle-treated mice were euthanized after 10 days of dosing due to disease-related moribundity. Statistical significance of tumor growth inhibition was determined with the 10 mg/kg or 30 mg/kg dose of BLU-285 and was highly statistically significant ($P < 0.001$ as measured by one-way analysis of variance).
Right panel: All doses of BLU-285 were well tolerated as indicated by body weight measurements. Data points represent group mean and error bars represent standard error of the mean for 10 mice per cohort.

In the GIST PDX model, BLU-285 administered orally (PO) for 27 days resulted in antitumor activity sustained for 4 weeks after the completion of BLU-285 dosing, with demonstrated inhibition of both KIT activity and downstream signaling (Figure 2).

Figure 2: Efficacy of BLU-285 and Inhibition of KIT Exon 11/Exon 17 Mutant Signaling in a GIST Patient-Derived Xenograft Model



Abbreviations: Akt = v-akt murine thymoma viral oncogene homolog; ERK = extracellular signal-regulated kinase; GIST = gastrointestinal stromal tumor; KIT = v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; p = phosphorylated; PDX = patient-derived xenograft; QD = once daily.

Mice bearing KIT exon 11/exon 17 mutant GIST PDXs were dosed once daily, orally with vehicle, 30 mg/kg, or 100 mg/kg BLU-285 for 27 days.
Left panel: Tumor growth was measured twice weekly for the 27-day dosing period followed by a 28-day observation period. BLU-285 induced tumor regression and sustained tumor growth inhibition at both doses tested. BLU-285 antitumor activity was highly statistically significant ($P < 0.0001$ by one way analysis of variance). Data points represent group mean and error bars represent standard error of the mean for 9 mice per cohort.
Right panel: After 7 days of once-daily dosing with vehicle, 30 mg/kg BLU-285, or 100 mg/kg BLU-285, tumors were harvested from 3 mice per group, 24 hours after the last dose. Tumor homogenates demonstrated inhibition of KIT signaling by analysis of KIT autophosphorylation and the downstream signaling markers p-ERK and p-AKT.

Safety pharmacology studies revealed that BLU-285 inhibits the human ether-a-go-go related gene channel activity in vitro with an average IC_{50} of 2.4 μM by single cellular electrophysiologic recordings. BLU-285 was further evaluated in a cardiovascular safety pharmacology study in conscious radiotelemetry-instrumented male Beagle dogs to assess the effects of electrocardiogram (ECG) intervals, as well as blood pressure, body temperature, and respiratory parameters. Administration of BLU-285 at dose levels of 15, 30, or 45 mg/kg did not result in BLU-285-related effects on any cardiovascular parameter, including ECG waveform morphology, duration of time elapsed from the P wave to the R wave (PR), time elapsed from the Q/R wave to the end of the S wave (QRS), time between consecutive R waves, interval between the Q/R wave and T wave (QT), and QT interval corrected using van de Water's formula intervals, body temperature, or respiratory parameters.

A Good Laboratory Practice (GLP)-compliant study performed to evaluate the effects of BLU-285 on the gross behavioral, physiological, and neurological state of female Sprague-Dawley rats (Irwin test) demonstrated, in a minority of animals, an increase in sensitivity to stimuli that are potentially underlying indicators of preconvulsive activity at the mid and high doses; no BLU-285 related effects were noted at the lowest dose level tested. In a separate study performed in conscious radiotelemetry-instrumented male

Beagle dogs, no effects of BLU-285 were noted on any cardiovascular or respiratory parameter, or the clinical condition of the animals.

1.1.2 Toxicology

Sprague-Dawley rats and Beagle dogs were chosen as the nonclinical test species for assessing chemical structure- and pharmacology-mediated toxicity of BLU-285 on the basis of the following criteria: a) these species are pharmacologically responsive to the effects of BLU-285; b) these species have historically been used to assess potential human adverse effects, and; c) these species are qualitatively similar in hepatocyte metabolism profiles to humans.

Good Laboratory Practice-compliant 28-day repeated dose toxicology studies were conducted in Sprague-Dawley rats. The cause of morbidity and/or mortality was considered to be inanition and metabolic perturbations, as evidenced by body weight losses, decreased food consumption, serum and urine chemistry parameter alterations, and tissue effects. The severely toxic dose in 10% of animals (STD_{10}) was 30 mg/kg/day (180 mg/m^2/day). Convulsions were occasionally observed at doses above the STD_{10}. Hematologic effects were observed, specifically depressed erythron, myeloid, and lymphoid parameters. Serum chemistry effects included increases in total bilirubin (likely secondary to impaired bile acid transport), mild to moderate increases in liver enzymes (without microscopic evidence of hepatic toxicity), and altered parameters suggesting impaired metabolism such as total cholesterol and serum cations. There were no morphologic brain alterations.

An additional non-GLP-compliant study was conducted in female rats to determine if the oral administration of BLU-285 evokes changes in electroencephalographic (EEG) measures consistent with seizures or altered seizure threshold. Administration of BLU-285 at 15 mg/kg or 30 mg/kg for 9 consecutive days did not result in a frank seizure or consistent pattern of EEG suggestive of lowered seizure threshold. Increased sensitivity to BLU-285 at 50 mg/kg was noted in two rats, one that developed sharp waves after the first day of dosing and another that had a frank seizure on the ninth day of dosing.

In a 28-day GLP-compliant toxicology study in male Beagle dogs, the dose-limiting effects were inanition and metabolic perturbations with vomiting, diarrhea, decreased food intake, body weight loss, hematologic and serum chemistry perturbations, and microscopic alterations in tissues. In addition, in the dog brain, a focal area of hemorrhage with vascular thrombus occurred at 30 mg/kg/day (reduced to 15 mg/kg/day) that may be associated with thrombocytosis and/or potential pharmacologic effects on the pericyte affecting vascular integrity. The highest non-severely toxic dose (HNSTD) was 7.5 mg/kg/day (150 mg/m^2/day). The microscopic effects in the brain had no effect on clinical examinations; specifically, no neurologic effects were observed during in-life observations. All findings reversed after the 2-week recovery period, except those in the gonad (hypospermatogenesis) and brain.

Subsequent 3-month GLP-compliant toxicology studies are currently ongoing in Sprague-Dawley rats and Beagle dogs to further characterize the dose-limiting toxicities (DLTs). Preliminary data are available from the study in dogs. At the high dose (30 mg/kg/day) tested in dogs, severe brain effects (including neurologic signs and brain and spinal cord hemorrhages) were noted in all animals. No neurologic signs or test-article related mortality occurred in dogs treated at the mid dose (15 mg/kg/day) or at the HNSTD (7.5 mg/kg/day).

Additional information can be found in the Investigator's Brochure (IB) for BLU-285.

1.2 Study Rationale

Targeting KIT exon 17 and PDGFRα D842 mutants with small molecule inhibitors has had limited success due to difficulties in creating potent molecules with sufficient selectivity; there are currently no approved agents that selectively target these mutant kinases. BLU-285 is a potent, selective, small molecule inhibitor of the ligand-independent KIT exon 17 and PDGFRα D842 mutants, significantly more potent against these targets than imatinib, sunitinib and regorafenib (Table 1).

BLU-285 has been shown to be tolerable at active doses in toxicology and safety pharmacology studies. Given the poor prognosis of patients with advanced GIST that has progressed after kinase-inhibitor therapy or that harbors a PDGFRα D842 mutation, along with the potential benefit/risk of BLU-285 in these patients, further development of this agent is warranted. The present clinical trial is a Phase 1, first-in-human (FIH) study of BLU-285 consisting of dose escalation (Part 1) and expansion (Part 2) parts. The objectives of Part 1 are to define the safety and tolerability of BLU-285, identify the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D), and to characterize the pharmacokinetics (PK) and pharmacodynamics (PD), and preliminary antineoplastic activity of BLU-285.

Part 2 will begin once an MTD or RP2D has been determined in Part 1, and will permit a more complete assessment of safety, PK, PD, and antitumor activity in patients with GIST. Three groups of patients will be enrolled: 1) patients with GIST that has progressed following treatment with imatinib and at least 1 other kinase-inhibitor therapy (N~100); 2) patients with GIST harboring a D842V mutation in the PDGFRα gene, regardless of prior therapy (N~35); and 3) patients with GIST that has progressed and/or patients who experienced intolerance to imatinib and have not received additional kinase-inhibitor therapy (N~50). This will permit assessment of antitumor activity in each of these populations of treatment-refractory GIST. Additionally, approximately 20 patients at selected sites will be evaluated with ECGs extracted from Holter monitoring to evaluate the effect of BLU-285 on ECG parameters in Groups 1 and 2. Analysis of safety, tolerability, PK, PD, and preliminary antitumor activity will help guide the future clinical development of BLU-285. In Part 2 of the study ORR, the primary measure of antitumor activity, will be evaluated for all patients, to determine if the observed ORR excludes a true ORR ≤ 10%, with 2-sided type I error of 0.05.

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

1.3 Rationale for the Starting Dose and Dosing Regimen

Selection of the safe starting dose in clinical trials for anticancer small molecules is based on either one-tenth the allometrically scaled STD_{10} in the most sensitive species (female rat) based on the administered dose, or one-sixth the allometrically scaled HNSTD in the other species (dogs) if they cannot tolerate one-tenth of the allometrically scaled rat STD_{10}. The STD_{10} in the female rat is 30 mg/kg/day or 180 mg/m^2/day, one-tenth of which equals 18 mg/m^2/day. The HNSTD in the dog is 7.5 mg/kg/day or 150 mg/m^2/day, indicating that the dog can tolerate one-tenth of the rat STD_{10}. Therefore, the safe starting dose for this FIH Phase 1 trial will be 18 mg/m^2/day, which equals a flat dose of 30 mg/day based on a 1.7 m^2 human body surface area. Based on a calculated elimination half-life of 22 hours, once daily (QD) dosing is appropriate.

1.4 BLU-285-1101 Study Update

On 14 February 2017, the MTD for the BLU-285-1101 study was determined to be 400 mg QD. Thirty-eight patients have initiated treatment in the dose expansion part (Part 2) of the study at 400 mg per day. However, based on a joint Investigator and Sponsor review of the available safety, PK, PD, and clinical activity data on 13 June 2017, a new starting dose of 300 mg QD was selected as the initiation dose of avapritinib for the remainder of the expansion part of the study. There was an option of dose escalation to 400 mg after 2 consecutive treatment cycles in adherence with Section 6.4.3, Dose Modifications, if avapritinib was well tolerated.

As of 11 October 2017, a total of 116 patients were treated with avapritinib at starting doses of 30 to 600 mg, including 46 patients enrolled in Part 1, dose escalation, and 70 patients enrolled in Part 2, dose expansion. Thirty-seven (32%) patients had PDGFRα Exon 18 D842 mutation (34 D842V, 1 D842Y, 1 DI 842-843V, and 1 D842H845), 2 (2%) patients had PDGFRα Exon 14 N659K mutation, 76 (66%) had KIT mutations, and 1 patient was KIT and PDGFRα wild type.

Response was assessed using Response Evaluation Criteria in Solid Tumors, version 1.1 modified for patients with GIST (mRECIST version 1.1) based on blinded central review of CT/MRI scans. Of the 31 PDGFRα D842 patients with ≥ 1 radiographic assessment, 1 (3%) patient had CR (pending confirmation), 21 (68%) patients had PR (18 confirmed and 3 pending confirmation). The ORR was 71% (95% CI: 52% - 86%). The remaining 9 patients had stable disease (SD) as their best response, resulting in a disease control rate of 100% (Table 2). Median duration of response (DOR) among PDGFRα D842 responders had not been reached, the estimated 1-year DOR rate was 65%. Of the 43 KIT patients with ≥ 1 radiographic assessment, 6 (14%) patients had PR (5 confirmed and 1 pending confirmation). The ORR was 14% (95% CI: 5% - 28%). Twenty-three (53%)

had SD, resulting in a DCR of 67% (Table 2). All 6 responders were still on treatment at the time of the data cut off, with DOR ongoing and ranging from 3 to 16 months.

Table 2: Best Radiological Response with BLU-285 by Central Assessment per mRECIST Version 1.1

Best Response [a]	PDGFRα D842 (N=31) n (%)	KIT (N=43) n (%)
CR	1 (3)[b]	0
PR	21 (68)[c]	6 (14)[d]
ORR (CR + PR)	22 (71)	6 (14)
SD	21 (68)	23 (53)
DCR (PR + SD)	31 (100)	29 (67)
PD	0	14 (33)

Abbreviations: DCR = disease control rate; KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; mRECIST = Response Evaluation Criteria in Solid Tumors modified for patients with GIST; PD = progressive disease; PDGFRα = platelet-derived growth factor receptor alpha; PR = partial response; SD = stable disease.

[a] Per mRECIST 1.1 based on central radiology review with data cutoff of 11 October 2017.

[b] 1 pending confirmation

[c] 3 pending confirmation

[d] 1 pending confirmation

Eighty-three of the 116 patients started at a dose level of 300 mg QD (RP2D, n=33) or 400 mg QD (MTD, n=50), including 18 PDGFRα D842 patients, 1 PDGFRα Exon 14 patient, and 64 KIT patients. Twelve of the 18 PDGFRα D842 patients had ≥ 1 radiographic assessment, 10 patients had PR, the ORR was 83%. Thirty of the KIT patients had ≥ 1 radiographic assessment, 5 patients had PR, the ORR was 17%. Median PFS among the 64 KIT patients was 11.5 months (95% CI: 9.3 months – not estimable). The estimated 6-month PFS rate was 69%.

As of the 11 October 2017, 67 patients remained on treatment (31 PDGFRα patients and 36 KIT patients). Forty-nine patients discontinued study treatment, including 6 patients due to adverse events, 40 patients due to disease progression, and 3 patients withdrew consent.

Table 3: Overall Summary of Adverse Events by Severity and Relationship in ≥ 20% of Patients (BLU-285-1101, Safety Population, N=116)

Safety Population N=116		**Severity n (%)**					**Relationship n (%)**
Preferred Term	**Any Events n (%)**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Related**
Patients with at least 1 AE	112 (97)						
Nausea	65 (56)	41 (35)	17 (15)	7 (6)	0	0	62 (53)
Fatigue	62 (53)	23 (20)	31 (27)	8 (7)	0	0	56 (48)
Periorbital edema	50 (43)	42 (36)	8 (7)	0	0	0	49 (42)
Vomiting	48 (41)	36 (31)	9 (8)	3 (3)	0	0	39 (34)
Edema peripheral	39 (34)	28 (24)	9 (8)	2 (2)	0	0	32 (28)
Anemia	36 (31)	7 (6)	10 (9)	17 (15)	2 (2)	0	23 (20)
Diarrhea	36 (31)	26 (22)	8 (7)	2 (2)	0	0	26 (22)
Cognitive Effects[a]	35 (30)	20 (17)	10 (9)	4 (3)	1 (1)	0	32 (28)
Lacrimation increased	35 (30)	29 (25)	6 (5)	0	0	0	31 (27)
Decreased appetite	33 (28)	24 (21)	6 (5)	3 (3)	0	0	28 (24)
Dizziness	27 (23)	21 (18)	6 (5)	0	0	0	15 (13)
Constipation	25 (22)	18 (16)	6 (5)	0	1 (1)	0	8 (7)
Hair color changes	25 (22)	24 (21)	0	0	0	0	25 (22)

Abbreviation: AE = adverse event.
[a] Cognitive Effects include the following preferred terms: cognitive disorder, confusional state, disturbance in attention, memory impairment, mental impairment, personality change, and speech disorder.

2 STUDY OBJECTIVES

2.1 Primary Objectives:

2.1.1 Part 1

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

2.1.2 Part 2

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

2.2 Secondary Objectives

- To characterize the PK profile of avapritinib, and correlate drug exposure with safety assessments, including changes in ECG intervals.
- To assess evidence of antineoplastic activity of BLU-285 as measured by DOR, progression free survival (PFS), and clinical benefit rate (CBR).
- To assess antitumor activity as measured by Choi Criteria.
- To compare PFS on avapritinib with PFS on last prior anti-cancer therapy.
- To assess mutations in KIT, PDGFRα, and other cancer-relevant genes in tumor tissue at baseline and at the end of treatment (EOT).
- To assess the KIT, PDGFRα and other cancer relevant gene mutant allele fractions measured in circulating tumor deoxyribonucleic acid (ctDNA) at baseline, and the

biologic activity of avapritinib based on changes in the mutant allele fractions measured in ctDNA.

[redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoints

3.1.1 Part 1

- MTD and RP2D of avapritinib.
- Overall safety profile of BLU-285, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs, serious AEs (SAEs), and changes in vital signs, ECGs, and safety laboratory tests.

3.1.2 Part 2

- ORR, defined as the rate of confirmed CR or PR by mRECIST version 1.1.
- Overall safety profile of avapritinib, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs, SAEs, and changes in vital signs, ECGs, and safety laboratory tests.

3.2 Secondary Endpoints

- PK parameters of avapritinib: Maximum plasma drug concentration (C_{max}), time to maximum plasma drug concentration (T_{max}), time of last quantifiable plasma drug concentration (T_{last}), area under the plasma concentration versus time curve from time 0 to 24 hours postdose (AUC_{0-24}), plasma drug concentration at 24 hours postdose (C_{24}); apparent volume of distribution (V_z/F), terminal elimination half-life ($t_{½}$), apparent oral clearance (CL/F), accumulation ratio (R), and correlations between PK parameters and safety findings of interest, including ECG intervals.
- DOR, PFS, and CBR, as per mRECIST version 1.1 (Appendix 1).
- Response rate as defined by Choi Criteria.
- PFS on last prior anti-cancer therapy.
- KIT, PDGFRα, and other cancer-relevant mutations present in tumor tissue at baseline and EOT.
- Change from baseline in the levels of KIT, PDGFRα, and other cancer-relevant mutant allele fractions in peripheral blood.

[redacted]

[redacted]

4 STUDY PLAN

4.1 Study Design

This is a Phase 1, open-label, FIH dose-escalation study designed to evaluate the safety, tolerability, PK, PD and preliminary antineoplastic activity of BLU-285, administered PO in adult patients with unresectable GIST or other relapsed or refractory solid tumors. The study schematic is shown in Section 4.2.

The study consists of 2 parts: dose-escalation part (Part 1) and expansion (Part 2).

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 study eligibility during the Screening period within 56 days (8 weeks) before study drug administration on Day-3 for patients participating in Part 1 or Cycle 1 Day 1 (C1D1) for patients participating in Part 2.

A treatment cycle is 28 days in duration. In order to better evaluate the half-life of BLU-285, which is predicted to be long, patients in Part 1 (Dose-Escalation) will participate in a 3-day PK-Lead in stage.

In Part 1, patients will present to the study center on Day -3 for the first dose of study drug and serial PK sampling, PD sample collection, vital sign measurement, ECG monitoring, safety monitoring and AE recording. The dose received on D-3 will be the dose of the patient's assigned cohort. Patients will return on days -2, -1, and 1 (24, 48, and 72 hours after study drug administration) for PK sampling and safety monitoring. Patients will not receive BLU-285 on Days -2 and -1. Immediately after the 72-hour PK sample is obtained, the C1D1 dose will be administered, and daily dosing will begin.

Patients in Part 2 (Expansion) will present to the study center on C1D1 for the first dose of study drug and serial PK sampling (Groups 1 and 2), PD sample collection, vital sign measurement, ECG monitoring, safety monitoring and AE recording. Approximately 20 patients in Groups 1 and 2, at selected sites will participate in continuous ECG (Holter) monitoring for extraction of ECGs at the times of PK sampling; Holter recordings will be collected in Cycle 1 on Days 1, 2, and 15.

During Cycle 1 (C1), following the PK Lead-in (Part 1), patients are to attend study center visits on C1D1 (Parts 1 and 2), Days 8, 15, and 22 (Part 1), and Days 2 (Part 2, Groups 1 and 2) and 15 (Part 2). On C1D8 and C1D22, patients will undergo safety monitoring, and on C1D15 safety monitoring and dense PK sampling (Part 1). On Day 15 (Part 2), patients will undergo simplified safety monitoring, and dense PK sampling (Groups 1 and 2), and sparse PK sampling (Group 3).

During Cycle 2 (C2), all patients are to attend study center visits on Day 1 (D1) and Day 15 (Part 1), and on Day 1 only (Part 2) for safety monitoring and PK blood draws, and then on D1 of subsequent cycles. After C2, patients will return to the study center on Day 1 of each subsequent cycle to Cycle 13 for safety monitoring and (through Cycle 4

Day 1) PK blood draws. After C2 (C3D1) and every 2 cycles thereafter, patient's tumor status will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) through Cycle 13. After 13 cycles have been completed on trial, patients are to attend study center visits every 3 cycles on Day 1 for safety monitoring and a tumor status assessment (e.g., C16D1, C19D1, C22D1). This decreases the visit frequency and radiation exposure to the patient.

It is anticipated that patients will receive at least 1 cycle of BLU-285; no maximum treatment duration has been set. After C1, patients may continue to receive BLU-285 until precluded by toxicity, noncompliance, withdrawal of consent, physician decision, progressive disease, death, or closure of the study by the Sponsor.

All patients will attend an EOT visit within 14 (±7) days after the last dose of study drug. A safety Follow-up (f/u) telephone contact for resolution of any residual 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. Thereafter, patients are to be followed for disease assessment, subsequent antineoplastic therapy and survival approximately every 3 months until death, withdrawal of consent, or closure of the study by the Sponsor.

The study visits are listed in the Schedule of Assessments and Schedules for PK sample collection and ECG monitoring (Table 8, Table 9, and Table 10).

Part 1 (Dose Escalation)

The dose escalation part of the study will enroll patients with unresectable GIST or a relapsed or refractory solid tumor. Patients with GIST must have disease that has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase-inhibitor agent, or disease with a D842 mutation in the PDGFRα gene. Patients with an advanced solid tumor other than GIST must have relapsed or refractory disease without an available effective therapy. A standard 3+3 dose-escalation design using cohorts of 3 patients will be employed.

The first cohort of patients will receive BLU-285 at a starting dose of 30 mg QD. The dose escalation increment for the first escalation step will be a maximum of 100%; all subsequent dose escalation increments will be a maximum of 50%.

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

In cohorts in which the administered dose is < 100 mg QD, enrolled patients may have the diagnosis of either GIST or a relapsed/refractory solid tumor. To assure that the safety

profile of BLU-285 is adequately described in patients with GIST, at least 2 of 3 patients in each cohort (4 of 6 patients if the cohort is expanded) dosed at ≥ 100 mg QD must have the diagnosis of GIST.

The specific dose for each subsequent cohort will be determined at a dose-escalation meeting by teleconference that includes the Study Investigators and the Sponsor's study team (including but not limited to the study physician and clinical study manager). The dose must be agreed to by the study investigator at each study center and the Sponsor Clinical Study Team. Dose-escalation meetings will occur after all patients in the current cohort have completed at least 28 days of observation after their first dose of BLU-285, or have experienced a DLT. Patients enrolled into enrichment cohorts at lower dose levels need not have completed 28 days of observation for a dose-escalation meeting to occur.

Dose escalation will continue until the MTD or a RP2D below the MTD has been determined. In addition, based on evaluation of the data, alternative dosing regimens (e.g., twice daily [BID]) or schedules (e.g., 3 weeks on, 1 week rest) may be explored.

Additional details on the dose-escalation process, estimation of the MTD/RP2D, and DLTs are provided in Section 6.4.

Expansion (Part 2)

Once the MTD or RP2D has been determined, 3 groups of patients with the following characteristics will be enrolled and treated with BLU-285:

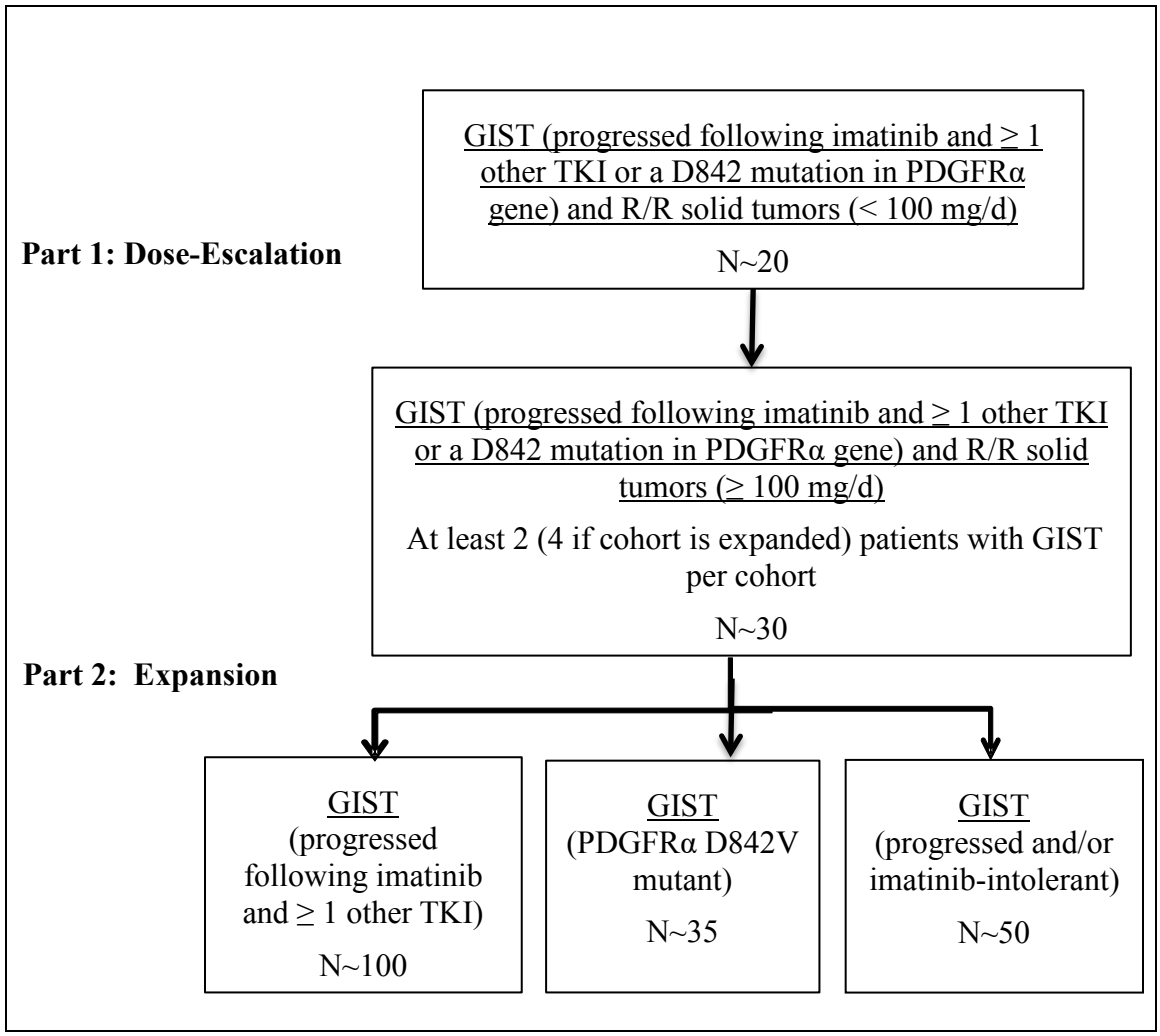
- Group 1: Patients with unresectable GIST that has progressed following treatment with imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase-inhibitor therapy and who do not have a D842V mutation in PDGFRα (N~100).

- Group 2: Patients with unresectable GIST harboring a D842V mutation in the PDGFRα gene (N~35). The PDGFRα mutation will be identified by local and central assessment, either in archival tissue or a new tumor biopsy obtained, prior to treatment with BLU-285.

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

Patient safety will be reviewed on an ongoing basis (approximately every 1 – 2 months) at a safety review meeting that includes the Study Investigators and the Sponsor Clinical Study Team. All safety data collected to date will be reviewed to confirm that no unexpected, significant, or unacceptable risks have been discovered. Available tumor response, PK, and PD data will also be reviewed.

4.2 Study Schematic



Abbreviations: GIST = gastrointestinal stromal tumor; PDGFRα = platelet-derived growth factor receptor alpha; R/R = relapsed/refractory; TKI = tyrosine kinase inhibitor.

5 POPULATION

5.1 Number of Patients

Approximately 235 patients will be enrolled in this study, including:

- Part 1 (Dose Escalation):
    - Approximately 50 patients with unresectable GIST or other advanced solid tumors.
- Part 2 (Expansion):
    - Group 1: Approximately 100 patients with unresectable GIST that has progressed following treatment with imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase-inhibitor therapy and who do not have a known D842V mutation in PDGFRα.
    - Group 2: Approximately 35 patients with unresectable GIST harboring a D842V mutation in the PDGFRα gene. The PDGFRα mutation will be identified by local and central assessment, either in archival tissue or a new tumor biopsy obtained, prior to treatment with BLU-285.
    - Group 3: Approximately 50 patients with unresectable GIST that has progressed and/or those who have experienced intolerance following treatment with imatinib (including in the adjuvant setting) and have not received additional kinase-inhibitor therapy and do not have a known D842V mutation in PDGFRα.

The total number of patients to be enrolled in Part 1 is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to identify the MTD, or a lower RP2D for further study in Part 2 if an MTD is not determined.

5.2 Inclusion Criteria

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

1. Patient is ≥ 18 years of age.
2. For Part 1: Histologically- or cytologically-confirmed diagnosis of unresectable GIST or another advanced solid tumor. Patients with unresectable GIST must have disease that has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase-inhibitor agent, or disease with a D842 mutation in the PDGFRα gene. Patients with an advanced solid tumor other than GIST must have relapsed or refractory disease without an available effective therapy.

- At daily doses < 100 mg QD patients may have the diagnosis of either GIST or a relapsed or refractory solid tumor.

- At daily doses ≥ 100 mg QD, at least 2 patients in a cohort (4 patients if the cohort is expanded) must have the diagnosis of GIST.

3. For Part 2:

   - Group 1: Patients must have a confirmed diagnosis of unresectable GIST that has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase-inhibitor agent, and the patient does not have a D842V mutation in PDGFRα.

   - Group 2: Patients must have a confirmed diagnosis of unresectable GIST with a D842V mutation in the PDGFRα gene. The PDGFRα mutation will be identified by local or central assessment, either in an archival tissue sample or a new tumor biopsy obtained prior to treatment with BLU-285.

   - Group 3: Patients must have a confirmed diagnosis of unresectable GIST that has progressed and/or patients must have experienced intolerance to imatinib and not received additional kinase-inhibitor therapy. Patients must not have a known D842V mutation in PDGFRα.

   - Groups 1, 2, and 3: At least 1 measurable lesion defined by the mRECIST version 1.1 for patients with GIST (Appendix 1).

   - Groups 1 and 2: A tumor sample (archival tissue or a new tumor biopsy) has been submitted for mutational testing.

4. Patient has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2.

5. Patient or legal guardian, if permitted by local regulatory authorities, provides informed consent to participate in the study.

5.3 Exclusion Criteria

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

1. Patient has any of the following within 14 days prior to the first dose of study drug:

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

   b. Total bilirubin > 1.5 × ULN; > 3 × ULN with direct bilirubin > 1.5 × ULN in the presence of Gilbert's Disease.

c. Estimated (Cockcroft-Gault formula) or measured creatinine clearance < 40 mL/min.

d. Platelet count < 90×10^9/L.

e. Absolute neutrophil count (ANC) < 1.0×10^9/L.

f. Hemoglobin (Hgb) < 9 g/dL. Transfusion and erythropoietin may be used to reach at least 9 g/dL, but must have been administered at least 2 weeks prior to the first dose of study drug.

2. Patient received a prior anti-cancer drug less than 5 half-lives or 14 days (whichever is shorter) prior to the first dose of study drug.

3. Patient has received neutrophil growth factor support within 14 days of the first dose of study drug.

4. Group 3: Patients known to be KIT wild type.

5. Patient requires therapy with a concomitant medication that is a strong inhibitor or strong inducer of cytochrome P450 (CYP) 3A4 (see Appendix 2).

6. Patient has had a major surgical procedure (minor surgical procedures such as central venous catheter placement, tumor needle biopsy, and feeding tube placement are not considered major surgical procedures) within 14 days of the first dose of study drug.

7. Patient has a history of another primary malignancy that has been diagnosed or required therapy within 1 year prior to the first dose of study drug. (The following are exempt from the 1-year limit: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ of any site.)

8. Patient has a QT interval corrected using Fridericia's formula (QTcF) > 450 milliseconds.

9. Patient has a history of a seizure disorder (e.g., epilepsy) or requirement for anti-seizure medication.

10. Patient has a history of a cerebrovascular accident or transient ischemic attacks within 1 year prior to the first dose of study drug.

11. Patient has a known risk of intracranial bleeding, such as a brain aneurysm or history of subdural or subarachnoid bleeding.

12. Patient has a primary brain malignancy or metastases to the brain.

13. Patient has clinically significant, uncontrolled, cardiovascular disease, including congestive heart failure Grades II, III or IV according to the New York Heart

Association classification, myocardial infarction or unstable angina within the previous 6 months, or poorly controlled hypertension.

14. Patient has a known diagnosis of human immunodeficiency virus infection or active viral hepatitis; viral testing is not required.

15. Patient is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures and study restrictions.

16. Women who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least 30 days after the last dose of study drug. Refer to Section 9.6 for acceptable methods of contraception.

17. Pregnant women as documented by a serum beta human chorionic gonadotropin (β-hCG) pregnancy test consistent with pregnancy obtained within 7 days prior to the first dose of study drug. Women 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 excluded. Women of non-childbearing potential (postmenopausal; hysterectomy; bilateral salpingectomy; or bilateral oophorectomy) do not require a serum β-hCG pregnancy test.

18. Women who are breast feeding.

19. Patient has a prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the Investigator's opinion, could affect the safety of the patient, alter the absorption, distribution, metabolism or excretion of the study drug, or impair the assessment of study results.

5.4 Patient Identification and Registration

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

During the dose-escalation part, upon identification of an eligible patient, study centers will submit a request to the Sponsor or designee to register each patient for enrollment. Enrollment will be granted based on availability in each dose-escalation cohort. Further instructions will be provided in the study manual.

The Medical Monitor will confirm eligibility for all patients prior to receipt of the first dose of BLU-285.

5.5 Study Completion

Patients will be considered to have completed the study if they withdraw from the study for any of the criteria listed in Section 5.6.

5.6 Patient Withdrawal Criteria

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

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

- Withdrawal of consent.
- AE.
- Disease progression.
- Death.
- Investigator decision.
- Protocol deviation.
- Pregnancy.
- Lost to follow-up.

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

All AEs should be followed until resolution or for a period of 30 days from the last dose of study drug, whichever is shorter. If a patient withdraws from treatment because of an AE, every effort must be made to perform protocol-specified safety follow up procedures, as outlined in Section 7.6.

In the event a patient is withdrawn from study drug or the follow-up phase 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.

5.7 Replacement of Patients

Part 1: In order to be evaluable for DLT assessment, each patient in a cohort must have received at least 75% of their prescribed BLU-285 doses in C1 (i.e., ≥ 21 doses) and completed follow-up safety evaluations through C1D28 or experienced a DLT. Patients

not evaluable for DLT assessment will be replaced to ensure that data are available from 3 or 6 evaluable patients (as required for that cohort) prior to the dose-escalation meeting.

Part 2: Patients may be added in order to have 100 antitumor assessment-evaluable patients in Group 1, 31 antitumor assessment-evaluable patients in Group 2, and 50 antitumor assessment-evaluable patients in Group 3, as defined in Section 4.1. Safety data will be collected for all patients, whether or not they are evaluable for antitumor assessments.

6 STUDY CONDUCT

6.1 General Conduct

The study will be conducted at multiple study centers in the United States (US), European Union (EU), and Asia.

The schedule of assessments for the study is provided in Table 8, Table 9, Table 10 and Table 11.

The end of the study is defined as the time that the last patient completes his/her last visit, including assessments performed as a part of PSF follow-up, if the patient enters the PFS follow-up part of the study. See Table 8 for details of all study assessments.

6.2 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.
- Failure to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Plans to modify, suspend, or discontinue the development of study drug.
- Other administrative reasons.

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

6.2.1 Rules for Early Termination of Enrollment in Dose Expansion

To help ensure patient safety, the study incorporates an enrollment stopping rule that terminates further enrollment in Part 2, Group 3 if there is an excess of permanent treatment discontinuations due to study drug-related AEs.

After 10 patients in Group 3 of Part 2 have received at least 1 dose of BLU-285, the rate of permanent treatment discontinuations due to drug-related AEs will be assessed at least every 3 months.

Adverse events meeting all of the following criteria will be included in the assessment:

- The AE is considered drug-related and is the reason for permanent discontinuation of treatment;
- The AE is Grade ≥3 or meets the criteria for DLT (including events that meet the criteria for DLT but occur after C1);
- The AE occurred after the first dose of study drug, but prior to initiation of a subsequent anticancer therapy;
- The AE occurred at a dose that does not exceed the MTD.

Further enrollment to Group 3 of Part 2 will be terminated if the lower bound of the 1-sided 70% exact binomial confidence interval of the discontinuation rate due to AE is >15%.

Table 4 below presents the operating characteristics for the early study termination assessment.

Table 4: Examples of Implementing the Early Stopping Rule

Number of Patients Discontinued due to Study Drug Related Adverse Events	Number of Patients Treated	70% Exact Binomial CI, 1-sided lower bound	Action
2	10	10.9%	No stop
3	10	19.26%	Stop
3	15	12.8%	No stop
4	15	18.6%	Stop
4	20	13.9%	No stop
5	20	18.36%	Stop
7	40	13.64%	No stop
8	40	15.93%	Stop

In addition, the study implements early stopping rules that terminate enrollment due to lack of treatment effect in Group 3 of Part 2. Early stopping due to lack of treatment effect will be assessed using mRECIST version 1.1 response (CR+PR) rate. For Group 3 of Part 2, it is assumed that a true response rate ≥15% is clinically meaningful and that the probability of observing at least 2 responders among 20 patients is about 82%. If after 20 patients have had at least one post baseline mRECIST version 1.1 response assessment, ≥2 responders (including an unconfirmed response in a patient who remains on treatment) are observed, the study will continue to the full enrollment of 50 patients, otherwise enrollment will be discontinued due to lack of efficacy.

6.3 Dose and Administration

BLU-285 will be administered PO, QD, in the morning, on D1 to 28 in 28-day cycles. In order to better evaluate the half-life of BLU-285, which is predicted to be long, patients in Part 1 (Dose Escalation) will participate in a 3-day PK-Lead in stage. For patients in Part 1, a single dose of BLU-285 will also be administered on Day-3 (the same dose as the patient's assigned cohort dose). Patients will return on days -2, -1, and 1 (24, 48 and 72 hours after study drug administration) for PK sampling, and will not receive BLU-285 on days -2 and -1. Dosing will be continuous, with no inter-cycle rest periods. If warranted based on the emerging data, alternative dosing regimens (e.g., BID) or intermittent dosing (e.g., 3 weeks on, 1 week off) schedules may be explored. Patients will be dispensed the appropriate number of Sponsor-packaged, labeled bottles on D1 of each cycle to allow dosing for 28 days; alternatively, patients may be dispensed the appropriate bottle(s) until the next scheduled visit. Patients must return all unused capsules (or the empty bottles) at each scheduled visit.

BLU-285 doses should be administered with a glass of water (at least 8 ounces or 250 mL) in a fasted state, with no food intake from 2 hours before until 1 hour after study drug administration. Each dose should be administered at approximately the same time each day. Patients should be instructed to swallow capsules whole and to not chew the capsules. Patients should be instructed to avoid proton pump inhibitors and H_2-receptor antagonists. Furthermore, antacids should not be taken within 3-4 hours before or after BLU-285 administration.

On study day clinic visits, patients will take their dose of BLU-285 in the study clinic under observation.

If the patient forgets to take their morning dose, he/she should take BLU-285 by 4 pm that day (the BLU-285 dose should be administered with a glass of water in a fasted state, with no food intake from 2 hours before until 1 hour after study drug administration). If the dose has not been taken by 4 pm, then that dose should be omitted and the patient should resume treatment with the next scheduled dose, the following morning. If a patient vomits during or after taking their BLU-285, re-dosing is not permitted until the next scheduled dose.

A temporary discontinuation (up to 2 weeks) in BLU-285 dosing is allowed for patients who require an interruption (e.g., for surgery or other procedure) during the treatment period. BLU-285 should be discontinued 48 hours before the procedure and resumed 48 hours after the procedure is completed.

6.4 Guidelines for Dose Escalation

Dose-escalation decisions will be made by the Study Investigators and Clinical Study Team.

The dose escalation part of the study (Part 1) will enroll patients with GIST or a relapsed or refractory solid tumor. A 3+3 dose-escalation design using cohorts of 3 patients will be employed.

The first cohort of patients will receive BLU-285 at a starting dose of 30 mg QD. The dose escalation increment for the first escalation step will be a maximum of 100%. However, if ≥ 1 patient treated at the starting dose level has a ≥ Grade 2 non-hematologic AE or a ≥ Grade 3 hematologic AE and the AE (non-hematologic or hematologic) is not clearly attributable to a cause other than BLU-285, then the maximum dose escalation increment for the first escalation step will be 50%. All subsequent dose escalation increments will be a maximum of 50%.

Three patients will be enrolled initially in each cohort and an additional 3 patients (for a total of 6) will be enrolled should the cohort require expansion due to a DLT. After the current escalation cohort is full, up to 3 additional patients, all of whom must have the diagnosis of GIST, may be enrolled into an enrichment cohort that included only 3 patients evaluable for DLT, was reviewed at a dose-escalation meeting, and did not exceed the MTD. Enrollment of patients into an enrichment cohort requires written approval from the Sponsor. Data from these patients will allow for further exploration of PK, PD, and safety in patients with GIST. Dose-limiting toxicities occurring in patients enrolled into enrichment cohorts will be included in the assessment of the MTD as described in Table 5.

If the second or third patients enrolled in the first cohort of the study are enrolled at a site in the UK, those patients may only be dosed if there is no safety concern at least 24 hours after the first patient was dosed.

In cohorts in which the administered dose is < 100 mg QD, enrolled patients may have the diagnosis of either GIST or a relapsed/refractory solid tumor. To assure that the safety profile of BLU-285 is adequately described in patients with GIST, at least 2 of 3 patients in each cohort (4 of 6 patients if the cohort is expanded) dosed at ≥ 100 mg QD must have the diagnosis of GIST.

Dose escalation will continue until the MTD or a RP2D below the MTD has been determined. In addition, based on evaluation of the data, alternative dosing regimens (e.g., BID) or schedules (e.g., 3 weeks on, 1 week rest) may be explored.

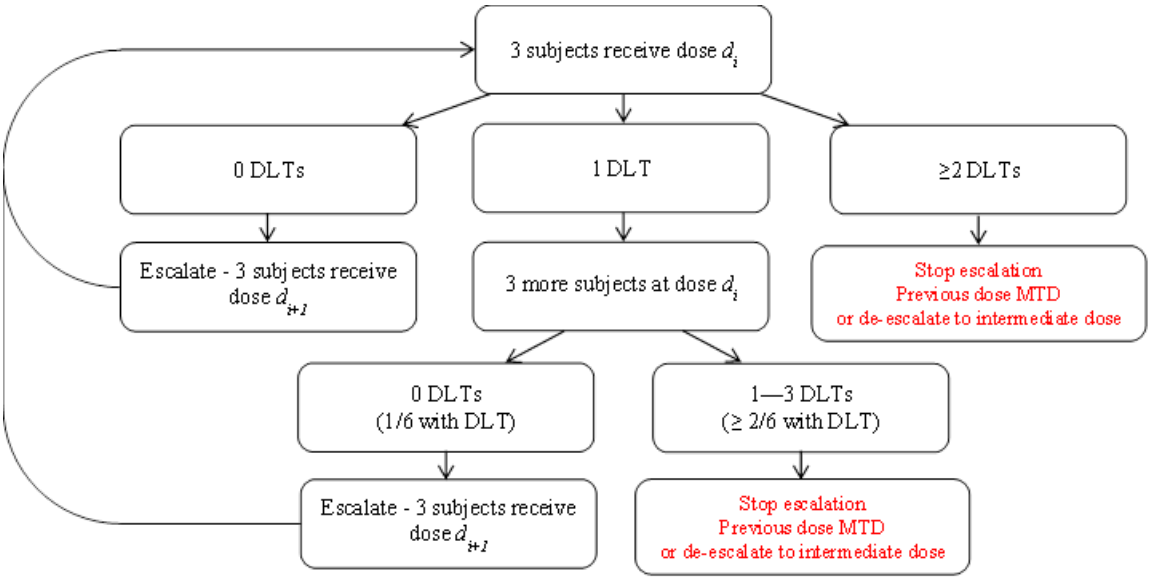
A summary of the dose-escalation scheme is presented Table 5 and Figure 3. Provisional dose-escalation levels are presented in Table 6.

Table 5: Dose-escalation Scheme

No DLT	Escalate by ≤ 50% to next dose level (≤ 100% for the first escalation step)
1 DLT in 3 patients	Expand cohort up to 6 patients
1 DLT in 6 patients	Escalate by ≤ 50% to next dose level (≤ 100% for the first escalation step)
> 1 DLT in ≤ 6 patients (including patients enrolled into enrichment cohorts)[a]	Stop dose escalation Expand highest prior dose level to 6 evaluable patients, if 6 evaluable patients not already treated Highest prior dose with ≤ 1 DLT in 6 patients is MTD Possibly explore lower doses to determine RP2D

Abbreviations: DLT = dose-limiting toxicity, MTD = maximum tolerated dose, RP2D = recommended Phase 2 dose.
[a] If a DLT in an enrichment patient results in a second DLT in 6 patients at a prior dose level, escalation will stop and the dose level with > 1 DLT will have exceeded the MTD.

Figure 3: Dose-escalation Schematic



Abbreviations: d_i = initial dose, d_{i+1}= 1 level above the initial dose, DLT = dose-limiting toxicity, MTD = maximum tolerated dose.

Table 6: Provisional Dose-escalation levels

Dose Level Cohort	Dose (mg)	% Change from Previous Dose Level
-2	10	-50%
-1	20	-33%
1 (starting Dose Level)	30	-
2[a]	60	100%

Dose Level Cohort	Dose (mg)	% Change from Previous Dose Level
3	90	50%
4	135	50%
5[b]	200	48%

[a] Dose level 2 is limited to ≤ 1.5 times dose level 1 if ≥ 1 patient treated at dose level 1 has a ≥ Grade 2 non-hematologic AE or a ≥ Grade 3 hematologic AE and the AE (non-hematologic or hematologic) is not clearly attributable to a cause other than BLU-285.
[b] Subsequent escalations are ≤ 1.5 times the prior dose.

6.4.1 Intra-patient Dose Modification

To minimize the number of patients treated at potentially inactive doses, intra-patient dose escalation may be permitted after a patient has completed ≥ 2 cycles of treatment without experiencing Grade ≥ 3 toxicity. The patient's dose may then be escalated to a dose that has been reviewed at a dose-escalation meeting and does not exceed the MTD. Intra-patient dose escalation requires written approval from the Sponsor.

6.4.2 Dose Limiting Toxicity

Dose-limiting toxicity is defined as any treatment-emergent AE of Grade ≥ 3 occurring during C1 and not clearly attributable to a cause other than BLU-285, with the following exceptions:

- Thrombocytopenia is a DLT only if it is Grade 4 and persists > 3 days or Grade 3 and associated with bleeding.
- Neutropenia is a DLT only if it is Grade 4 and either persists > 3 days or is of any duration and requires growth factor support.
- Anemia is a DLT only if it is Grade 4.
- Lymphopenia is a DLT only if it is Grade 4 and persists > 7 days.
- Nausea is a DLT only if it is Grade 3 and persists > 3 days despite therapy.
- Vomiting is a DLT if it is Grade 4, or Grade 3 and persists > 3 days despite therapy.
- Diarrhea is a DLT only if it is Grade 4, or Grade 3 and persists > 3 days despite therapy.
- Total bilirubin Grade ≥ 2 is a DLT if associated with ALT ≥ Grade 2.
- Infection is a DLT if it is Grade 4 or if it is Grade 3 and persist > 7 days.
- Fever in the absence of neutropenia is a DLT if it is Grade 4 despite antipyretic therapy.

- Abnormalities of serum calcium, magnesium, and phosphate are DLTs only if they are Grade 4, or Grade 3 and the patient is clinically symptomatic, requires hospitalization, or if the specific abnormality is not able to be corrected to Grade ≤ 2 within 3 days.

- Fatigue is a DLT only if it is Grade 3 and persists > 7 days.

- Other clinically important AEs that do not meet the specified DLT criteria may be considered to be a DLT upon review at a Dose-escalation meeting.

6.4.3 Dose Modifications

BLU-285 will be administered PO at a starting dose of 300 mg QD in continuous 28-day cycles. If the treating investigator considers it to be in the patient's best medical interest. the dose may be increased to 400 mg QD under the following circumstances:

- The patient has received two or more cycles of BLU-285 without any treatment-related AEs ≥ Grade 3 (unless the AE has resolved to Grade 1 or less), and without any cognitive, mood or intracranial bleeding AEs ≥ Grade 2 (regardless of resolution), and there is evidence of tumor increase.

- The patient has received four or more cycles of BLU-285 without any treatment-related AEs ≥ Grade 3 (unless the AE has resolved to Grade 1 or less), and without any cognitive, mood or intracranial bleeding AEs ≥ Grade 2 (regardless of resolution), and the patient has not had a PR or CR.

Dose reduction guidelines for BLU-285-related toxicity are summarized in Table 7. These guidelines for dose reductions should be followed by clinical investigators; however, for an individual patient, dose interruptions, reductions, and treatment discontinuation should also be based on clinical circumstances. Adverse events should be graded according to NCI CTCAE, v4.03. Deviation from these guidelines must be documented and communicated with the Sponsor.

It is recommended that patients with hematologic AEs (neutropenia, thrombocytopenia and anemia) of Grade 4 be evaluated at least twice-weekly and those with non-hematologic toxicity of Grade 3 or worse be evaluated at least once-weekly until resolution of the AE(s).

A maximum of 3 dose reductions are permitted; no dose reductions are permitted below the 100 mg daily dose level.

In case of dose re-escalation due to resistance or loss of response, the Sponsor must be contacted and must provide written approval for the patient to continue on treatment and to be escalated to the next dose level.

Table 7: Dose Modification Guidelines for BLU-285-related Toxicity

Toxicity	Modification
General	
Grade 1 or Grade 2	• No dose modification required
Grade 3 or Grade 4 of any duration	• Hold until event is Grade 2 or less, or has returned to baseline, and then resume by reducing the dose by 100 mg less than the current dose • If the patient is already receiving a dose of 100 mg QD, and continued treatment is considered in the best interest of the patient due to the underlying GIST, treatment may be resumed at 100 mg, after the adverse event has improved to Grade 2 or less
Cognitive or mood effects[a]	
Grade 1 with only mild impairment	• No dose modification required
Grade 1, other than mild 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 not required, 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 while still at Grade 2, if continued treatment is considered in the best 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 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 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 interest of the patient due to the underlying GIST, treatment may be resumed at 100 mg, after the cognitive effect has improved to Grade 2 or less

Toxicity	Modification
Intracranial Bleeding	
Grade 1	• Interrupt dosing for a minimum of 7 days, and re-image brain. • Resume dosing without dose reduction, if the bleed is stable or improving, and continued treatment is considered in the best interest of the patient due to the underlying GIST.
Grade 2	• Interrupt dosing for a minimum of 14 days and re-image brain. • Resume dosing with a dose reduction of 100 mg when the intercranial bleeding has improved to Grade 1 or less, or while still at Grade 2, if continued treatment is considered in the best 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 interest of the patient due to the underlying GIST, treatment may be resumed at 100 mg
Grade 3-4	• Permanently discontinue BLU-285 treatment.

Abbreviations: GIST = gastrointestinal stromal tumor; QD = once daily
[a] Changes in cognition, memory, attention, mood, or speech (thought to originate in the central nervous system).

6.4.4 Maximum Tolerated Dose

The MTD is defined as the highest dose level at which ≤ 1 patient experiences DLTs in C1 during Part 1 of the study. At least 6 patients must be treated at this dose in order to determine that it is the MTD.

6.4.5 Recommended Phase 2 Dose

The RP2D will not exceed the MTD and will be determined at a dose-escalation meeting during Part 1 of the study. Additionally, observations related to PK, PD, and any cumulative toxicity observed after multiple cycles may be included in the rationale supporting the RP2D below the MTD. If an MTD is not identified, then PK, PD, and safety data, along with pertinent non-clinical data suggestive of a dose-effect relationship, will be used to define a RP2D. Six patients must be treated at this dose in order to confirm that it is the RP2D.

6.4.6 Alternate Dosing Schedule

Alternate dosing schedules, such as BID and intermittent dosing may be evaluated if supported by PK, PD, safety, or efficacy data. A decision to change the treatment schedule, including the choice of a starting dose for the new schedule, will only occur after agreement has been reached among the study Investigators at each study center and the Sponsor Clinical Study Team; should any of these people not have attended the meeting, approval will be obtained in writing. The protocol will be amended prior to evaluating new dosing schedules.

6.5 Prior and Concomitant Therapy

All medications administered and procedures within 28 days of the first dose of study drug should be recorded on the eCRF. In addition, all prior treatments for the underlying malignancy should be recorded.

6.5.1 Prohibited Concomitant Therapy

- In vitro studies with recombinant human CYP enzymes demonstrated that BLU-285 phase I metabolism is predominantly mediated by CYP3A4, with CYP2C9 playing a minor role. Therefore, concomitant treatment with drugs that are strong CYP3A4 inhibitors or strong CYP3A4 inducers is prohibited (refer to Appendix 2 for a list of strong CYP3A4 inhibitors and inducers).

- Any investigational agent or device other than BLU-285.

- Any antineoplastic agent other than study drug.

- Neutrophil growth factor support is prohibited within 14 days prior to the first dose of study drug and throughout C1, unless the patient experiences a DLT of neutropenia.

Radiation therapy to target lesions or surgical removal of target lesions is considered indicative of progressive disease.

6.5.2 Concomitant Therapy to be used with Caution

In vitro, BLU-285 is a reversible inhibitor of CYP2C8, CYPC9, and CYP3A4/5 at clinically relevant concentrations ([I]/Ki > 0.1). BLU-285 also has demonstrated time-dependent inhibition of CYP3A4/5 in vitro with an estimated K_{inact} and K_I of 0.0301 min^{-1} and 12.3 μM, respectively. Therefore, clinical drug-drug interactions with comedications for which CYP2C8, CYP2C9, or CYP3A-mediated metabolism constitutes the primary mechanism of clearance is likely. In vitro, BLU-285, at concentrations of 0.3 to 3 μM, induced CYP3A4 mRNA expression with a maximal 3.25-fold induction observed at 3 μM.

In vitro, BLU-285 is an inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), and multidrug and toxin extrusion protein (MATE1, MATE2K). Therefore, BLU-285 may have the potential to increase plasma concentrations of co-administered substrates of these transporters. Medications that are CYP2C9, CYP3A4, or BCRP substrates with a narrow therapeutic index should be used with caution (refer to Appendix 3 for a list of these medications).

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

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

6.5.3 Permitted Concomitant Therapy

Medications and treatments other than those specified in Section 6.5.1 and Section 6.5.2, including palliative and supportive care for disease-related symptoms are permitted during the study.

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

Antiemetic 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. During Part 1 of the study prophylaxis for nausea or vomiting may be instituted beginning on C2D1 in patients who experience these toxicities during C1, and during C1 for patients who experienced a DLT of nausea or vomiting. During Part 2 of the study, prophylaxis for nausea and vomiting may be instituted at the Investigator's discretion. Anti-diarrhea medications may also be used at the Investigator's discretion.

6.6 Additional Precautions

The light absorption characteristics of BLU-285 suggest the possibility the BLU-285 treatment will be associated with phototoxicity. Therefore, patients should use clothing and sunscreen to avoid direct sun exposure.

Table 8: Schedule of Assessments

Study Activities[a]	**Screening**	**Study Treatment**											**EOT[c]**	**Safety Follow-up**	**PFS Follow-up[d]**
Cycle		**PK Lead-in[b]**			**C1**					**C2**		**≥ C3**			
Study Day	**-59 to -4[e] -56 to -1**	**D-3**	**D-2**	**D-1**	**D1**	**D2**	**D8[f]**	**D15**	**D22[f]**	**D1**	**D15[f]**	**D1**	**14 days post last dose**	**30 days post last dose[g]**	**Every 3 months after Safety F/U**
Window (Days)							**±1**	**±2**	**±2**	**+3[h]**	**±3**	**±7**	**±7**	**±7**	**±14**
Informed consent	X														
Inclusion/Exclusion criteria	X														
Demographics	X														
Medical history[i]	X														
Physical examination[j]	X	X[k]			X[l]		X	X	X	X	X	X	X		
Vital signs[m]	X	X[k]			X[l]	X[l]	X	X	X	X	X	X	X		
Serum Pregnancy (β-hCG) test[n]	X											X			
Performance status (ECOG)[dd]	X	X[k]			X[l]		X	X	X	X	X	X	X		
12-lead ECG/ECG extraction from Holter monitor	X	Refer to Table 9, Table 10, and Table 11 for ECG schedule.													
Hematology[o]	X	X[k,p]			X[l,p]		X	X[q]	X	X	X	X	X		
Coagulation[r]	X	X[k,p]			X[l,p]		X	X[q]	X	X	X	X	X		

Study Activities[a]	**Screening**	**Study Treatment**											**EOT[c]**	**Safety Follow-up**	**PFS Follow-up[d]**
Cycle		**PK Lead-in[b]**			**C1**					**C2**		**≥ C3**			
Study Day	**-59 to -4[e] -56 to -1**	**D-3**	**D-2**	**D-1**	**D1**	**D2**	**D8[f]**	**D15**	**D22[f]**	**D1**	**D15[f]**	**D1**	**14 days post last dose**	**30 days post last dose[g]**	**Every 3 months after Safety F/U**
Window (Days)							**±1**	**±2**	**±2**	**+3[h]**	**±3**	**±7**	**±7**	**±7**	**±14**
Serum chemistry[s]	X	X[k,p]			X[l,p]		X	X[q]	X	X	X	X	X		
Urinalysis	X	X[k,p]			X[l,p]								X		
BLU-285 administration[t]		X			X										
PK Blood Samples[u]		X	X	X	X[cc]	X[l]		X		X		X			
Plasma Sample for Biomarkers[v]		X[p]			X[p]			X[cc]		X		X	X		
Tumor sample[w]	X												X		
Tumor Imaging[x]	X											X	X		X[y;]
MRI or CT of the brain[z]	X									X		X[z]			
AE Monitoring[aa]		X													
SAE Monitoring[bb]	X														
Concomitant medications[bb]	X														

Abbreviations: AE = adverse event, ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; C = cycle, CT = computed tomography, D = day, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = end-of-treatment, F/U = follow-up; GIST = gastrointestinal stromal tumor; Hgb = hemoglobin; mRECIST = Response Evaluation Criteria in Solid Tumors modified for patients with GIST; MRI = magnetic resonance imaging, PFS = progression-free survival, PD = pharmacodynamic(s), PK = pharmacokinetic(s), QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; ULN = upper limit of normal.

Note: Every effort should be made to keep the schedule of assessments on time for each patient.

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 (e.g., 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 The PK lead-in stage will occur during Part 1.
c If an alternate treatment is to be started within 14 days after the last study drug dose, the EOT visit should be conducted prior to the first dose of alternate therapy. End-of-treatment procedures do not need to be repeated if they were completed within 7 days (or within 28 days for disease response assessments).
d After completing the Safety Follow-up, patients are to be followed every 3 months (±14 days) until death, withdrawal of consent, or closure of the study by the Sponsor.
e Screening will occur from D-59 through D-4 for patients in Part 1 and from D-56 through D-1 for patients in Part 2.
f Only Part 1. These visits are not required for patients enrolled in Part 2 of the study.
g The 30-day Safety Follow-up may be performed by phone.
h In the event that a patient requires a delay up to 14 days (e.g., for toxicity), this visit can be delayed for up to 14 days.
i 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.
j A complete physical examination including weight, height, 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 the GIST (or relapsed or refractory solid tumor), changes from previous physical examinations, neurologic, mental status, and mood examinations, and AEs. Complete physical examinations should be completed by all patients on Day 1 of each cycle through and including Cycle 13. After Cycle 13, physical examinations will be performed every 3 cycles (C16D1, C19D1, etc.), and at EOT.
k Only Part 1; these values will be considered "Baseline" and do not need to be repeated on D1.
l Only Part 2 Group 1 and 2 patients.
m Vital signs include temperature, pulse, and systolic/diastolic blood pressure. Vital signs should be completed by all patients on Day 1 of each cycle through and including Cycle 13. After Cycle 13, vital signs will be performed every 3 cycles (C16D1, C19D1, etc.), and at EOT.
n To be performed for women of child-bearing potential. Baseline is to be obtained within 7 days of the first dose of study drug (D -3 for patients in Part 1; C1D1 for patients in Part 2) and on D1 of every odd numbered cycle (e.g., C3, C5) through and including Cycle 13. After Cycle 13, pregnancy test will be performed every 3 cycles (C16D1, C19D1, etc.), and at EOT. For Belgium and Poland only, pregnancy test will be performed on D1 of every cycle.
o Hematology parameters to be measured include Hgb, white blood cell (WBC) with differential count, and platelet count. On days when safety ECGs are to be obtained in the clinic, the ECG will be acquired within 2 hours prior to the collection of the blood sample. Hematology testing should be completed by all patients on Day 1 of every cycle through and including Cycle 13. After Cycle 13, hematology testing will be completed every 3 cycles (C16D1, C19D1, etc.), and at EOT.
p Baseline (D-3 for patients in Part 1; C1D1 for patients in Part 2) safety laboratory tests and samples for PD markers are to be obtained within 7 days before the first study drug dose. Should Screening tests occur within 7 days of D-3 (Part 1) or C1D1 (Part 2), they do not need to be repeated.
q Only Part 1. These assessments are not required for patients enrolled in Part 2.
r Coagulation studies include international normalized ratio (INR) and activated partial thromboplastin time (aPTT). If they are within the normal range through C3D1 then they can be discontinued and obtained only as clinically indicated.

s The comprehensive serum chemistry panel includes sodium, potassium, blood urea nitrogen (BUN) or urea, bicarbonate (venous), creatinine, calcium, chloride, magnesium, phosphorus, albumin, AST, ALT, alkaline phosphatase (ALP), and total bilirubin (direct bilirubin if total bilirubin is > ULN). Comprehensive serum chemistry panel should be completed by all patients on Day 1 of every cycle through and including Cycle 13. After Cycle 13, serum chemistry testing will be completed every 3 cycles (C16D1, C19D1, etc.), and at EOT.

t BLU-285 will be administered QD in the morning at least 2 hours after and 1 hour before eating. On study visit days when PK samples are collected, patients will take their dose of BLU-285 under observation at the study clinic after the pre-dose (trough) PK sample has been obtained.

u PK sampling will be performed as specified in Table 9 (Part 1), Table 10, and Table 11 (Part 2). Additionally, Investigators may obtain blood samples for PK analysis at the time(s) that significant drug-related AEs and SAEs occur.

v Plasma samples for biomarkers are drawn at baseline, C1D15, C2D1, C3D1, every odd cycle post C3 until and including C11 and EOT for Groups 1 and 2 (Part 2). Plasma samples for biomarkers are drawn at baseline, C2D1, C3D1, every odd cycle post C3 until and including C11 and EOT for Group 3 (Part 2). See Table 12 for further details regarding schedule of PD sample acquisition.

w Archival or new tumor biopsy samples required for Part 2 Group 1 and 2 patients. Archival or new tumor biopsy samples optional for Part 2 Group 3 patients. For further details refer to Table 12.

x Disease response assessment (per mRECIST version 1.1) will be based on local assessments of computed tomography (CT) / magnetic resonance imaging (MRI) scans. Computed tomography with intravenous (IV) contrast of the chest and CT or MRI with IV contrast of the abdomen and pelvis will be performed at Screening. Imaging of body regions containing sites of disease (target or non-target) will be repeated in all patients on C3D1 and then after every 2 cycles through and including Cycle 13. After Cycle 13, tumor assessment will be performed every 3 cycles (C16D1, C19D1, etc), and at EOT. 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.

y Patients are to be seen in follow-up every up every 3 months to assess their disease status by imaging. Patients will not be required to participate in these visits once they either start a new antineoplastic therapy, or their tumor demonstrates progressive disease.

z MRI or CT of the brain to be performed at screening, C2D1, C3D1, and C4D1.

aa AEs are to be collected from the start of study drug administration through the Safety Follow-up.

bb SAEs and concomitant medications are to be collected from the date of the informed consent signature through the Safety Follow-up.

cc Only Part 1 and Part 2 Group 1 and 2 patients.

dd Performance status will be assessed for all patients on Day 1 of each cycle through and including Cycle 13. After Cycle 13, performance status will be assessed every 3 cycles (C16D1, C19D1, etc.), and at EOT.

Table 9: Pharmacokinetics Sample Collection and ECG Schedule – Part 1

Cycle	**Lead-in**									**C1**							**C2-4**	**EOT**
Day	**D-3**							**D-2**	**D-1**	**D1**	**D15**						**D1**	
Time (hours)	**Pre-dose**	**0.5**	**1**	**2**	**4**	**8**	**10**	**24**	**48**	**72**	**Pre-dose**	**0.5**	**1**	**2**	**4**	**8**	**Pre-dose[a]**	
Window		**±5 min**	**±5 min**	**±5 min**	**±10 min**	**±10 min**	**±15 min**	**± 2 hours**	**± 2 hours**	**± 2 hours**		**±5 min**	**±5 min**	**±5 min**	**±10 min**	**±10 min**		
PK Sampling	X[a]	X	X	X	X	X	X	X	X	X[a]	X[a]	X	X	X	X	X	X	
Standard 12-Lead ECG	X										X						X	X

Abbreviations: C = cycle; D = day; ECG = electrocardiogram; EOT = End-of-treatment; min = minutes; PK = pharmacokinetics.
a Sample to be obtained just prior to BLU-285 administration.

Table 10: Pharmacokinetics Sample Collection and Holter Monitoring/ECG Schedule - Part 2 (Groups 1 and 2)

Cycle	**C1**													**C2 – C4**	**EOT**
Day	**D1**						**D2**	**D15**						**D1**	**≤ 14 days post last dose**
Time (hours)	**Pre-dose[a]**	**0.5**	**1**	**2**	**4**	**8**	**24**	**Pre-dose[a]**	**0.5**	**1**	**2**	**4**	**8**	**Pre-dose[a]**	
Window		**±5 min**	**±5 min**	**±5 min**	**±10 min**	**±10 min**	**± 2 hours**		**±5 min**	**±5 min**	**±5 min**	**±10 min**	**±10 min**		
PK Sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Holter monitoring (for ECG extractions)[b]	X[c]	X	X	X	X	X	X	X	X	X	X	X	X		
Standard 12-lead ECG	X[d]							X[d]						X	X

Abbreviations: C = cycle; D = day; ECG = electrocardiogram; EOT = End-of-Treatment; min = minutes; PK = pharmacokinetics.

a PK sample to be obtained just prior to BLU-285 administration but after ECG acquisition in patients undergoing 12-lead Holter recordings.

b At selected sites ECGs will be extracted in replicates from 12-lead Holter monitor recordings. Instructions for placement of the 12-lead Holter monitors will be provided in a separate manual.

c Three time points will be extracted within 1 hour prior to dosing (e.g., -45 minutes, -30 minutes, -15 minutes).

d Patients not participating in Holter monitoring will have a single standard 12-lead ECG obtained, ≤ 1 hour prior to the blood draw for PK sampling.

Table 11: Pharmacokinetics Sample Collection and ECG Schedule - Part 2 (Group 3)

Cycle	**C1**					**C2 –C4**	**EOT**
Day	**D1**	**D15**				**D1**	**≤ 14 days post last dose**
Time (hours)	**Pre-dose**	**Pre-dose**	**1**	**4**	**6-8**	**Pre-dose**	
Window			**±5 min**	**±10 min**	**±10 min**		
PK Sampling		X	X	X	X	X	
Standard 12-lead ECG	X[a]	X				X	X

Abbreviations: C = cycle; D = day; ECG = electrocardiogram; EOT = End-of-Treatment; min = minutes; PK = pharmacokinetics

a Patients will have a single standard 12-lead ECG obtained, ≤ 1 hour prior to the blood draw for PK sampling.

7 DESCRIPTION OF STUDY PROCEDURES

7.1 Screening

Following informed consent, all patients will participate in screening procedures to determine eligibility within 56 days (8 weeks) prior to dosing on D -3 (for patients participating in the PK lead-in stage [Part 1]) or C1D1 (for patients not participating in the PK lead-in stage [Part 2]).

During Part 2 of the study, all patients must submit a formalin-fixed, paraffin-embedded tumor sample for PDGFRα mutational testing at a central laboratory prior to beginning treatment with BLU-285. The tumor sample may be archival or from a new tumor biopsy. The tumor sample should be submitted as two tissue blocks (preferred) or as 20 unstained slides. Additional details on the sample requirements are described in the laboratory manual. The tumor samples may be submitted under the Tissue Screening ICF, before the Study ICF has been completed, or it may be submitted under the Study ICF.

The following procedures will also be performed at the Screening visit:

- Obtain Informed Consent
- Obtain demographic data, including gender, date of birth/age, race, and ethnicity;
- Complete medical history, including a history of GIST and other malignancies, prior treatments, response to each treatment (if available), and concurrent illnesses.
- Obtain list of concomitant medications
- Complete physical examination, including height, 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.
- ECOG PS
- Obtain tumor samples (mandatory for Part 2, Group 1 and 2 patients only) and send for central laboratory assessment as described above, and in Section 7.4.2.
- Tumor imaging: CT with intravenous (IV) contrast of the chest; MRI with IV contrast or CT with IV contrast of the abdomen and pelvis. If a patient is not tolerant of IV contrast, non-contrast scans may be performed.
- Vital signs including temperature, pulse, and systolic/diastolic blood pressure;
- Single 12-lead ECG.

- Clinical laboratory assessment (hematology, coagulation, serum chemistry, urinalysis).

- Serum pregnancy test (for women of childbearing potential only) within 7 days prior to dosing on D -3 for patients participating in the PK lead-in stage or C1D1 for patients not participating in the PK lead-in stage.

- CT scan or MRI of the brain is required for all patients.

7.2 Safety Assessments

The schedule of safety assessments is described in Table 8. Additional safety assessments may be performed when clinically indicated, at the Investigator's discretion.

7.2.1 Physical Examination

A complete physical examination will be performed at the Screening visit. Subsequent physical examinations will be performed as outlined in Table 8 and will focus on signs and symptoms of GIST (or other solid tumors), AEs, and changes from previous physical examinations.

7.2.2 Eastern Cooperative Oncology Group Performance Status

Determination of ECOG PS will be performed at the time points outlined in Table 8. Please refer to Appendix 4 for ECOG PS scoring.

7.2.3 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 8.

Assessments should be conducted while the patient is seated or supine. Blood pressure is to be obtained in the same position at each visit.

7.2.4 ECGs

A single 12-lead ECG will be obtained for all patients at the time points outlined in Table 9, Table 10, and Table 11.

Twelve-lead ECGs are to be conducted/extracted after at least 5 minutes of recumbency or semi-recumbency.

In Part 2 of the study only, continuous ECG Holter monitoring will be performed in approximately 20 patients at select study centers. Replicate 12-lead ECGs will be extracted from the continuous recording at the time points outlined in Table 10.

Instructions for acquisition of ECG data will be provided in a separate ECG manual.

7.2.5 Clinical Laboratory Tests

Clinical laboratory evaluations will be performed at the local laboratory. Prior to starting the study, the Investigator will provide the Sponsor (or its designee) copies of all laboratory certifications and normal ranges for all laboratory parameters to be performed by that laboratory.

Clinical laboratory evaluations will be conducted at the time points outlined in Table 8. 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[a]:	Hgb, white blood cell with percent differential count, platelet count
Coagulation[a,b]:	International normalized ratio and activated partial thromboplastin time
Serum chemistry[a]:	Sodium, potassium, blood urea nitrogen or urea, bicarbonate (venous), creatinine, calcium, chloride, magnesium, phosphorus, albumin, AST, ALT, alkaline phosphatase, total bilirubin (direct bilirubin if total bilirubin is > ULN)
Urinalysis (dipstick):	pH, specific gravity, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, protein, urobilinogen
Serum pregnancy[c]:	β-hCG

a On days when study drug is to be administered in the clinic, blood must be drawn prior to study drug administration.
b If coagulation tests are within the normal range through C3D1, then beginning in C4 they can be discontinued and obtained only as clinically indicated.
c For women of childbearing potential only, as defined in Section 9.6.

7.2.6 Imaging of the Brain

Imaging of the brain by CT scan or MRI will be performed at screening, C2D1, C3D1 and C4D1, as outlined in Table 8.

7.2.7 Adverse Events and Concomitant Medications

Each patient must be carefully monitored for the development of any AEs throughout the study from the start of study drug administration (or from the time of signing informed consent, for SAEs that are assessed as possibly or probably related to study related procedures) to 30 days after the last dose. In addition, SAEs that are assessed as possibly or probably related to study treatment that occur 30 days post-treatment are also to be reported.

Complete details on AE and SAE monitoring are provided in Section 9 and Section 10.

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

7.3 Pharmacokinetic Assessment

Serial blood samples will be collected at the time points outlined in Table 9 (Part 1) and Table 10 (Part 2, Groups 1 and 2) to determine systemic concentrations of BLU-285, including metabolites when relevant. Sparse blood samples will be collected at the time points outlined in Table 11 (Part 2, Group 3). Additionally, Investigators may obtain blood samples for PK analysis at the time(s) that significant drug-related AEs and SAEs occur.

When the timing of a blood sample coincides with the timing of an ECG measurement or extraction, the ECG will be completed within 1 hour prior to the collection of the blood sample.

The timing of blood samples drawn for BLU-285 concentration determination may be changed if the emerging data indicates that an alternate sampling scheme is needed for better characterization of the BLU-285 PK profile. Moreover, the total number of samples may be decreased if the initial sampling scheme is considered unnecessarily intensive. Should the number of required samples increase, the protocol and informed consent form will be amended.

7.4 Pharmacodynamic / Biomarker Assessment

7.4.1 Blood Samples for Pharmacodynamic / Biomarker Assessment

Blood samples will be collected at the time points outlined in Table 12 to characterize the mutant allele fraction in plasma ctDNA of KIT or PDGFRα at baseline and during treatment with BLU-285, and to measure changes from baseline in the levels of KIT, PDGFRα, and other cancer-relevant mutant allele fractions.

The timing of blood samples drawn for PD/biomarker assessments may be changed based on emerging data. Should the number of required samples increase, a protocol amendment and updated informed consent form will be created and distributed.

Additional details will be provided in a laboratory manual.

7.4.2 Tumor Samples for Biomarker Assessment

To meet the secondary objectives, tumor tissue will be obtained at the time points detailed in Table 12. During Part 2, tumor mutation analysis of an archival tumor sample or new tumor biopsy will be performed by a central laboratory, and a sample must be submitted for PDGFRα D842V testing prior to initiating treatment with BLU-285 for Group 1 and 2 patients only.

For new biopsies, efforts should be made to obtain biopsies from progressing lesions. If a new tumor biopsy is obtained, it should be by core needle biopsy according to local institutional practices and fixed in formalin. If feasible, tumor biopsies will also be obtained at the EOT in patients who discontinue for progression, ideally from progressive lesions.

In addition to the screening central laboratory testing for PDGFRα D842V, tumor tissue will be analyzed centrally for assessment of KIT, PDGFRα and other cancer relevant mutations in a retrospective manner.

Additional exploratory biomarker research may be performed using the plasma sample for exploratory biomarkers, as well as residual tumor tissue samples and material derived from these samples in view of developing new genetic and mechanistic biomarkers to assess the effects of BLU-285 in patients with cancer.

Additional details will be provided in a laboratory manual.

Table 12: Schedule for Pharmacodynamic Biomarker Sample Collection

	Screening	Study Treatment					EOT
Cycle		**PK Lead-In**	**1**		**2**	**≥ 3**	
Day		**Day -3**	**1**	**15**	**1**	**1**	
Tumor Tissue Sample[a]	X[a]						X[b]
Plasma Sample for Biomarkers[c]		X[d]	X[e]	X[f]	X	X	X

Abbreviations: PK = Pharmacokinetic; EOT = End-of-Treatment.

[a] Mandatory submission of a tumor tissue sample at Screening except for Group 3 patients. Archival or new tumor tissue samples are to be collected for patients with GIST to identify the specific KIT or PDGFRα mutations. For patients with KIT mutated GIST, attempt should be made to obtain a new biopsy from a progressing lesion at study entry. Formalin-fixed, paraffin-embedded blocks should be of adequate size to obtain ≥ 10 5 micron sections. If blocks are not available ≥ 10 slides of 5 micron thickness are acceptable.

[b] For patients who have progressive disease at the EOT, additional tumor tissue should be obtained; if feasible, this biopsy should be from a progressing lesion.

[c] Plasma sample for biomarkers are drawn at baseline, C1D15, C2D1, C3D1, every odd cycle post C3 until and including C11, and EOT for Groups 1 and 2 (Part 2). Plasma sample for biomarkers are drawn at baseline, C2D1, C3D1, every odd cycle post C3 until and including C11 and EOT for Group 3 (Part 2).

[d] Only for patients participating in the PK Lead-In (Part 1).

[e] Only for patients not participating in the PK Lead-In (Part 2).

[f] Only for patients participating in Part 1 and Groups 1 and 2 (Part 2).

7.5 Disease Response Assessment

Investigator-assessed disease response in patients with GIST according to mRECIST version 1.1 for GIST will be based on local MRI or CT scans performed at the time

points outlined in Table 8. Computed tomography with IV contrast of the chest, and CT or MRI with IV contrast of the abdomen and pelvis will be performed at screening. At subsequent time points all body regions that contained sites of disease (target or non-target) at screening will be imaged. If a patient is not tolerant of IV contrast, non-contrast CT or MRI may be performed. For each patient, the same method of tumor imaging used at baseline should be used throughout the study.

Magnetic resonance imaging and CT scans will be reviewed locally at the study center, ideally by the same individual for each patient at each time point. Magnetic resonance imaging and CT scans will also be collected and reviewed centrally to provide a central assessment of response and progression.

7.6 End-of-treatment, Safety Follow-up, and PFS Follow-up

All patients will attend an EOT visit 14 (±7) days after the last dose of study drug (see Table 8 for a list of EOT assessments). If an alternate treatment is started within 14 days of the last dose of study drug, the EOT visit should be conducted prior to the first dose of alternate therapy. End-of-treatment procedures do not need to be repeated if they were completed within 7 days (or within 28 days for disease response [imaging] assessments).

A Safety Follow-up telephone contact to inquire about resolution of any residual AE(s) will be made 30 (+7) days after the last dose of study drug, or at the time the patient initiates another antineoplastic therapy for GIST or solid tumor. Thereafter, patients will be followed approximately every 3 months until death, withdrawal of consent or closure of the study by the Sponsor.

7.7 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 and/or tissue may be retained until 10 years after the completion of the study, or until the research is discontinued, whichever occurs first.

8 STUDY DRUG MANAGEMENT

8.1 Description

8.1.1 Formulation

BLU-285 will be administered as a drug in capsule formulation or an immediate release tablet for oral administration. The drug substance and drug product are manufactured and formulated following current Good Manufacturing Practices.

Each BLU-285 hard-gelatin capsule contains 5 mg (size 4 dark green opaque), 10 mg (size 3 white opaque), 30 mg (size 2 gray opaque), or 100 mg (size 1 light blue opaque) of the active drug substance.

Each BLU-285 tablet is blended with compendial excipients. The formulation blend is roller compacted, compressed into white round tablets and aesthetically film coated. BLU-285 tablets are prepared as 100 mg in strength.

All study drugs are for investigational use only and should only be used within the context of this study.

8.1.2 Storage

BLU-285 capsules and tablets must be stored at room temperature in their original container, according to the package label.

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

8.2 Packaging and Shipment

BLU-285 capsules and tablets will be supplied in to the study center packaged in 60 cc Wide Mouth Round high-density polyethylene bottles. Each bottle will be induction-sealed and capped with a 33 mm child-resistant closure.

Packaging will meet all regulatory requirements.

8.3 Accountability

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

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the 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 study drug received from the Sponsor. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The Sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

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

Patients will receive instructions for home administration of BLU-285.

All study drug that is either unused or dispensed and returned should be retained at the site until it is inventoried by the study monitor. All used, unused, or expired study drug will be returned to the Sponsor or its designee, or if authorized, disposed of at the study site per the site's Standard Operating Procedures and documented. All material containing BLU-285 will be treated and disposed of as hazardous waste in accordance with governing regulations.

8.4 Compliance

Patients will be dispensed the appropriate number of study drug bottles to allow for dosing for a full cycle, or until the next scheduled visit. Patients are to return all unused capsules and tablets (or the empty bottles) on D1 of each treatment cycle or at the next scheduled visit. Compliance with the dosing regimen will be assessed based on return of unused drug (or empty bottles).

9 ADVERSE EVENTS

Monitoring of AEs will be conducted throughout the study. Adverse events will be recorded in the eCRF from the time of first study drug dose through 30 days after the last dose of study drug. SAEs and serious pretreatment events (see Section 10) will be recorded in the eCRF from the time of signing informed consent through 30 days after the last dose of study drug. In addition, SAEs that are assessed as possibly or probably related to study treatment that occur > 30 days post-treatment will also be reported. All AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.1 Definitions

9.1.1 Definition of Adverse Event

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 (e.g., 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 (e.g., 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.

9.1.2 Suspected Adverse Reaction

A suspected adverse reaction is any treatment-emergent AE that is not clearly attributable to a cause other than BLU-285.

9.1.3 Unexpected Adverse Event

An unexpected AE is one for which the nature or severity of the event is not consistent with the applicable product information, e.g., the IB.

9.2 Documenting Adverse Events

Each patient must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded in the appropriate section of the eCRF. Any clinically significant value in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the eCRF. A laboratory value may also be considered an AE when it qualifies as a SAE, when it requires medical intervention, or when it affects dosing with study drug. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

9.3 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 4.03. 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.

9.4 Assessment of Causality

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

- Not Related: Exposure to the study treatment did not occur, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to the study treatment.

- Possibly Related: The study treatment and the AE were reasonably related in time, and the AE could be explained equally well by causes other than exposure to the study treatment.

- Probably Related: The study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the study treatment than by other causes, or the study treatment was the most likely cause of the AE.

9.5 Pretreatment Events

A pretreatment event is any untoward occurrence in a patient who has signed informed consent to participate in a study but before administration of any study drug. It does not necessarily have a causal relationship with study participation. A serious pretreatment event meets the criterion of a pretreatment event and satisfies any of the 6 criteria specified for an SAE as described in Section 10.

9.6 Pregnancy Reporting

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (e.g., 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 on study drug, or within 30 days of the patient's last dose of study drug, are considered immediately reportable events. If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking BLU-285 should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. In pregnant female patients, study drug is to be discontinued immediately and the patient instructed to return any unused BLU-285 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 (e.g., 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.

9.6.1 Contraception Requirements

Women of childbearing potential must agree to use a highly effective method of contraception (Clinical Trial Facilitation Group, 2014) throughout the study drug administration period until at least 30 days after the last dose of BLU-285. Women are considered to be of childbearing potential following menarche and until becoming post-menopausal (defined as no menses for at least 12 months without an alternative medical cause) unless permanently sterile. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy (Clinical Trial Facilitation Group, 2014). Because BLU-285 is a potential CYP3A4 inducer, women should use hormonal contraception with caution and supplement with other highly effective methods.

Men with partners who are women of reproductive potential must agree that they will use condoms and their partners will use highly effective contraceptive methods throughout the study drug administration period until at least 90 days after the last dose of BLU-285.

Highly effective forms of contraception are defined as the following (Clinical Trial Facilitation Group, 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 implanted 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 surgical success.

- Sexual abstinence (men and women), when this is the preferred and usual lifestyle of the patient. Periodic abstinence (such as a calendar, symptothermal and post-ovulation 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 (Clinical Trials Facilitation Group, 2014):

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

9.6.2 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 informed of the possibility of gamete and embryo banking.

10 SERIOUS ADVERSE EVENT

10.1 Definition of Serious Adverse Event

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

- Death.
- Life-threatening.

  An AE 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 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 in the offspring of a subject who received BLU-285.
- 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:

- 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.

10.2 Reporting Serious Adverse Events

All SAEs or serious pretreatment events that occur during the course of the study must be promptly reported by the Investigator to Chiltern International. Deaths and AEs assessed as life-threatening are to be reported immediately and SAEs that meet other criteria are to be reported within 24 hours from the point in time when the Investigator becomes aware of the SAE. All SAEs must be reported whether or not they are considered causally related to BLU-285. Serious AE forms will be completed and the information collected will include patient number, a narrative description of the event, and an assessment by the Investigator as to the severity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by the Sponsor or Medical Monitor.

If there are serious, unexpected adverse drug reactions associated with the use of BLU-285, the Sponsor will notify the appropriate regulatory agency(ies) and all participating Investigators on an expedited basis. The local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be promptly notified based on local regulations where required by the IRB/IEC of all serious, unexpected adverse drug reactions involving risk to human patients.

All AEs, whether serious or not, will be described in the source documents and in the appropriate section of the eCRF. All new events, as well as those that worsen in intensity or frequency relative to baseline, which occur after signing the informed consent through 30 days following the last dose of study drug, must be recorded. Adverse events that are ongoing at the time of treatment discontinuation should be followed through the 30-day follow up assessment. Serious AEs felt by the Investigator to be related to BLU-285, however, must be reported any time the Investigator becomes aware of such an event, even if this occurrence is more than 30 days after the last dose of study drug.

Information to be reported in the description of each AE 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 9.3 for definitions).
- Relationship of the event to study treatment (see Section 9.4 for definitions).
- Action taken: none; change in the study drug administration (e.g., temporary interruption in dosing); drug treatment required; non-drug 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 (notify the Medical Monitor immediately, and complete the SAE form).

10.2.1 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 BLU-285) 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.

11 STATISTICS

11.1 General Procedures

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 classification. Appropriate confidence intervals will also be presented. Time to event data will be summarized using Kaplan-Meier methods, which will include the estimated median with 95% CIs and 25th and 75th percentiles.

Safety, efficacy, PK, and PD evaluations will be assessed in the appropriate populations. These data will be summarized descriptively by dose level, dose groups, and overall as appropriate. Statistical hypothesis testing will be applied to the analysis of ORR in patients with starting dose of 300 or 400 mg QD (RP2D and MTD, respectively) in the following groups of patients: patients with PDGFRα D842V mutation, patients with no PDGFRα D842V mutation in second line treatment, and patients with no PDGFRα D842V mutation in 3+ line treatment.

The primary analysis for patients with PDGFRα D842V and patients with no PDGFRα D842V mutation in 3+ line treatment will occur after the number of patients specified in the sample size calculations for each group have enrolled and had the opportunity for 8 months of treatment or have ended treatment earlier. A clinical study report will be written using this analysis. The final database lock will occur after all patients enrolled in Part 2 have had an opportunity for 8 months of treatment or have ended treatment earlier. A clinical study report addendum will be written to include the primary efficacy analysis for patients with no PDGFRα D842V mutation in second line treatment and update clinical study report analyses with further follow up data from all patients.

All data will be provided in by-patient listings.

A separate Statistical Analysis Plan (SAP) will be finalized prior to locking the database.

11.2 Analysis Populations

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

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

- Dose Determining (DD) Population: The DD population includes all patients in Part 1 who have received at least 75% of their prescribed doses (i.e., ≥ 21 doses) of the study drug in C1 and completed follow-up through C1D28 or experienced a DLT regardless of extent of study drug exposure. The DD population will be the default

analysis population for the dose escalation phase for all MTD related analyses. Patients will be analyzed according to the dose they receive.

- Response-Evaluable (RE) Population: The RE population includes all patients in the safety population who have at least 1 target lesion per mRECIST version 1.1, at baseline, have at least 1 postbaseline disease assessment by central radiology per mRECIST version 1.1, and have experienced no major protocol violations. Subjects will be analyzed according to the dose they receive. Selected efficacy analyses may be performed using the RE population.

Within each of the safety, DD, and RE populations, selected analyses may be conducted based on subpopulations such as PDGFRα D842V, PDGFRα Exon 18, PDGFRα, and non- PDGFRα D842V.

- PK Population: The PK population includes patients who have sufficient plasma concentration-time data to reliably estimate the PK parameters of BLU-285.

- ECG Population: The ECG population includes patients who undergo continuous Holter monitoring and have sufficient ECG tracings so that the QT interval corrected for heart rate (QTc) parameter can be evaluated.

11.3 Sample Size

The total number of patients to be enrolled in the Part 1 is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD or identify the RP2D. It is expected that approximately 50 patients who meet the criteria for the DD Population will be enrolled in Part 1.

Sample size calculation for Part 2 takes into consideration patients treated at the RP2Ds in Part 1.

For patients with PDGFRα D842V mutation, a sample size of 31 patients will allow testing the null hypothesis of ORR ≤ 10% versus the alternative hypothesis of ORR ≥ 35% using Fisher's exact test with 90% power assuming a 2-sided type I error rate of 0.05.

For patients with no PDGFRα D842V mutation in second line treatment, a sample size of 50 patients will allow testing the null hypothesis of ORR ≤ 10% versus the alternative hypothesis of ORR ≥ 25% using Fisher's exact test with 83% power assuming a 2-sided type I error rate of 0.05.

For patients with no PDGFRα D842V mutation in 3+ line treatment, a sample size of 100 patients will allow testing the null hypothesis of ORR ≤ 5% versus the alternative hypothesis of ORR ≥ 15% using Fisher's exact test with 90% power assuming a 2-sided type I error rate of 0.05.

11.4 Procedures for Handling Missing, Unused, and Spurious Data

No imputation will be performed for missing data elements. Dates that are partially missing or impossible will be imputed using the method described in the SAP.

11.5 Statistical Methods

11.5.1 Disposition

A tabulation of the disposition of patients will be presented, including the number enrolled, the number treated, and the reasons for study discontinuation. Entry criteria and protocol deviations will be listed.

11.5.2 Demographic and Baseline Characteristics

Demographic and baseline disease characteristic data will be summarized descriptively.

11.5.3 Exposure Analysis

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

11.5.4 Primary Endpoint(s)

Parts 1 and 2:

Safety evaluations will be based on the incidence, severity, and type of AEs, and changes in the patient's vital signs, clinical laboratory results, and ECG findings. Summarization will focus on incidence of any SAEs, AEs, drug-related AEs, and AEs leading to discontinuation or death, and will be presented in tabular form by system organ class and preferred term. Tabulations of the incidence of DLTs at each dose level will be provided.

Adverse events will be assessed for severity according to the NCI CTCAE, version 4.03, and the verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities for purposes of summarization.

Treatment-emergent AEs will be tabulated, where treatment-emergent is defined as any AE that occurs during or after administration of the first dose of study drug through 30 days after the last dose of study drug, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered study drug-related by the Investigator.

Part 2:

Overall response rate is defined as the proportion of patients with a confirmed best response of CR or PR. Overall response rate will be estimated and 95% CI based on the exact binomial distribution will be presented.

An observed ORR of ≥ 26% in 31 patients in Group 2 will result in an exact binomial 95% CI with a lower bound greater than 10% (Table 13), which is clinically meaningful, and exceeds the ORR expected with available therapies Cassier et al, 2012; Yoo et al, 2015).

An observed ORR of ≥ 20% in 50 patients in Group 3 will result in an exact binomial 95% CI with a lower bound greater than 10% (Table 14), which is clinically meaningful, and exceeds the ORR expected with available therapies (Goodman et al, 2007; Sutent [package insert]).

An observed ORR of ≥ 11% in 100 patients in Group 1 will result in an exact binomial 95% CI with a lower bound greater than 5% (Kang et al, 2013; Stivarga [package insert]). An observed ORR of ≥ 17% in 100 patients will result in an exact binomial 95% CI with a lower bound greater than 10% (Table 15).

Table 13: Confidence Interval of Observed Response Rate, N = 31

Observed ORR	Number of Confirmed CR/PR	Exact 95% CI
23%	7	(9.59; 41.10)
26%	8	(11.86; 44.61)
52%	16	(33.06; 69.85)
55%	17	(36.03; 72.68)

Abbreviations: ORR = overall response rate; CR = complete response; PR = partial response; CI = confidence interval.

Table 14: Confidence Interval of Observed Response Rate, N = 50

Observed ORR	Number of Confirmed CR/PR	Exact 95% CI
18%	9	(8.58; 31.44)
20%	10	(10.03; 33.72)
28%	14	(16.23; 42.49)
34%	17	(21.21; 48.77)
40%	20	(26.41; 54.82)

Abbreviations: ORR = overall response rate; CR = complete response; PR = partial response; CI = confidence interval.

Table 15: Confidence Interval of Observed Response Rate, N = 100

Observed ORR	Number of Confirmed CR/PR	Exact 95% CI
10%	10	(4.90; 17.62)
11%	11	(5.62; 18.83)
15%	15	(8.65; 23.53)
16%	16	(9.43; 24.68)
17%	17	(10.23; 25.82)

Abbreviations: ORR = overall response rate; CR = complete response; PR = partial response; CI = confidence interval.

ECG Assessment:

In Part 2, the effects of BLU-285 on ECG parameters will be evaluated for approximately 20 patients using 12-lead ECGs extracted from continuous recordings (12-lead Holter) on C1D1 and C1D15. Individual ECGs will be extracted in replicate from the 12-lead Holter recordings at specified time points and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for heart rate (QTc) using Fridericia's correction factors. The primary QTc parameter will be QTcF. Secondary parameters (heart rate, PR, and QRS, and T-wave morphology) will also be evaluated.

Potential effects of BLU-285 will be evaluated as change-from predose baseline heart rate, PR, QRS, and QTcF by post-dosing time point. For the purpose of QT assessment, exposure-response analysis will be performed on the relationship between BLU-285 systemic levels and change in QTcF.

11.5.5 Secondary Endpoint(s)

Pharmacokinetics:

Pharmacokinetic parameters will be calculated from the plasma concentration-time data using standard non-compartmental methods and/or by suitable models that describe BLU-285 disposition. Descriptive statistics (i.e., n, mean, standard deviation, geometric mean, coefficient of variation, median, minimum, maximum, and 95% CIs) will be used to summarize PK parameters for each dose level. The dose versus systemic exposure relationships will be assessed graphically. Pharmacokinetic parameters of interest will include maximum plasma drug concentration (C_{max}), time to maximum plasma drug concentration (T_{max}), time of last quantifiable plasma drug concentration (T_{last}), area under the plasma concentration versus time curve from time 0 to 24 hours postdose (AUC_{0-24}), plasma drug concentration at 24 hours postdose (C_{24}); apparent volume of distribution (V_z/F), terminal elimination half-life ($t_{½}$), apparent oral clearance (CL/F), and accumulation ratio (R). Additional details of the PK analyses, including combined analyses of the ECG and PK parameters, will be contained in the statistical analysis plan (SAP).

Efficacy:

Progression free survival is defined as the time from the start of treatment to the date of first documented disease progression or death. Progression free survival will be described using Kaplan-Meier methods and will include the estimated median with 95% CIs and 25th and 75th percentiles. Estimated PFS rate at 3-, 6-, and 12-month landmarks will also be presented. If a patient has not had an event, PFS is censored at the date of last response assessment that is stable or better.

Duration of response is defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death; and is limited to the subset of patients with confirmed CR or PR. Duration of response will be described using Kaplan-Meier methods and will include the estimated median with 95% CIs and 25th and 75th percentiles. Censoring rules for DOR will be the same as those for PFS.

Clinical benefit rate is defined as the proportion of patients with a confirmed CR/PR, or stable disease lasting for 4 cycles from the start of treatment. Clinical benefit rate will be summarized similarly as ORR.

Response rate per Choi criteria will be summarized descriptively.

Progression free survival on last prior anticancer therapy will be summarized. Estimated PFS rate at 3-, 6-, and 12-month landmarks will also be presented. Statistical testing such as log-rank test; and z-test for PFS rate at 3-, 6-, and 12-month landmarks maybe performed to further understand the differences between PFS on avapritinib versus PFS on last prior anticancer therapy.

KIT, PDGFRα, and other cancer-relevant mutations present in tumor tissue at baseline:

Mutation analysis results will be presented descriptively including those reported on the case report form and central assessment of the KIT, PDGFRα and other cancer-relevant mutations.

Biologic Activity:

Change in KIT, PDGFRα and other cancer relevant mutant allele fractions in ctDNA will be presented descriptively.

[redacted]

[redacted]

11.6 Procedures for Reporting Deviations to Original Statistical Analysis Plan

All deviations from the original SAP will be provided in the final clinical study report.

12 ETHICS AND RESPONSIBILITIES

12.1 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 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.

12.2 Data and Safety Monitoring Committee

A formal independent data monitoring committee will not be used for this study. This is an open-label, Phase 1 study in which all patients receive single-agent BLU-285. The Sponsor will have access to the safety data on a regular basis. The Sponsor Clinical Study Team will host Investigator teleconferences on a regular basis during the study. During the Part 1 of the study, the Sponsor Clinical Study Team and the Investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose-escalation teleconference, safety information, including DLTs and all Grade 2 or worse AEs reported during C1, and all available PK data will be described and reviewed for each patient in the current dose cohort. Updated safety, PK and other data for all other ongoing patients, including data from later cycles, will also be discussed.

Dose-escalation decisions will be based on an evaluation of all relevant, available data, and not solely on DLT information. The selection of the dose for the next cohort of patients will be limited to a 100% increase for the first escalation and 50% thereafter, or to the addition of 3 patients with no dose increase, as described in Section 6.4. However, the actual dose level chosen may be less than the maximum permitted, and will be based on a medical review of relevant clinical and available PK data. The Sponsor Clinical Study Team and the Investigators must reach agreement on whether to determine that the MTD has been achieved, to escalate the dose further, or to de-escalate to a lower dose.

12.3 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 sites 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.

12.4 Informed Consent

The Investigator at each 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.

After the study has been fully explained, written informed consent, including separate consent for exploratory biomarker research to be conducted on biological samples collected during the study, will be obtained from either the patient or his/her guardian or legal representative prior to study participation.

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).

12.5 Records Management

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

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

12.6 Source Documentation

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

patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

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

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

The Investigator will retain all completed source documents.

12.7 Study Files and Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained 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.

12.8 Liability and Insurance

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

13 AUDITING AND MONITORING

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

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

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

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

14 AMENDMENTS

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

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

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

15 STUDY REPORT AND PUBLICATIONS

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

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

16 STUDY DISCONTINUATION

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

17 CONFIDENTIALITY

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

Identification of patients and eCRFs shall be by initials and screening and treatment numbers only.

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19 APPENDICES

19.1 Appendix 1

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

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

2. No bone lesions to be chosen as target lesions

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

4. A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria in order to be regarded as unequivocal evidence of progressive disease according to the aforementioned GIST-specific modifications to RECIST 1.1:

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

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

Source: (Demetri et al, 2013).

19.2 Appendix 2

STRONG INHIBITORS AND INDUCERS OF CYP3A4

Inhibitors	Inducers
Boceprevir	Carbamazepine
Clarithromycin	Phenytoin
Conivaptan	Rifampin
Cobicistat	St. John's Wort
Grapefruit, Grapefruit juice	Phenobarbital
Indinavir	
Itraconazole	
Ketoconazole	
Lopinavir	
Nefazodone	
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Voriconazole	

Source: (FDA, 2016).
This list is not intended to be exhaustive. A similar restriction will apply to other drugs that are known to strongly modulate CYP3A4; appropriate medical judgement is required. Please contact Blueprint Medicines with any queries relating to this issue.

19.3 Appendix 3

SUBSTRATES OF CYP3A4, CYP2C9 OR BCRP WITH A NARROW THERAPEUTIC RANGE

CYP3A4 Substrates	CYP2C9 Substrates	BCRP Substrates
Alfentanil	Warfarin	Rosuvastatin
Cyclosporine		Lapatinib
Dihydroergotamine		Methotrexate
Ergotamine		
Fentanyl		
Midazolam		
Pimozide		
Quinidine		
Sirolimus		
Simvastatin		
Tacrolimus		
Terfenadine		

Source: (FDA, 2016).
This list is not intended to be exhaustive. A similar restriction will apply to other drugs that are sensitive substrates; appropriate medical judgement is required. Please contact Blueprint Medicines with any queries relating to this issue.

19.4 Appendix 4

EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Symptomatology
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., 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).

19.5 Appendix 5

BLU-285-1101

A PHASE 1 STUDY OF BLU-285 IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMORS (GIST) AND OTHER RELAPSED AND REFRACTORY SOLID TUMORS

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BLU-285 are the confidential and proprietary information of Blueprint Medicines, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Blueprint Medicines.

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

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

Principal Investigator Name (printed)	Signature
Date	