CLINICAL RESEARCH PROTOCOL

DRUG:	Avapritinib (BLU-285)
STUDY NUMBER:	BLU-285-2202
PROTOCOL TITLE:	An Open-label, Single Arm, Phase 2 Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis
IND NUMBER:	124159
EudraCT NUMBER	2017-004836-13
SPONSOR:	Blueprint Medicines Corporation 45 Sidney Street Cambridge, MA 02139
ORIGINAL PROTOCOL DATE:	09 January 2018
VERSION NUMBER:	Amendment 7.1
VERSION DATE:	21 April 2020

CLINICAL PROTOCOL

Protocol Title:	**An Open-label, Single Arm, Phase 2 Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis**
Study No:	**BLU-285-2202**
Original Protocol Date:	**09 January 2018**
Protocol Version No:	Amendment 7.1
Protocol Version Date:	21 April 2020

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

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

[redacted]

Date

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

STUDY SUMMARY

Title	An Open-label, Single Arm, Phase 2 Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis
Study Centers	The study will be conducted at multiple centers in the United States, Canada, and Europe.
Introduction and Rationale	Gain-of-function mutations in *KIT* (V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) promote ligand-independent, oncogenic signaling, which appears central to the pathogenesis of systemic mastocytosis (SM), a clonal disorder of neoplastic mast cells (MCs). Systemic mastocytosis includes aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL), which together are referred to as Advanced SM (AdvSM). Mutations in *KIT* D816 are demonstrated in 95% of patients with SM. Midostaurin, a multikinase inhibitor that inhibits wild type *KIT* as well as *KIT* D816V, is the first agent approved for the treatment of ASM, SM-AHN and MCL. It was approved by the United States Food and Drug Administration (US FDA) in April 2017 and by the European Medicines Agency in September 2017 based on an open-label, single arm, Phase 2 clinical study in 116 patients (89 evaluable) with AdvSM and an open-label single arm Phase 2 study in 26 patients. Overall response rate (ORR) reported in US Package Insert was 21% using modified Valent criteria and 17%, including complete remission (CR) and partial remission (PR), in an ad hoc analysis using International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) consensus response criteria. Overall response rate, including CR + PR + clinical improvement (CI), using the IWG-MRT-ECNM criteria reported in the European summary of product characteristics was 28.3%. Median progression-free survival (PFS) was 14.1 months. However, treatment discontinuation due to adverse events (AEs) occurred in 21% of patients and 56% of patients required dose modification due to toxicity; therefore, there is a need for more efficacious and better tolerated agents. Avapritinib was developed to selectively target *KIT* D816V and other *KIT* exon17 mutations. Avapritinib has demonstrated potent and selective activity against *KIT* D816V in vitro, robust growth inhibition in a tyrosine kinase inhibitor (TKI)-resistant mastocytoma model in vivo, and tolerability at active doses in toxicology and safety pharmacology studies. Data from the ongoing Phase 1 study of avapritinib in patients with AdvSM or other myeloid malignancies (BLU-285-2101) demonstrate a modified IWG-MRT-ECNM ORR (CR+CR with partial recovery of peripheral blood [PB] counts [CRh]+PR+CI) of 83%, supporting the efficacy and safety of avapritinib in the AdvSM population and further evaluation in this study.

	The primary objective of this study is to determine the efficacy of avapritinib in AdvSM, as measured by adjudicated ORR by modified IWG-MRT-ECNM criteria. This will be determined based on improvements in quantifiable objective findings of SM related organ damage, known as modified IWG-MRT-ECNM C-findings (such as Grade 2 anemia) and reductions in measures of mast cell burden (such as tryptase). Approximately 63 patients with AdvSM who have 1 or more modified IWG-MRT-ECNM evaluable C-findings at baseline (or have MCL, regardless of C-findings) will be prospectively enrolled into Cohort 1 and considered for the primary objective. Due to the rarity of AdvSM, high unmet unmedical need, and need for supportive data for secondary efficacy and safety endpoints, this study will enroll additional patients with AdvSM that are not considered evaluable by the modified IWG-MRT-ECNM criteria. Although they cannot inform the primary objective, they can contribute to the key secondary objective of assessing mean change in patient-reported outcomes (PROs) on study from baseline, using the Advanced Systemic Mastocytosis-Symptom Assessment Form (AdvSM-SAF), Total Symptom Score (TSS). Patients with AdvSM may experience a wide variety of subjective symptoms, including fatigue, nausea, vomiting, abdominal pain, rash, flushing, itching and allergy symptoms, which can range from very severe to life threatening and can dramatically reduce quality of life (QoL). Symptoms are poorly correlated with objective findings, such as those measured by modified IWG-MRT-ECNM C-findings. Approximately 40 patients with AdvSM who are not considered eligible for the primary objective of adjudicated response (because they lack C-findings or do not have MCL) will be enrolled into Cohort 2 and contribute, along with Cohort 1, to the key secondary objective of PROs, as well as Investigator-assessed response, safety, and additional secondary and exploratory objectives.
Number of Patients	Approximately 103 patients will be enrolled in this study, including approximately 63 patients in Cohort 1 and up to 40 patients in Cohort 2. Approximately 30 sites in the United States, Canada, and Europe will participate.
Objectives	**Primary:** • The primary objective is to determine adjudicated ORR (CR/ CRh + PR + CI) based on modified IWG-MRT-ECNM consensus response criteria in patients with AdvSM treated with avapritinib and enrolled in Cohort 1. **Secondary**: • The key secondary objective for patients in Cohorts 1 and 2 is to assess mean change from baseline in AdvSM-SAF TSS.

Additional secondary objectives for patients in Cohorts 1 and 2 are to:

- Determine local Investigator assessed ORR based on modified IWG-MRT-ECNM consensus response criteria, using C-findings when present at baseline
- Determine time-to-event outcomes including time-to-response (TTR), duration of response (DOR), PFS, and overall survival (OS).
- Determine morphologic response (CR/CRh+ PR) based on Pure Pathological Response criteria.
- Determine ORR and other clinical outcome measures (DOR, PFS, OS) analyzed by prior therapy and by genotype.
- Assess changes in the following individual measures of MC burden:
    - Bone marrow (BM) MCs.
    - Serum tryptase.
    - *KIT* mutation burden (eg, D816V) in PB and BM.
    - Liver and spleen volume by imaging.
- Assess additional PROs using the AdvSM-SAF, including change from baseline in:
    - Symptom domain scores.
    - Individual symptom scores.
- Assess changes in QoL measures, including the [redacted]
- Assess the safety of avapritinib by AEs, vital signs, electrocardiograms (ECGs), and laboratory tests.
- Assess the pharmacokinetics (PK) of avapritinib.
- Correlate avapritinib exposure with safety and efficacy endpoints.

[redacted]

	[redacted]
Study Design	This is an open-label, single arm, Phase 2 study evaluating the efficacy and safety of avapritinib in patients with a centrally confirmed World Health Organization (WHO) diagnosis of AdvSM, including patients with ASM, SM-AHN, and MCL. Patients will be allocated by the Study Steering Committee (SSC) chair (or designee) into 1 of 2 cohorts before enrollment. The patients in Cohort 1 are those with a) AdvSM with 1 or more modified IWG-MRT-ECNM C-finding(s) at baseline or b) MCL regardless of baseline C-findings. Cohort 1 patients will be the evaluable population for the primary objective of determining ORR, based on modified IWG-MRT-ECNM ORR as adjudicated by the SSC, after 63 patients in Cohort 1 have had the opportunity to receive 10 cycles of avapritinib. An interim analysis will be performed after the first 32 patients in Cohort 1 are evaluable for response. The patients in Cohort 2 are those with AdvSM (except MCL) without any modified IWG-MRT-ECNM C-findings at baseline. Cohort 2 patients will not contribute to the primary objective of determining adjudicated response but will contribute for all other secondary and exploratory objectives. Both cohorts will participate in the key secondary objective of determining symptomatic efficacy, with an endpoint of AdvSM-SAF TSS improvement from baseline. Investigator-assessed efficacy, safety, and additional secondary and exploratory objectives will also be studied in both cohorts.

Informed consent will be obtained within the 56 days (8 weeks) before initiation of treatment with avapritinib. Management of symptoms should be optimized, including stabilization of BSC medication dose and schedule for symptom management before Cycle 1 Day -8 (C1D-8), and eligibility will be confirmed by the study site before or on C1D-8. Note: timeframes for Screening assessments (eg, between C1D-56 and C1D-8 or between C1D-7 and C1D-1) represent the maximum duration of time. Activities can be completed sooner than the last possible day or within a shorter timeframe.

The diagnosis of SM for study eligibility is to be assessed centrally using WHO criteria for diagnosis of SM and WHO criteria for subclassification of AdvSM. Patient symptoms will be collected daily during Screening using the AdvSM-SAF in all patients.

The SSC chair or designee will confirm eligibility between C1D-7 and C1D-1. Confirmation of eligibility will include review of Central Pathology of BM samples (screening samples, and other tissue samples, when available), serum tryptase, local *KIT* D816V mutation data, evaluable C-findings attributable to SM, and other relevant clinical data.

Study enrollment will be limited to patients with ASM, SM-AHN, or MCL meeting eligibility per the SSC. Patients meeting eligibility criteria will be allocated by the SSC to Cohort 1 or Cohort 2 as described above.

Once eligibility is confirmed by the SSC, patients will initiate therapy with avapritinib. Treatment cycles are 28 days in duration. Avapritinib dosing will continue until confirmed progression of SM or clinical progression of SM or AHN, which in the opinion of the Investigator requires immediate initiation of cytoreductive therapy, or until the drug is no longer tolerated or the patient withdraws or dies.

For patients in Cohort 1, adjudicated ORR will be assessed using modified IWG-MRT-ECNM response criteria by the SSC. In addition, all patients in both cohorts will be assessed by the local Investigator for ORR using modified IWG-MRT-ECNM criteria, using C-findings when they are present at baseline. Patients with a myeloid AHN, response of the AHN component will be assessed using criteria for AHN response.

Assessments required for evaluation of response include BM biopsy, aspirate and PB smear; BM cytogenetics; liver and spleen imaging for volume; serum tryptase, hematology, serum chemistry results and physical examination; and data on transfusions and treatment of ascites and pleural effusions. The Investigator will assess attribution to SM and response using local BM assessments, while the SSC will use central BM assessments to determine response.

Mastocytosis in skin will be assessed using standardized photography with response determined by an independent Skin Assessment Committee.

	For patients demonstrating CR/CRh, PR, and CI, response will be confirmed 12 weeks (± 4 weeks) after initial response. For patients with progressive disease (PD), progression of disease will be confirmed 4 weeks after initial documentation, unless the patient has clinical progression which, in the opinion of the Investigator, requires an immediate change in therapy. The AdvSM-SAF will be collected daily from Screening to ensure at least 7 days of baseline data before C1D1, through Cycle 17 or until the patient discontinues the study, if earlier than Cycle 17. The [redacted] will be collected at each scheduled study visit through Cycle 17 and at end-of-treatment (EOT), if EOT is at or before Cycle 17. All patients are to have an EOT visit 14 days after discontinuation of study treatment. Patients who discontinue from the study drug for reasons other than confirmed PD or initiation of other cytoreductive therapy will have response assessments (including BM biopsy and aspirate, PB smear, liver and spleen imaging, and laboratory and other C-finding assessments) performed at the EOT visit unless the assessments were performed within the preceding 24 weeks, in which case they need not be repeated (or preceding 16 weeks if EOT is before Cycle 11). Thereafter, all patients discontinued from study drug without confirmed PD or initiation of other cytoreductive therapy will be followed every 24 weeks for assessment of response status until PD or initiation of other cytoreductive therapy. Patients who experience PD or initiate another cytoreductive therapy during follow-up for PD will subsequently be followed every 12 weeks for OS. All patients will have a Safety follow-up 30 days after discontinuation of study drug. Patients with PD or who initiate another cytoreductive therapy will be followed with telephone calls every 12 weeks to determine OS unless the reason for discontinuation is death, withdrawal of consent, lost to follow-up, or closure of the study by Sponsor.
Duration of Treatment	Study drug will be administered until the patient has confirmed PD of SM, clinical progression of SM or AHN, which in the opinion of the Investigator requires immediate initiation of cytoreductive therapy, or until the drug is no longer tolerated, the Investigator withdraws the patient, or the patient withdraws or dies.
Duration of Patient Participation	The minimum duration of patient participation is approximately 16 weeks, including an 8-week Screening period to assess study eligibility; a treatment period of at least 28 days; an EOT visit at least 14 days (± 7 days) after the last dose of study drug; and a follow-up telephone contact for resolution of any AEs 30 days (± 7 days) after the last dose of study drug, or at the time the patient initiates another cytoreductive therapy.
Duration of Study	The expected enrollment period is approximately 12 months and the expected duration of the study is approximately 54 months.

Target Population	Main entry criteria:

1. Patients who are ≥ 18 years of age.
2. Patients must have 1 of the following diagnoses as confirmed by WHO diagnostic criteria. Before enrollment, the SSC must confirm the diagnosis of AdvSM (based on Central Pathology Laboratory assessment of BM).
   - ASM.
   - SM-AHN. The AHN must be myeloid, with additional criteria defined in the protocol.
   - MCL, including diagnoses with an AHN component.
3. Patients with SM-AHN should have received prior treatment for the AHN component of disease if, in the opinion of the Investigator, such therapy was appropriate.
4. Patient must have a BM biopsy taken within 56 days of C1D1, assessed by the Central Pathology Laboratory.
5. Cohort 1 only: Patient must have at least 1 measurable C-finding per modified IWG-MRT-ECNM, attributed to SM (unless diagnosis is MCL, which does not require a C-finding). Laboratory abnormality C-findings should not be assessed until the required washout period from the last cytoreductive therapy has been met. If a C-finding improves during the Screening period, prior to dosing, and no longer meets criteria for evaluability, it can no longer be counted as a C-finding. In addition:
   - Patients must have documented evidence of MC aggregates in the BM or other extracutaneous organ based on central pathology.
   - Patients must be willing to have follow-up biopsies of affected organ(s) to document response.
6. Patient must have a serum tryptase ≥ 20 ng/mL.
7. Patients receiving cytoreductive therapy within the preceding 12 weeks must have discontinued therapy due to disease progression, refractory disease, lack of efficacy, or intolerance.

8. Patient's non-antineoplastic SM therapies (ie, BSC; eg, H1 and H2 blockers) must be stable (same dose, no new medications for SM) for ≥ 14 days before C1D-8. This criterion is not applicable if a patient has progressive disease and it is in the patient's best interest to enroll in the study rapidly with Medical Monitor approval.

9. If the patient is receiving corticosteroids, the dose must be ≤ 20 mg/d prednisone or equivalent and dose must be stable for ≥ 14 days before C1D-8. This criterion is not applicable if the patient has progressive disease, and it is in the patient's best interest to enroll in the study rapidly with Medical Monitor approval.

10. Patient has an Eastern Cooperative Oncology Group Performance Status of 0 to 3.

11. Patient must not have received prior treatment with avapritinib.

12. Patient must not have received any cytoreductive therapy (including midostaurin and other TKIs, hydroxyurea, azacitidine) or investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy (eg, brentuximab vedotin) less than 28 days before obtaining the Screening BM biopsy for this study. If the patient has progressive disease and it is in the patient's best interest to enroll in the study rapidly, cytoreductive therapy may be discontinued 1 day before the screening BM biopsy with approval from the Medical Monitor. Cytoreductive therapy may not be restarted during Screening or while on study.

13. Patient must not have received prior radiotherapy within 14 days before the Screening BM biopsy, unless given to palliate specific sites of disease (eg, bone lesion).

14. Patient must not have received any hematopoietic growth factor within 14 days of the Screening BM biopsy.

15. Patient must not require therapy with a concomitant medication that is a strong inhibitor, strong inducer, or moderate inducer of CYP3A4.

16. Patient must not be a candidate for allogeneic hematopoietic stem cell transplantation for treatment of SM, in the opinion of the Investigator.

17. Patient does not have eosinophilia and known positivity for the *FIP1L1-PGDFRA* fusion, unless the patient has demonstrated relapse or PD on prior imatinib therapy. Patients with eosinophilia ($> 1.5 \times 10^9$/L), who do not have a detectable *KIT* D816 mutation, must be tested for a *PDGFRA* fusion mutation by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR).

18. Patient must not meet any of the following laboratory criteria:

    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 × upper limit of normal (ULN); no restriction if due to suspected liver infiltration by MCs.

    - Bilirubin > 1.5 × ULN; no restriction if due to suspected liver infiltration by MCs or Gilbert's disease. (In the case of Gilbert's disease, a direct bilirubin > 2.0 × ULN would be an exclusion.)

    - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 or creatinine> 1.5 × ULN.

    - Platelet count < 50,000/µL (within 4 weeks of the first dose of study drug) or receiving platelet transfusion(s)

19. Patient must not have a QT interval corrected using Fridericia's formula (QTcF) of > 480 msec.

20. Patient must not have a history of a seizure disorder (eg, epilepsy) or requirement for antiseizure medication.

21. Patient must not have a history of a cerebrovascular accident or transient ischemic attacks within 1 year before the first dose of study drug.

22. Patient must not have a known risk or recent history (12 months before the first dose of study drug) of intracranial bleeding (eg, brain aneurysm, concomitant vitamin K antagonist use).

23. Patient must give written informed consent.

Endpoints

Primary:

- Adjudicated ORR (CR/CRh + PR + CI) based on modified IWG-MRT-ECNM criteria, confirmed 12 weeks after initial response in patients in Cohort 1 only.

Secondary:

- Mean change from baseline in AdvSM-SAF TSS in patients in Cohorts 1 and 2.

Additional secondary endpoints for patients in Cohorts 1 and 2:

- Local Investigator assessed ORR (CR/CRh + PR + CI) based on modified IWG MRT ECNM criteria, using C-findings when present, confirmed 12 weeks after initial response.
- Objective response rate (CR/CRh + PR) based on Pure Pathological Response criteria.
- Time-to-event outcomes including TTR, DOR, PFS, and OS.
- CR/CRh + PR and clinical benefit (CR/CRh + PR + CI + SD) based on modified IWG-MRT-ECNM criteria.
- Overall response rate and other clinical outcome measures (DOR, PFS, OS) analyzed by prior therapy and by genotype.
- Changes in BM MCs, serum tryptase, *KIT* mutation burden (eg, D816V) in PB and BM, and liver and spleen volume by imaging.
- Mean change from baseline in AdvSM-SAF domain and individual symptom scores.
- Changes in [redacted]
- Safety of avapritinib, as assessed by AEs, changes in vital signs, ECGs, and laboratory testing.
- PK of avapritinib.
- Correlations between avapritinib exposure and safety and efficacy endpoints.

[redacted]

[redacted]

Statistical Methods	The primary objective of this study is to determine adjudicated ORR (CR/CRh + PR + CI) based on modified IWG-MRT-ECNM criteria in patients with AdvSM treated with avapritinib and enrolled in Cohort 1. Assuming the null hypothesis ORR of 28% versus the alternative hypothesis ORR of 50%, and a 1-sided type I error rate of 0.025, a sample size of 63 patients in Cohort 1 will have 93.5% power using the exact 1-sample binomial test. Enrollment of the SM-AHN subgroup will be capped at approximately 70% of the 63 total Cohort 1 patients (ie, a maximum of 45 patients) to ensure the study population reflects the general AdvSM patient population. This sample size will also allow statistical testing of the key secondary objective of patients with symptom reduction based on AdvSM-SAF TSS. One interim analysis for superiority will be performed at approximately 50% of the information fraction (ie, the first 32 patients enrolled in Cohort 1 are evaluable for response). The primary efficacy analysis will include all patients in the response-evaluable population. Overall response is defined as confirmed CR/CRh, PR, or CI per SSC review. The response-evaluable population will include all patients who receive at least 1 dose of study drug, have a diagnosis of AdvSM, and are evaluable per modified IWG-MRT-ECNM criteria at baseline as assessed by SSC review, and have at least 2 complete postbaseline response assessments (inclusive of BM and/or other involved tissue biopsy and liver and spleen imaging) and had been on study for at least 6 cycles (28 × 6 = 168 days), or had end of study visit. In addition to the primary efficacy analysis, the response-evaluable population will be used for all secondary efficacy analyses related to response, such as TTR, DOR, PFS, CI rate, and clinical benefit rate.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AdvSM	Advanced systemic mastocytosis
AdvSM-SAF	Advanced Systemic Mastocytosis-Symptom Assessment Form
AE	Adverse event
AHN	Associated hematologic neoplasm
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASM	Aggressive systemic mastocytosis
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the systemic plasma concentration versus -time curve from zero through 24 hours
β-hCG	Beta human chorionic gonadotropin
BM	Bone marrow
BSC	Best supportive care
CBC	Complete blood count
C-finding	Finding indicative of organ damage due to systemic mastocytosis
CI	Clinical improvement
C_{max}	Maximum systemic concentration
CML	Chronic myeloid leukemia
CR	Complete remission
CRh	Complete remission with partial recovery of peripheral blood counts
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
CYP	Cytochrome P450
DOR	Duration of response
DXA	Dual x-ray energy assessment (bone densitometry scan)
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form

EMA	European Medicines Agency
[redacted]	[redacted]
EOT	End-of-treatment
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GCP	Good clinical practice
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
IB	Investigator’s brochure
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
ISM	Indolent systemic mastocytosis
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis
KIT	V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
MAF	Mutation allele fraction
MC	Mast cell
MCL	Mast cell leukemia
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PB	Peripheral blood
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PO	Orally (per os; by mouth)

PR	Partial remission
PRBC	Packed red blood cells
PRO	Patient-reported outcome
QD	Once daily
QOD	Every other day
QoL	Quality of life
QTcF	QT interval corrected using Fridericia's formula
RAC	Response Assessment Committee
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SD	Stable disease
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with an associated hematologic neoplasm of non-mast-cell lineage
SSC	Study steering committee
SSM	Smoldering systemic mastocytosis
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TSS	Total symptom score
TTR	Time-to-response
ULN	Upper limit of normal
UP	Urticaria pigmentosa
WBC	White blood cells
WHO	World Health Organization

1 BACKGROUND AND RATIONALE

1.1 Background

Systemic mastocytosis (SM) is a clonal hematological disorder of mast cells (MCs) characterized by increased MC burden, with focal and/or diffuse infiltrates of neoplastic MCs in skin, bone marrow (BM), spleen, liver, gastrointestinal (GI) tract, and other organs, and increased release of MC mediators. Nearly all patients have BM involvement. Based on a cohort study conducted in Denmark, the incidence of SM (all subtypes including urticaria pigmentosa [UP]) was 0.89 per 100,000 per year (Cohen, et al., 2014). The World Health Organization (WHO) has established criteria for diagnosis and classification of SM (Gotlib, et al., 2013). In the most recently proposed WHO update (Valent, et al., 2017), SM is subclassified as indolent SM (ISM), smoldering SM (SSM), SM with an associated hematologic neoplasm of non-MC lineage (SM-AHN), aggressive SM (ASM), and MC leukemia (MCL). The latter 3 subclassifications are associated with reduced overall survival (OS) and are grouped together as advanced SM (AdvSM). Advanced SM is associated with a poor prognosis, with a median OS of 3.5 years in ASM, 2 years in SM-AHN, and less than 6 months in MCL. Indolent SM is associated with a normal or near-normal life-expectancy; the prognosis of SSM is intermediate (Lim, et al., 2009).

The major criterion for SM is the multifocal accumulation and clustering of MCs in the BM or other extracutaneous organs. Minor criteria confirm the clonal nature of the disease and include abnormal MC morphology (spindling), expression of CD2 and/or CD25 in MCs, expression of an activating mutation in codon 816 of V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*) exon 17 (usually D816V) and a serum tryptase level > 20 ng/mL. AdvSM is characterized by the presence of organ damage due to MC infiltration (C-findings), whereas ISM and SSM may have evidence of high MC burden in multiple hematopoietic lineages (B-findings) but no organ function impairment. Indolent SM is defined by the presence of less than 2 B-findings; smoldering SM is defined by the presence of 2 or more B-findings (Valent, et al., 2017).

In all subtypes of SM, and in most patients with the disease, neoplastic MCs display a mutation at the D816 position in exon 17 of *KIT*, which results in ligand-independent activation of *KIT* kinase activity. Wild-type MCs require *KIT* activity for their differentiation and survival and therefore constitutive activation of *KIT* through D816V mutation is thought to be a pathogenic driver for SM (Chabot, et al., 1988). Specifically, *KIT* D816V mutations are found in 90% to 95% of patients with SM, with rare *KIT* D816Y, D816F, and D816H variants identified (Garcia-Montero, et al., 2006; Valent, 2013; Verstovsek, 2013). Based on these findings, *KIT* D816V is considered a major therapeutic target in AdvSM (Valent, et al., 2017) and several agents targeting this mutation have been studied.

Patients with AdvSM have limited treatment options. Mast cell-mediated symptoms are managed with a variety of agents that have no impact on the disease burden or course. A number of cytoreductive agents, including interferon alpha (Lim, et al., 2009; Valent, et al., 2010) and cladribine (Barete, et al., 2015; Lim, et al., 2009), have been used to reduce MC disease burden and alter the course of the disease with varying degrees of efficacy. Imatinib, a tyrosine kinase inhibitor (TKI) that targets *KIT*, as well as other kinases, is approved in the US for treatment of ASM, but only in patients without the *KIT* D816V mutation, where it has no activity (Glivec SmPC).

Midostaurin, a multikinase inhibitor that inhibits wild-type *KIT* as well as *KIT* D816V, is the first agent approved for the treatment of ASM, SM-AHN, and MCL. It was approved by the United States Food and Drug Administration (US FDA) in April 2017 and by the European Medicines Agency (EMA) in September 2017 based on an open-label, single arm, Phase 2 clinical study in 116 patients (89 evaluable) with AdvSM and an open-label single-arm Investigator-sponsored Phase 2 study in 26 patients with AdvSM (Rydapt, 2017a; Rydapt, 2017b). Overall response rate (ORR) reported in the US package insert was 21% using modified Valent criteria (and 17%, including Complete Remission [CR] and Partial Remission [PR], in an ad hoc algorithmic analysis using International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis [IWG-MRT-ECNM] consensus response criteria). Overall response rate, including CR + PR + Clinical Improvement (CI), using the IWG-MRT-ECNM criteria reported in the European summary of product characteristics (SmPC) was 28.3%. It is important to note that although all patients with AdvSM have clinical or pathological evidence of advanced disease, the IWG-MRT-ECNM response criteria are only applicable to a subset of patients with AdvSM that have specific, quantifiable types of organ damage. Median progression-free survival (PFS) was 14.1 months (Gotlib, et al., 2016). However, treatment discontinuation due to adverse events (AEs) occurred in 21% of patients and 56% of patients required dose modification due to toxicity; therefore, there is a need for more efficacious and better-tolerated agents.

Avapritinib (formerly BLU-285) was developed to selectively target *KIT* D816V as well as other *KIT* mutations. Avapritinib (trade name: AYVAKIT™) was approved by the United States (US) FDA in January 2020 for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. Avapritinib is not approved for the treatment of any other indication in the US or in any other jurisdiction by the FDA or any other health authority. It has demonstrated potent activity against *KIT* D816V in vitro, robust growth inhibition in a TKI-resistant mastocytoma model in vivo, and tolerability at active doses in toxicology and safety pharmacology studies. An ongoing Phase 1 study of avapritinib in patients with AdvSM (BLU-285-2101) is evaluating safety and preliminary efficacy. The recommended Phase 2 dose (RP2D) for expansion was initially identified as 300 mg once daily (QD); however, based on efficacy, time to response, and long-term safety and dosing data, the starting dose was transitioned to 200 mg QD for all patients. The BLU-285-2101 study is also validating the AdvSM Symptom Assessment Form (AdvSM-SAF) that was developed by Blueprint Medicines and Adelphi Values to assess the impact of avapritinib on symptom improvement in patients with AdvSM.

Preliminary data from the Phase 1 study show that 93% of patients have a ≥ 50% decrease in bone marrow mast cell burden, with 67% of patients in complete marrow remission (N=57). Overall, 100% of patients in the Phase 1 study, have had a ≥ 50% decrease in serum tryptase levels, with 66% falling below 20 mg/mL (N=56). In the subset of patients with AdvSM (N=29) with severe enough organ damage to be considered eligible for a modified IWG-MRT-ECNM response, the ORR (CR/CRh + PR + CI) was 83%. Patients who were assessed for patient-reported outcomes (PROs, N=32) had significant symptom reduction and improved quality of life (QoL) for the most severely symptomatic patients at baseline, based on the AdvSM-SAF Total Symptom Score (TSS) and the [redacted]

Due to the rarity of the diagnosis and applicability of modified IWG-MRT-MRT to only a subset of the AdvSM population (those with evaluable C-findings), the Phase 1 study (BLU-285-2101) enrolled patients with AdvSM who were not evaluable for modified IWG-MRT-ECNM response. These patients still contributed important supportive data for safety and secondary efficacy objectives such as reductions in mast cell burden or improvements in AdvSM symptoms. For these reasons, the Phase 2 study (BLU-285-2202) will now enroll patients who lack an evaluable C-finding at baseline or do not have MCL for supportive data in a separate cohort (Cohort 2).

This Phase 2 study is being conducted to demonstrate the efficacy of avapritinib based on adjudicated ORR by modified IWG-MRT-ECNM consensus response criteria in modified IWG-MRT-ECNM evaluable patients (Cohort 1), to assess the effect of avapritinib on PROs (Cohorts 1 and 2), and to further characterize the efficacy, safety, pharmacodynamic, and pharmacokinetic (PK) profile of avapritinib in patients with AdvSM (Cohorts 1 and 2).

1.2 Avapritinib

1.2.1 Overview

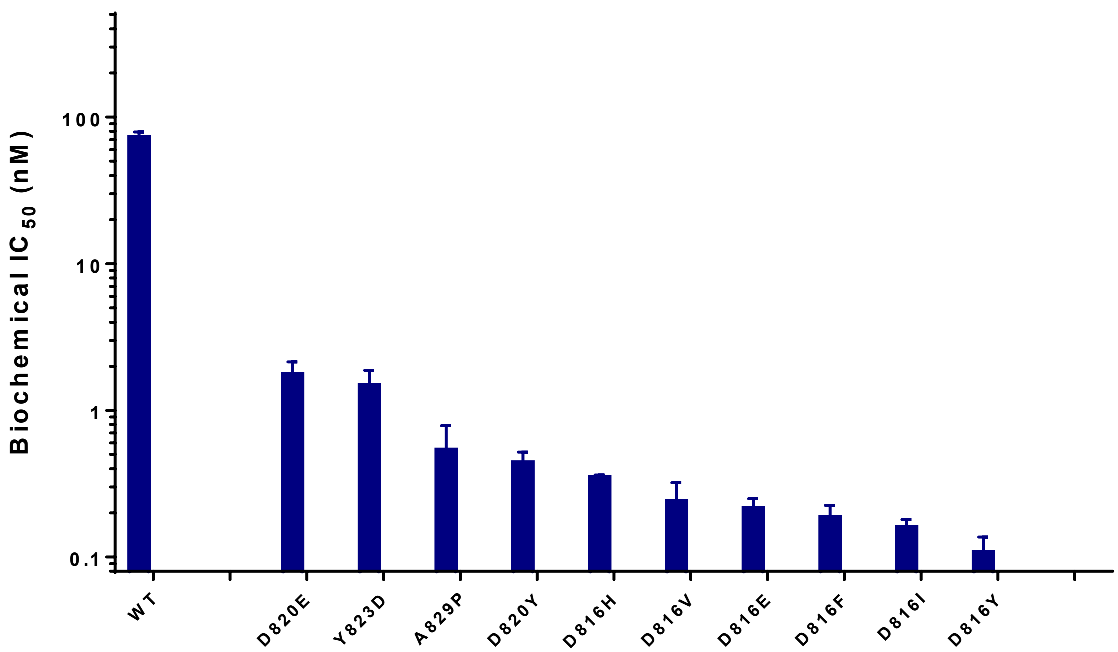
Avapritinib is a highly potent, selective, small molecule inhibitor of *KIT* D816V and other *KIT* exon 17 mutations that mediate ligand independence. Avapritinib demonstrates potent biochemical in vitro activity against *KIT* D816V (half-maximal inhibitory concentration [IC_{50}] = 0.27 nM), as well as all D816 mutations reported in SM patients. It has limited activity against wild-type *KIT* (Table 1 and Figure 1). Avapritinib is highly selective for *KIT* exon 17 mutations compared to other TKIs with activity against *KIT*, as shown by the kinome trees for avapritinib, dasatinib, imatinib, masitinib, and midostaurin (Figure 3). Furthermore, these nonselective TKIs are also less potent in their inhibition of *KIT* D816V mutations than avapritinib (Table 2). Midostaurin has an IC_{50} of 2.8 nM against D816V and is also active against wild-type *KIT*, but is a nonselective inhibitor with activity against all major isoforms of protein kinase C, vascular endothelial growth factor and numerous mutated TKIs, including PDGFR, FGFR1, and FLT3 (Gotlib, et al., 2016). Avapritinib was designed to treat SM by selectively targeting *KIT* D816V and other *KIT* exon 17 mutations.

Table 1: Biochemical Activity of Avapritinib Activity against *KIT* Exon 17 D816 Mutants

D816 Mutation	IC_{50} (nM)
Wild-type	73
D816V	0.24
D816Y	0.11
D816I	0.16
D816F	0.19
D816E	0.22
D816H	0.35

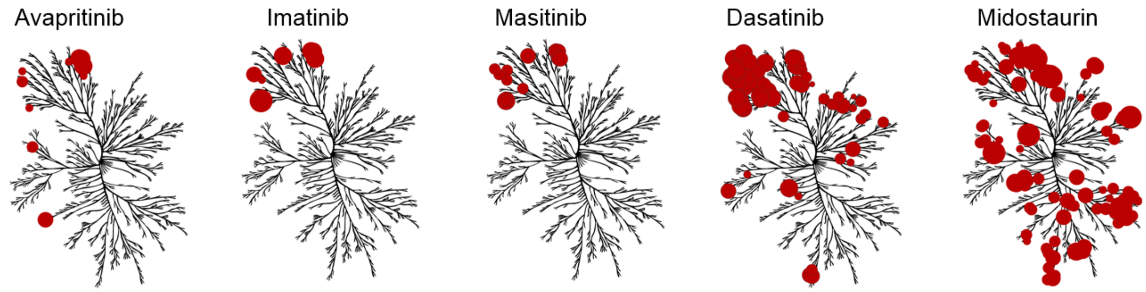
Abbreviations: IC_{50} = half-maximal inhibitory concentration of enzyme activity; *KIT* = V-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog.

Figure 1: Biochemical Activity of Avapritinib against *KIT* Exon 17 Mutants



Abbreviations: IC_{50} = half-maximal inhibitory concentration of enzyme activity; *KIT* = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; WT = wild-type.

Figure 2: *KIT* D816V Inhibition: Selectivity Profile at 3 µM



Abbreviation: *KIT* = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog.
Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc (www.cellsignal.com).

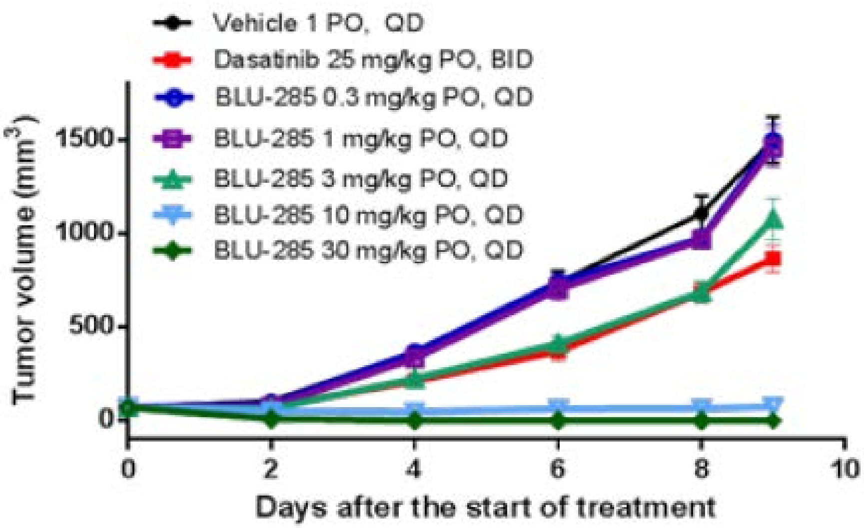
Table 2: Biochemical Activity of Avapritinib and Other Agents with Activity against *KIT* Exon 17 Mutants

Compound	*KIT* D816V IC_{50} (nM)
Avapritinib	0.27
Dasatinib	1.6
Imatinib	8150
Masitinib	> 10,000
Midostaurin	2.8

Abbreviations: IC_{50} = half-maximal inhibitory concentration of enzyme activity; *KIT* = V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog.

In vivo, antitumor efficacy with avapritinib was demonstrated in a P815 mouse mastocytoma cell line allograft model. Avapritinib administered by mouth (PO) in doses ranging from 0.3 mg/kg/day to 30 mg/kg/day resulted in robust and dose-dependent growth inhibition of P815 allograft tumors when assayed after 10 days. At daily doses of either 10 mg/kg or 30 mg/kg, avapritinib resulted in complete tumor growth inhibition and regressions. In contrast, the maximum-tolerated dose (MTD) of the nonselective *KIT* inhibitor dasatinib (25 mg/kg twice daily) resulted in only marginal tumor growth inhibition and rapid weight loss in mice throughout the course of the experiment (Figure 3).

Figure 3: Efficacy of Avapritinib in a *KIT* Exon 17 Mutant-Driven P815 Mouse Mastocytoma Allograft Model



Abbreviations: BID = twice daily; BLU-285 = avapritinib; *KIT* = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PO = orally; QD = once daily.
Mice bearing P815 tumors were dosed PO QD with vehicle, 0.3, 1, 3, 10, or 30 mg/kg avapritinib or 25 mg/kg dasatinib BID. A dose-dependent decrease in tumor growth was observed with QD oral dosing of avapritinib. Oral dosing with avapritinib QD at 10 and 30 mg/kg produced complete tumor growth inhibition with several tumor regressions over a 10-day dosing period. Statistical significance of tumor growth inhibition was determined for the 10 and 30 mg/kg daily doses of avapritinib after 10 days of dosing and was highly statistically significant ($P < 0.001$, as measured by 1-way analysis of variance).

1.2.2 Summary of Clinical Studies of Avapritinib

The avapritinib clinical development program was initiated in August 2015 and includes 2 ongoing Phase 1 clinical studies (in GIST and AdvSM) and an ongoing Phase 3 study in third line GIST. In addition to this study in patients with AdvSM, a Phase 2 study for patients with ISM and SSM is ongoing.

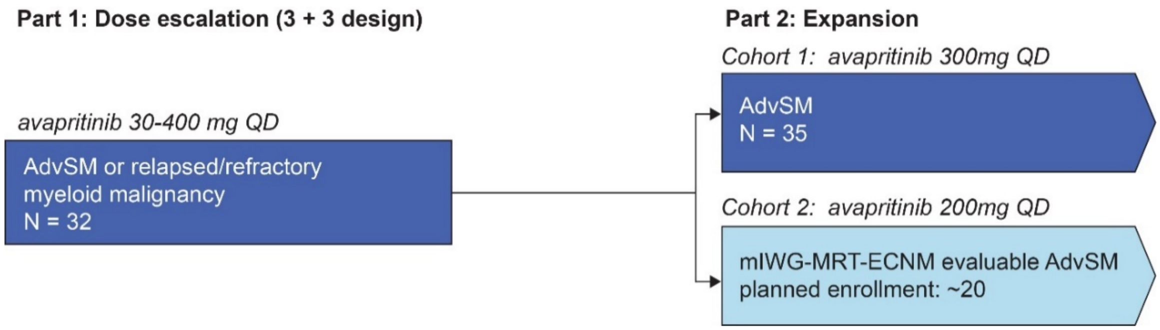
A summary of the data from the Phase 1 study of avapritinib in GIST (BLU-285-1101) is provided in the Investigator’s Brochure (IB).

1.2.2.1 Study BLU-285-2101

BLU-285-2101 is an ongoing 2-part, open label, multicenter, Phase 1 study for patients with AdvSM or relapsed / refractory myeloid malignancies. The study’s primary objective is to determine the MTD, RP2D, safety, and tolerability for avapritinib in patients with AdvSM. Secondary and exploratory objectives include assessing anti-neoplastic activity as measured by changes in serum tryptase, spleen size, mast cell burden, *KIT* D816V mutation allele fraction (MAF) and ORR by centrally adjudicated modified IWG-MRT-ECNM criteria. Additional objectives included assessing duration of response (DOR), OS, and changes in PROs and QoL measures from baseline.

As of 02 January 2019, the study has enrolled 69 patients: 32 in Part 1 Dose Escalation and 37 in Part 2 Cohort 1 Expansion. The study design is presented in Figure 4.

Figure 4: BLU-285-2101 Study Design



Abbreviations: AdvSM = advanced systemic mastocytosis; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; QD = once daily.

Patients in Part 1 received doses ranging from 30 mg to 400 mg daily. The RP2D initially was identified as 300 mg QD, consistent with that in patients with GIST. This was based on a global assessment of safety, in patients with AdvSM from Study BLU-285-2101, as well as additional safety data in patients with GIST from Study BLU-285-1101. Additional long-term safety, efficacy, and exposure data revealed 200 mg QD retained rapid time-to-response, but was better tolerated long-term, so the starting dose of the study was transitioned to 200 mg QD for all patients.

All patients were enrolled with a local diagnosis of AdvSM (or SSM in 2 cases); however, retrospective central pathological review and adjudication found that 53 patients had AdvSM, including 7 patients with ASM, 37 patients with SM-AHN and 9 patients with MCL. There were 15 patients who had ISM or SSM.

At the time of data cutoff, 49 (71%) patients remained on-treatment. The most common reason for discontinuation of study treatment was disease progression in 9 (13%) patients. A total of 3 (4%) patients discontinued treatment for related AEs.

1.2.2.1.1 Efficacy

Overall Response by Modified IWG-MRT-ECNM Criteria

The IWG-MRT-ECNM consensus criteria for AdvSM were established in 2013 (Gotlib, et al., 2013). For the BLU-285-2101 study, at the suggestion of the SM experts on the Response Assessment Committee (RAC), modifications to the IWG-MRT-ECNM criteria were made to increase the number of study eligible evaluable patients by including patients with enlarged spleens that were palpable (≥5 cm instead of >5 cm) below the left costal margin, removed the requirement for a symptomatic spleen, and added a C-finding of medically documented weight loss of >10% within 24 (± 12) weeks.

With these modifications, 39 patients could be evaluated by modified IWG-MRT-ECNM criteria and were adjudicated by the RAC.

The modified IWG-MRT-ECNM criteria also shorten the time to confirmation of progressive disease, and introduce the response category of CRh, which describes patients with deeper than PR responses which fall just shy of meeting CR criteria due to persistent moderate cytopenias.

According to the modified IWG-MRT-ECNM criteria, avapritinib demonstrated a 77% confirmed ORR (CR+CRh+PR+CI) in 39 evaluable patients with AdvSM (Table 3).

Table 3: Overall Response Rate by Modified IWG-MRT-ECNM Criteria in Study BLU-285-2101

Response Category, n (%)	ASM N=3 n (%)	SM-AHN N=28 n (%)	MCL N=8 n (%)	All AdvSM N=39 n (%)
ORR (CR+CRh+PR+CI)[a]	3(100)	21 (75)	6 (75)	30 (77)
95% confidence interval	(29.2-100)	(55.1-89.3)	(34.9-96.8)	(60.7-88.9)
Best response				
CR	0	2 (7)	1 (13)	3 (8)
CRh	0	5 (18)	1 (13)	6 (15)
PR	3 (100)	13 (46)	2 (25)	18 (46)
CI	0	1 (4)	2 (25)	3 (8)
SD	0	7 (25)	2 (25)	9 (23)
PD	0	0	0	0
NE	0	0	0	0

Abbreviations: AdvSM = advanced systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial remission; SD = stable disease.

Responses were seen in each of the 3 AdvSM subtypes. No patients had progressive disease as their best response.

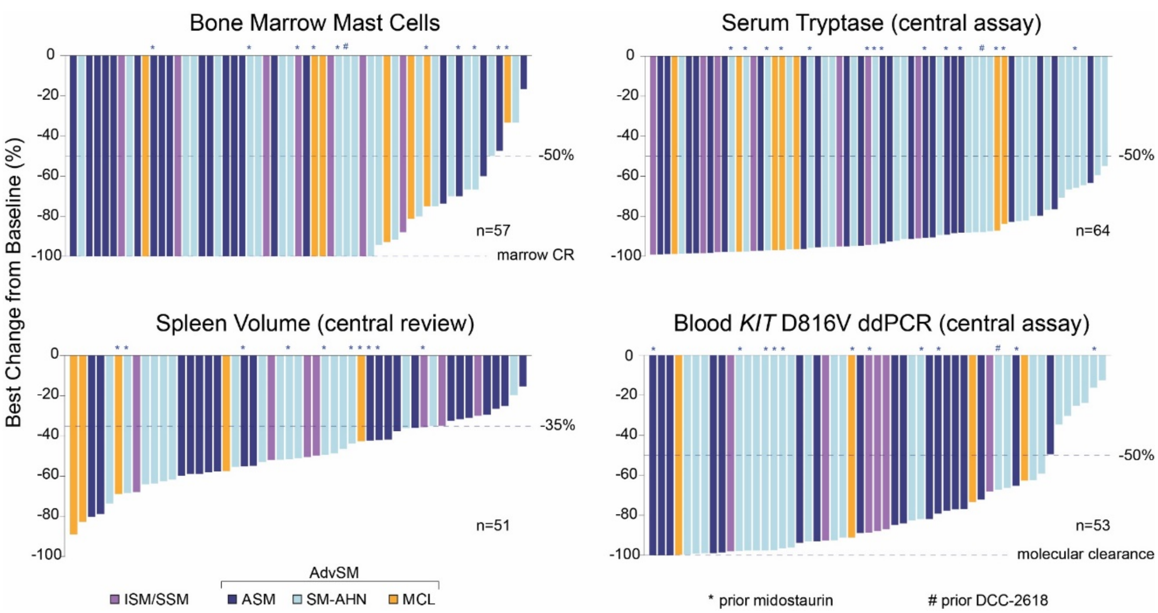
The responses were durable. The median DOR was not reached. The 12-month DOR was 74%. Initial responses occur rapidly, with a median time to initial response of 2 months, the time of the first bone marrow assessment on study. Patients have remained on therapy up to 34 months (and ongoing) and responses have deepened over time, with median time to CR or CRh of 16 months.

Efficacy in Individual Components of Mast Cell Burden

Objective reductions in measures of mast cell burden is a critical component of IWG-MRT-ECNM response, including bone marrow mast cells, serum tryptase and spleen size. In addition, changes in the *KIT* D816V MAF can be measured in the vast majority of patients. Overall, a very high rate of response was observed for each measure of mast cell burden. Avapritinib treatment led to ≥ 50% reductions of bone marrow mast cells in 93% of patients, with marrow CR in 67%. Serum tryptase decreased > 50% in 100% of patients, with 65% of patients experiencing a return to normal serum tryptase levels. Overall, 82% of patients had ≥ 35% reduction in spleen volume (PR criteria), while 73% of palpable spleens became non-palpable (CR criteria). Furthermore, 85% had reduction in *KIT* D816V MAF by ≥ 50%, with 43% dropping below 1% (in those with baseline > 1%) by sensitive digital droplet polymerase chain reaction (PCR).

Similar improvements were observed across all subclasses of AdvSM, as well as in the 7 patients with ISM or SSM, those patients with prior midostaurin therapy. Waterfall plots showing changes in each measure of mast cell burden for all patients with available data (regardless of baseline level) are shown in Figure 5.

Figure 5: Waterfall Plots of Components of Mast Cell Response for Avapritinib



Abbreviations: ASM = aggressive systemic mastocytosis; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm of non-mast-cell lineage; SSM = smoldering systemic mastocytosis.

Patient-Reported Outcomes

Patients with SM frequently have debilitating symptoms which are associated with a poor QoL. The FDA has provided guidance that PROs instruments should be developed with input from and validated in the intended patient population. Because no validated PRO tool has been developed for AdvSM, Blueprint Medicines collaborated with AdelphiValues (Boston, MA) to design the first PRO instrument specifically to measure symptom improvement in patient with AdvSM. Using input from literature, disease experts, regulatory agencies, and patients with AdvSM, Blueprint Medicines and Adelphi

Values designed the AdvSM-SAF (symptom assessment form), which is available in Appendix 15.

Patients in Part 2 of the BLU-285-2101 study were assessed for changes in SM symptoms from baseline using the AdvSM-SAF. As of the data cutoff date (30 September 2018), 32 patients had an imputed baseline TSS. The mean baseline TSS was 19 points (range 0 to 50.2 points). A subset of highly symptomatic patients (top 50th percentile of baseline TSS, n=16) had a mean TSS of 30 points (18 – 50.2 points). Across all patients, avapritinib reduced overall mastocytosis symptoms by about 40% at Cycle 7. Overall, 18 of 22 (80%) patients with baseline steroid use decreased their dose on study, while 9 of 22 (41%) patients discontinued their steroid dose entirely. There was a 60% mean reduction in the most bothersome symptom domain at Cycle 7. Decreases in symptom score were seen across all 8 symptoms, with symptoms in the GI domain improving the most rapidly. Lastly improvements in QoL were seen using the [redacted] instrument, particularly in the most symptomatic patients.

1.2.2.1.2 Safety

As of the 08 July 2019 data cut, most AEs were Grade 1 or Grade 2 in severity and consistent with the effects of wildtype *KIT* and *PDGFRA* inhibition, including anemia, diarrhea, edema (both periorbital and peripheral), nausea, fatigue, thrombocytopenia, vomiting, and hair color changes. Adverse events such as fatigue, nausea, vomiting and diarrhea are common with many tyrosine kinase inhibitors. Non-hematological AEs observed in at least 15% of patients treated with avapritinib as of the cutoff are listed in Table 4. Hematological AEs seen in at least > 10% patients are listed in Table 5.

Table 4: Summary of Non-Hematological Adverse Events by Severity and by Relationship in > 15% Patients in Study BLU-285-2101 (Safety Population; N=77)

		Severity n (%)						
Preferred Term	**Any Events n (%)**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade ≥ 3**	**Related n (%)**
Periorbital edema	55 (71)	40 (52)	12 (16)	3 (4)	0	0	3 (4)	53 (69)
Diarrhea	32 (42)	25 (32)	6 (8)	1 (1)	0	0	1 (1)	21 (27)
Edema peripheral	30 (39)	24 (31)	6 (8)	0	0	0	0	22 (29)
Nausea	29 (38)	18 (23)	8 (10)	2 (3)	1 (1)	0	3 (4)	24 (31)
Fatigue	28 (36)	13 (17)	9 (12)	6 (8)	0	0	6 (8)	19 (25)
Vomiting	24 (31)	19 (25)	2 (3)	2 (3)	1 (1)	0	3 (4)	17 (22)
Hair color changes	23 (30)	21 (27)	0	1 (1)	0	0	1 (1)	23 (30)
Arthralgia	18 (23)	10 (13)	7 (9)	1 (1)	0	0	1 (1)	4 (5)
Abdominal pain	16 (21)	10 (13)	4 (5)	2 (3)	0	0	2 (3)	8 (10)

		Severity n (%)						
Preferred Term	**Any Events n (%)**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade ≥ 3**	**Related n (%)**
Dizziness	14 (18)	11 (14)	2 (3)	1 (1)	0	0	1 (1)	7 (9)
Memory impairment	14 (18)	11 (14)	3 (4)	0	0	0	0	14 (18)
Constipation	13 (17)	9 (12)	3 (4)	1 (1)	0	0	1 (1)	6 (8)
Decreased appetite	13 (17)	9 (12)	3 (4)	0	0	0	0	6 (8)
Dysgeusia	13 (17)	11 (14)	2 (3)	0	0	0	0	10 (13)
Pruritus	13 (17)	11 (14)	2 (3)	0	0	0	0	2 (3)
Cough	12 (16)	10 (13)	2 (3)	0	0	0	0	2 (3)
Epistaxis	12 (16)	9 (12)	3 (4)	0	0	0	0	7 (9)
Headache	12 (16)	6 (8)	6 (8)	0	0	0	0	8 (10)
Hypokalemia	12 (16)	9 (12)	0	3 (4)	0	0	3 (4)	3 (4)

Data cut-off date: 08 July 2019.

The most common nonhematological AEs were related to edema and included periorbital edema (71%; 4% ≥ Grade 3), peripheral edema (39%; none ≥ Grade 3), , and pleural effusion (14%; 4% ≥ Grade 3). Gastrointestinal AEs were common and included diarrhea (42%; 1% ≥ Grade 3), nausea (38%; 4% ≥ Grade 3), vomiting (31%; 4% ≥ Grade 3), abdominal pain (21%; 3% ≥ Grade 3), and constipation (17%; 1% ≥ Grade 3).

Of note, alkaline phosphatase increases occurred (12%, 6% ≥ Grade 3), typically upon initiation of avapritinib, peaked by weeks 2-4, and improved without dose modification or other intervention. They often occurred in patients with baseline alkaline phosphatase elevation, often doubling or tripling the baseline value, without concomitant increases in other liver enzymes. In a few cases, Investigators reported that the increased alkaline phosphatase was fractionated and found to be mostly of bone origin and is hypothesized to be related to clearance of mast cells in the bone.

Table 5: Summary of Hematological Adverse Events by Severity and by Relationship in > 10% Patients in Study BLU-285-2101 (Safety Population; N=77)

		Severity n (%)						
Preferred Term	**Any Events n (%)**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade ≥3**	**Related n (%)**
Anemia	41 (53)	9 (12)	11 (14)	20 (26)	1 (1)	0	21 (27)	32 (42)
Thrombocytopenia	28 (36)	4 (5)	5 (6)	13 (17)	6 (8)	0	19 (25)	20 (26)
Neutropenia	10 (13)	0	0	7 (9)	3 (4)	0	10 (13)	10 (13)

Data cut-off date: 08 July 2019.

Cytopenias

Avapritinib may lead to cytopenias and may worsen baseline cytopenias due to SM and/or AHN involvement of the bone marrow. Cytopenias included anemia (53%; 27% ≥ Grade 3), thrombocytopenia (36%; 25% ≥ Grade 3) and neutropenia (13%, 13% ≥ Grade 3). Cytopenias were the most common ≥ Grade 3 AEs and they were the most common reason for dose modification on study. Decreases in platelet count can commonly occur within 1 or 2 weeks of initiating avapritinib, which often nadirs and stabilizes within 4 to 8 weeks without dose modification. In addition, severe decreases in platelet counts may occasionally occur as a late event, sometimes in the context of progressive disease.

Cognitive Effects

Cognitive effects have occurred in patients treated in avapritinib clinical trials. In AdvSM, these AEs include memory impairment (19%; 0% ≥ Grade 3), cognitive disorder (10%; 1% ≥ Grade 3), and confusional state (9%, 1% ≥ Grade 3). The majority of cognitive effect AEs were Grade 1 and Grade 2. Cognitive effects appear to be associated with higher starting doses and cumulative dose. Based on Investigator feedback, common complaints include short-term memory impairment, such as forgetting tasks, difficulty finding the right word and slowness with complex cognitive tasks, particularly those requiring short term memory. Encephalopathy has been reported in 3 patients (4%; 3% ≥ Grade 3), leading to treatment discontinuation in 1 patient.

Intracranial Bleeding

Subdural hematomas and intracranial hemorrhages have occurred in patients with SM and GIST. In patients with GIST, intracranial bleeding events occur in about 1.5% of patients. As of 08 July 2019, 7 of 86 (8.1%) patients have experienced intracranial bleeding events on studies of avapritinib in AdvSM, including the BLU-285-2101 and BLU-285-2202 clinical trials. Four patients had Grade 1 asymptomatic events, 2 patients had Grade 2 events, and 1 patient had a Grade 3 event.

In SM, intracranial bleeding events have occurred in the context of severe thrombocytopenia (< 50,000/µL platelets) in nearly all cases, which may occur at baseline or develop on study in the AdvSM population (such as in context of progressive AHN). Patients with severe thrombocytopenia or those receiving platelet transfusions at baseline were the most likely to remain severely thrombocytopenic on study, and these patients had the highest incidence of intracranial bleeding, with 4 events in 11 patients (36%).

As of 08 July 2019, 2 non-traumatic intracranial bleeding events have occurred in 75 patients (2.7%) with ≥ 50,000/µL platelets at baseline (87% of patients), who each subsequently developed < 50,000/µL platelets for weeks prior to documenting the intracranial bleeding event. In addition, one traumatic intracranial bleeding event occurred in a patient with normal platelet counts that tripped and fell down the stairs, hitting their head and breaking 3 ribs.

No evidence of re-bleeding has been reported in the 5 patients that resumed (after interruption and reduction in dose) or continued therapy after the intracranial bleeding event. Of the 2 patients that discontinued therapy: 1 patient stopped therapy after the intracranial bleeding event as it occurred in the context of progressive disease and 1 patient stopped due to the intracranial bleeding event and subsequently the intracranial bleeding resolved.

After the 08 July 2019 safety analysis, an additional intracranial bleeding event of subdural bleeds, Grade 5, occurred in a patient with SM-AHN who had been on therapy with relatively stable platelet counts out to 16 cycles. Then, the platelet count dropped from 96,000/µL to 55,000/µL over 2 months. After an additional 2 months and a missed study visit, the patient presented with severe headaches after a fall, with platelets of 40,000/µL and patient was found to have bilateral subdural hematomas, which resulted in a fatal outcome.

1.3 Study Rationale

Gain-of-function mutations in *KIT* promote ligand-independent, oncogenic signaling, which appears central to the pathogenesis of AdvSM (Theoharides, et al., 2015; Verstovsek, 2013), with 90-95% of SM patients demonstrating mutations in *KIT* D816 (Garcia-Montero, et al., 2006). Imatinib is a TKI that shows activity against *KIT* but is inactive against D816 mutations (Glivec SmPC). Midostaurin has activity against both wild-type and mutated *KIT*, including D816V, and recently received approval by both the FDA and EMA for treatment of AdvSM (Rydapt, 2017a; Rydapt, 2017b). However, by IWG-MRT-ECNM consensus response criteria, the rate of CR + PR was only 17% and CR + PR + CI was only 28%; treatment discontinuation due to AEs occurred in 21% of patients with 56% of patients requiring dose modification due to toxicity. Therefore, there is a need for more efficacious and better-tolerated agents.

Avapritinib was developed to selectively target *KIT* D816V and other *KIT* exon17 mutations. Avapritinib has demonstrated potent and selective activity against *KIT* D816V in vitro, robust growth inhibition of TKI-resistant mastocytoma models in vivo, and tolerability at active doses in toxicology and safety pharmacology studies. Data from the ongoing Phase 1 study of avapritinib in patients with AdvSM or other myeloid malignancies (BLU-285-2101) show an 83% modified IWG-MRT-ECNM ORR (CR+CRh+PR+CI) with a median DOR not reached, and 78% of patients remaining on study. This supports the efficacy and safety of avapritinib in the AdvSM population and further evaluation in this study.

The primary objective of this study is to determine the efficacy of avapritinib in AdvSM, as measured by adjudicated ORR by modified IWG-MRT-ECNM criteria. This will be determined based on improvements in quantifiable objective findings of SM related organ damage, known as modified IWG-MRT-ECNM C-findings (such as Grade 2 anemia) and reductions in measures of mast cell burden (such as tryptase). Although patients with AdvSM may have a range of signs and variable severity of organ damage, only those with 1 or more modified IWG-MRT-ECNM evaluable C-findings (or MCL, regardless of C-findings) will be prospectively enrolled into Cohort 1 and considered in the primary endpoint.

Rationale for Single Arm Study Design

BLU-285-2202 is a global Phase 2 study being conducted in the US, Europe, and Canada and was designed to confirm the high response rates observed in the ongoing Phase 1 study in AdvSM. The purpose of the BLU-285-2202 study is to obtain additional safety and efficacy data for avapritinib in patients with AdvSM, which may inform future trials in the clinical development program. A comparator trial with midostaurin is considered infeasible at this time due to the rarity of the disease, particularly with the limitations of studying only patients evaluable by modified IWG-MRT-ECNM criteria for the primary objective.

Rationale for the Continued Enrollment of Midostaurin-naïve Patients

The ongoing BLU-285-2101 avapritinib Phase 1 study was initiated in March 2016, before the approval of midostaurin in 2017 for AdvSM, and thus the vast majority of enrolled patients are midostaurin-naïve. As of 02 January 2019, the study had enrolled 54 midostaurin-naïve patients (78% of the total enrollment of 69 patients). Based on the encouraging results of the Phase 1 study, avapritinib has received Breakthrough Therapy Designation by the FDA for the treatment of AdvSM and Orphan Drug Designation by EMA in October 2018.

Modified IWG-MRT-ECNM evaluable patients with AdvSM treated with avapritinib (n=39) had a confirmed ORR of 77%, with a 23% confirmed CR/CRh rate. Among midostaurin-naïve AdvSM patients (n=29), the confirmed ORR was 83% with a 31% confirmed CR/CRh rate. In contrast, the recently EMA approved midostaurin had an IWG-MRT-ECNM confirmed ORR of only 28% and CR rate of only 1% on the pivotal D2201 study (Table 6). Avapritinib reduced objective measures of mast cell burden, including bone marrow mast cell burden, serum tryptase and spleen size in 100% of patients on study, regardless of modified IWG-MRT-ECNM evaluability (Figure 5). This is in contrast with midostaurin, for which 9% to 20% of patients on the D2201 study had increases in mast cell burden as their best response.

Table 6: Confirmed Overall Response Rate of Midostaurin Compared to Avapritinib with IWG-MRT-ECNM Criteria

Best Confirmed Response	Midostaurin D2201[a] All subtypes (N=113)	Avapritinib BLU-285-2101[b] All subtypes (N=39)	
		Prior Midostaurin Use| N=10	Midostaurin-naive N=29
ORR (CR+PR+CI)	32 (28%)	6 (60%)[c]	24 (83%)[c]
CR	1 (1%)	0	3 (10%)
CRh	N/A	0	6 (21%)
PR	17 (15%)	5 (50%)	13 (45%)
CI	14 (12%)	1 (10%)	2 (7%)

Abbreviations: CI = clinical improvement; CR = complete remission; CRh = Complete remission with partial recovery of peripheral blood counts; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis; ORR = overall response rate; PR = partial remission. N/A = not available.
[a] Source: European public assessment report for midostaurin (EMA, 2017).
[b] Data cutoff 02 January 2019. Modified IWG-MRT-ECNM criteria introduces CRh, which would be considered a PR by published IWG-MRT-ECNM criteria.
[c] Includes CRh.

Of note, midostaurin is frequently associated with GI side effects, including nausea (82%, 6% ≥ Grade 3) and vomiting (68%, 6% ≥ Grade 3), and treatment with prophylactic anti-emetics is recommended. In addition, there is significant pulmonary toxicity associated with midostaurin, including dyspnea (23%, 7% ≥ Grade 3), pneumonia (10%, 8% ≥ Grade 3) as well as cases of fatal interstitial pneumonitis.

As avapritinib may provide a substantial improvement over midostaurin, the Sponsor believes that midostaurin-naïve patients should continue to have access to avapritinib in this Phase 2 clinical study and that it should be studied in the midostaurin-naïve and post-midostaurin settings to understand its safety and efficacy in each.

Rationale for the Enrollment of Patients with AdvSM Beyond Those Evaluable by Modified IWG-MRT-ECNM Criteria

The primary objective of assessing modified IWG-MRT-MRT response requires that patients have a C-finding or a diagnosis of MCL and limits enrollment to a subset of the AdvSM population with sufficiently severe and quantifiable organ damage, or MCL. Secondary objectives such as assessing changes in PROs, reductions in mast cell burden, overall survival, PK, and safety do not require an evaluable C-finding for evaluation. Given the rarity of AdvSM, limiting enrollment to only those evaluable by modified

IWG-MRT-ECNM criteria substantially reduces the opportunity to generate additional data for these secondary objectives.

Importantly, patients with AdvSM have decreased survival, have limited treatment options, and can be highly symptomatic, even without the presence of modified IWG-MRT-ECNM C-findings, thus an alternative therapy is very important for these patients. If they are unable to participate in the trial, compassionate use of avapritinib would be the only route of access for avapritinib at this time.

Lastly, excluding patients who do not have a modified IWG-MRT-ECNM C-finding can occasionally lead to a very late screen failure, even at C1D1. This is because patients' laboratory C-findings can sometimes fluctuate at the border of eligibility. For example, a Study Steering Committee (SSC) approved patient who has a C-finding of anemia with a hemoglobin of 9.9 g/dL (Grade 2) in Screening may have a hemoglobin of 10.1 g/dL (Grade 1) on C1D1 and thus become ineligible by modified IWG-MRT-ECNM criteria. Excluding a patient at the last minute with a life-threatening disorder such as AdvSM, for a clinically insignificant fluctuation in laboratory test results, would be very distressing for a patient and investigator alike. Loss of a laboratory C-finding at C1D1 occurred in several patients on the Phase 1 study, however on that study it was not required for enrollment.

For these reasons, patients with AdvSM (ASM or SM-AHN), but without an evaluable modified IWG-MRT-ECNM C-finding at baseline (defined at the most recent lab results prior to dosing) will be eligible for enrollment in Cohort 2. This cohort will generate critical data for secondary endpoints, greatly improve the feasibility of the study and provide patients with AdvSM with an alternative treatment option.

Rationale for Key Secondary Objective Assessing Changes in Patient Symptoms

Patients with AdvSM may experience a wide variety of subjective symptoms, including fatigue, nausea, vomiting, abdominal pain, rash, flushing, itching, and allergy symptoms, which can be very severe or life threatening and can dramatically reduce QoL. These subjective symptoms of AdvSM are poorly correlated to objective findings of mast cell burden and patients without an objective modified IWG-MRT-ECNM C-finding may still have significant SM related symptoms and poor QoL and the objective ORR endpoint does not capture if a patient's symptoms are actually improving. To address this, the Sponsor designed the AdvSM-SAF, with input from experts, patients, and regulatory authorities, to measure changes in subjective symptoms with avapritinib. Change from baseline TSS, as measured by the daily AdvSM-SAF, is the key secondary endpoint of the study for all patients, regardless of the cohort.

Rationale for Dose Modifications and Exclusion Criteria for Severe Thrombocytopenia

As noted above, intracranial bleeding events have occurred in the Phase 1 BLU-285-2101 study and is higher (~8%) than the incidence in patients with GIST treated with avapritinib of approximately 1.5%. There is precedence for differences in intracranial bleeding rate between diseases/stage of disease, for example, in patients treated with imatinib. Central nervous system hemorrhage occurred in 9% of patients with chronic myeloid leukemia (CML) in myeloid blast crisis, 2% of patients with CML in chronic phase (interferon failure) but is not specifically noted as an AE for patients in GIST trials (Glivec SmPC). Of note, serious bleeding events have also been previously reported in the SM and AHN literature and have been attributed to disease-related coagulopathy and thrombocytopenia (Arias, et al., 2004; Kantarjian, et al., 2007; Sucker, et al., 2008).

In the BLU-285-2101 trial for SM patients, events appear to be strongly associated with severe thrombocytopenia and to a lesser extent, higher doses. Based on these associations, subsequent safety analysis, and guidance from investigators and regulatory authorities, several changes were instituted to reduce the risk of intracranial bleeding.

Patients with < 50,000/µL platelets (within 4 weeks of first dose of study drug) or receiving platelet transfusion(s) are at the highest risk of intracranial bleeding and are now excluded from enrollment in the study. Patients previously enrolled with low platelets or transfusions at baseline may continue on study if they follow the new monitoring dose modification guidance.

Platelet monitoring for all patients must now occur every 28 days, and for patients with platelet counts < 75,000/µL, every 14 days (See Table 8). Patients must interrupt avapritinib therapy if their platelet count drops below 50,000/µL. A patient's platelet count must then recover to ≥ 50,000/µL with interruption and/or with supportive care (growth factors or platelets transfusions) before restarting therapy with avapritinib.

Any coagulopathy should be corrected and followed at every study visit. Concomitant antithrombotic and anticoagulant medications should be discontinued when patients are severely thrombocytopenic. A focal neurological history and exam should be performed at every visit to assess for signs and symptoms of intracranial bleeding.

1.4 Risk/Benefit Assessment

Advanced systemic mastocytosis is a rare hematological malignancy characterized by infiltration of organs by abnormal MCs and symptoms related to MC degranulation and release of their contents. Patients with AdvSM have evidence of organ damage and decreased survival.

Midostaurin is a multikinase inhibitor that is approved for FLT3+ acute myeloid leukemia (AML) and is the only agent approved specifically for AdvSM. It is modestly active on *KIT* D816V, which translates into an IWG-MRT-ECNM ORR of 28% in AdvSM (Rydapt, 2017b). Midostaurin is frequently associated with GI side effects, including nausea (82%, 6% ≥ Grade 3) and vomiting (68%, 6% ≥ Grade 3), and treatment with prophylactic anti-emetics is recommended. In addition, there is significant pulmonary toxicity associated with midostaurin, including dyspnea (18%, 6% ≥ Grade 3), pneumonia (9%, 7% ≥ Grade 3) as well as cases of fatal interstitial pneumonitis.

Avapritinib is a highly potent, selective, small molecule inhibitor of *KIT* D816V mutant, which drives AdvSM in 90% to 95% of cases. Avapritinib demonstrates potent biochemical in vitro activity against D816V mutant *KIT*, as well as all D816 *KIT* mutations reported in SM patients. Avapritinib is highly selective for exon 17 mutant *KIT* compared to other TKIs with activity against *KIT*, including midostaurin.

In the ongoing Phase 1 study of avapritinib in patients with AdvSM or other refractory myeloid malignancies (BLU-285-2101), preliminary data from the 02 January 2019 data cut have demonstrated robust efficacy with a confirmed ORR of 77% as per modified IWG-MRT-ECNM criteria, a substantial improvement over midostaurin. A median DOR had not been reached. All patients had reductions in mast cell burden, such as bone marrow mast cells, serum tryptase and spleen size, regardless of subtype, prior therapy or co-mutation profile. Avapritinib received Breakthrough Therapy Designation by the FDA for the treatment of AdvSM and was designated as an orphan drug in the European Union for the indication of mastocytosis based on preliminary efficacy data from the BLU-285-2101 study.

In the BLU-285-2101 study, 64% of patients remain on study, with only 6 (8%) patients discontinuing for a treatment related AE (cognitive disorder, nausea, refractory ascites, encephalopathy, pleural effusion, and intracranial bleed). Most AEs have been Grade 1 or Grade 2 (see Section 1.2.2.1.2).

Cognitive effects have been observed in 31% of patients, including memory impairment and cognitive disorder. Early evidence suggests that these events are primarily Grade 1-2, and often improve with dose interruption and reduction and have led to treatment discontinuation in only a small number of patients.

Intracranial bleeding occurred in ~8% of AdvSM patients overall, with greatest risk in patients that were severely thrombocytopenic, or requiring platelet transfusions, at baseline. These patients will now be excluded from the clinical trial. In patients who were not severely thrombocytopenic and unsupported by platelet transfusions at baseline, the non-traumatic intracranial bleeding event rate was 2.7%. Each of these cases were associated with the development of severe thrombocytopenia on study, and increased monitoring of complete blood counts (CBCs) and stronger guidance for dose modifications for thrombocytopenia have been implemented to further reduce risk. The Sponsor believes that these events are primarily related to severe thrombocytopenia and thus are monitorable and manageable by exclusion of the most at-risk patients, increased monitoring and additional guidance around thrombocytopenia and other bleeding risk factors, as noted above. In addition, bleeding and management of thrombocytopenia is a common feature of other kinase inhibitors which treat hematological malignancies, such as imatinib, dasatinib and ruxolitinib, thus hematologists are commonly experienced in managing these issues.

AdvSM is a highly symptomatic neoplastic disease of mast cells which leads to decreased survival. Given the robust overall response rate of 77%, duration of response, improvements in patients symptoms and capability to manage adverse events through dose modification, we believe the benefit/risk assessment of avapritinib in AdvSM is positive and warrants further investigation and availability to both midostaurin-naïve and post midostaurin patients, with appropriate management guidance.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to determine adjudicated ORR of CR/CR with partial recovery of peripheral blood (PB) counts (CRh) + PR + CI based on modified IWG-MRT-ECNM consensus response criteria in patients with AdvSM treated with avapritinib and enrolled in Cohort 1.

2.2 Secondary Objectives

2.2.1 Key Secondary Objective

The key secondary objective for patients in Cohorts 1 and 2 is to assess mean change from baseline in AdvSM-SAF TSS.

2.2.2 Additional Secondary Objectives

Additional secondary objectives for patients in Cohorts 1 and 2 are to:

- Determine local investigator determined ORR based on modified IWG-MRT-ECNM consensus response criteria, using C-findings when present at baseline
- Determine time-to-event outcomes including time-to-response (TTR), DOR, PFS, and OS.
- Determine morphologic response (CR/CRh+ PR) based on Pure Pathological Response criteria and as defined in Appendix 8.
- Determine ORR and other clinical outcome measures (DOR, PFS, and OS) analyzed by prior therapy and by genotype.
- Assess changes in the following individual measures of MC burden:
    - BM MCs.
    - Serum tryptase.
    - *KIT* mutation burden (eg, D816V) in PB and BM.
    - Liver and spleen volume by imaging.
- Assess additional PROs using the AdvSM-SAF, including change from baseline in:
    - Symptom domain scores.
    - Individual symptom scores.

- Assess changes in QoL measures, including the [redacted]
- Assess the safety of avapritinib by AEs, vital signs, electrocardiograms (ECGs), and laboratory tests.
- Assess the PK of avapritinib.
- Correlate avapritinib exposure with safety and efficacy endpoints.

2.3 [redacted]

[redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is adjudicated ORR (CR/CRh + PR + CI) based on modified IWG-MRT-ECNM criteria, confirmed 12 weeks after initial response in patients in Cohort 1 only.

3.2 Secondary Endpoints

3.2.1 Key Secondary Endpoint

The key secondary endpoint is the mean change from baseline in AdvSM-SAF TSS in patients in Cohorts 1 and 2.

3.2.2 Other Secondary Endpoints

Additional secondary endpoints for patients in Cohorts 1 and 2 are:

- Local Investigator assessed ORR (CR/CRh + PR + CI) based on modified IWG-MRT-ECNM criteria, using C-findings when present, confirmed 12 weeks after initial response.
- Objective response rate (CR/CRh + PR) based on Pure Pathological Response criteria.
- Time-to-event outcomes including: TTR, DOR, PFS, and OS.
- CR/CRh + PR and clinical benefit (CR/CRh + PR + CI + SD) based on modified IWG-MRT-ECNM criteria.
- Overall response rate and other clinical outcome measures (DOR, PFS, OS) analyzed by prior therapy and by genotype.
- Changes in BM MCs, serum tryptase, *KIT* mutation burden (eg, D816V) in PB and BM, and liver and spleen volume by imaging.
- Mean change from baseline in AdvSM-SAF domain and individual symptom scores.
- Changes in [redacted]
- Safety of avapritinib, as assessed by AEs, changes in vital signs, ECGs, and laboratory testing.
- PK of avapritinib.

- Correlations between avapritinib exposure and safety and efficacy endpoints.

3.3 [redacted]

[redacted]

4 STUDY PLAN

4.1 Study Design

This is an open-label, single-arm, Phase 2 study evaluating the efficacy and safety of avapritinib in patients with a WHO diagnosis of AdvSM, including patients with ASM, SM-AHN, and MCL. Patients with a centrally confirmed WHO diagnosis of AdvSM will be enrolled into 1 of 2 cohorts. Cohort 1 will enroll patients, confirmed by a SSC; Section 4.1.1, to meet modified IWG-MRT-ECNM criteria for evaluable disease (have severe and quantifiable organ damage (an evaluable C-finding) or have MCL (regardless of C-findings). Cohort 1 patients will support the primary objective of determining adjudicated ORR by modified IWG-MRT-ECNM criteria.

Cohort 2 will enroll patients with AdvSM who are not considered eligible for an adjudicated response, those who were confirmed centrally to have ASM or SM-AHN but are lacking an evaluable C-finding (as determined by the SSC). Cohort 1 and Cohort 2 will be included in the key secondary objective of assessing efficacy on TSS improvement. Both cohorts will also support additional secondary and exploratory endpoints such as investigator determined response and safety.

Screening: Informed consent must be obtained within the 56 days (8 weeks) before initiation of treatment with avapritinib and before initiation of any Screening procedures. Patients will be instructed on use of the AdvSM-SAF daily diary and symptom collection should be initiated as soon as possible during Screening to ensure that handheld devices are functioning and transmitting data properly, that patients correctly understand the use the device and that at least 7 days of baseline data before C1D1 is recorded. Patients who are unable to consistently and accurately use the AdvSM-SAF tool due to disability, non-fluency in the available languages, or another reason may still enroll with written permission of the Sponsor. Management of symptoms should be optimized, including a stable dose of BSC medication and schedule for symptom management ideally for 14 days before Cycle 1 Day -8 (C1D-8).

A washout of any cytoreductive and investigator agents must occur before BM biopsy, aspirate and PB is taken for Screening. Two sets of BM and PB samples must be drawn at each timepoint, one for central review, the other for local review. Archival BM biopsy, and the corresponding CBC (within ± 7 days), aspirate, and PB may be submitted as the central sample if taken within 56 days of C1D1 and otherwise meets the same washout criteria. Hematology and serum chemistry and C-finding measurement and attribution must take place after washout as well. All eligibility assessments will be completed and eligibility are to be confirmed by the study site on or before Cycle 1 Day -8 (C1D-8), with the exception of confirmation of eligibility by the SSC. Refer to Appendix 3 for timeframes pertaining to the collection of Screening assessments. Note: timeframes for Screening assessments (eg, between C1D-56 and C1D-8 or between C1D-7 and C1D-1) represent the maximum duration of time. Activities can be completed sooner than the last possible day, or within a shorter timeframe.

The diagnosis of SM for study eligibility is to be assessed using WHO criteria for diagnosis of SM and subclassification of AdvSM (Appendix 4 and Appendix 5, respectively). A comparison of WHO and modified IWG-MRT-ECNM C-finding criteria is provided in Appendix 10.

Evaluation, measurement, assessment of attribution, and documentation of laboratory C-findings based on modified IWG-MRT-ECNM criteria for eligibility by the study site will be completed between C1D-14 and C1D-8 to allow sufficient time for data transfer and evaluation of eligibility by the SSC. Only patients meeting eligibility based on SSC review of Central Pathology Review of BM samples (screening samples, and other tissue samples when available) will be enrolled in the study. Patients with AdvSM confirmed by the SSC as having an evaluable C-finding per modified IWG-MRT-ECNM criteria attributable to SM or patients with MCL, regardless of C-findings will be enrolled in Cohort 1. Patients with AdvSM confirmed by the SSC as not having an evaluable C-finding per modified IWG-MRT-ECNM criteria will be enrolled in Cohort 2 (with the exception of MCL). Once eligibility is confirmed by the SSC, patients will initiate therapy with avapritinib.

Treatment: Avapritinib will be administered orally and continuously, in 28-day cycles (see Section 6.3). Guidelines for dose modification are in Section 6.3.1.

Study drug will be administered until the patient has confirmed progressive disease (PD) of SM, clinical progression of SM or AHN. Progressive disease of SM confirmed by modified IWG-MRT-ECNM criteria 4 weeks after initial documentation of PD, unless the patient has clinical progression of SM or AHN, which in the opinion of the Investigator requires immediate initiation of cytoreductive therapy, or until the drug is no longer tolerated, the Investigator withdraws the patient, or the patient withdraws or dies.

All patients will have study visits at C1D1, at the end of Week 2 (C1D15), Week 4 (C2D1), and Week 8 (C3D1), then every 8 weeks through Cycle 11, and then every 12 weeks. Complete blood counts must be performed every 4 weeks (28 days), and for patients with platelet counts < 75,000/µL, every 14 days, through EOT to monitor for thrombocytopenia. Assessments will be performed as detailed in the Schedule of Assessments (Appendix 1) and in Section 7, Description of Study Procedures.

At all study visits, CI response will be assessed based on local laboratory tests (hematology and serum chemistry) and other clinical findings (eg, transfusions, paracenteses, physical examination). Red blood cell (RBC) and platelet transfusion requirements, as well as requirements for paracentesis, thoracentesis, and diuretics to manage symptomatic ascites and/or pleural effusions will be monitored continuously. At each study visit, C-findings which have not resolved or are worsening must be assessed by the local investigator as to whether they are still attributable to SM, or if they are more likely due to another reason. Patients with baseline biopsy and documented involvement by SM in an extracutaneous organ may undergo repeat biopsy at any of these time points, at the discretion of the Investigator, to assess response of SM to treatment with avapritinib in that organ or assist in determining if ongoing organ damage is attributable to SM.

All patients will have the following assessments performed on C3D1, C7D1, and C11D1, then every 6 cycles for response assessment: serum tryptase, *KIT* D816V and other mutations; BM biopsy and aspirate, and PB collection; BM aspirate for cytogenetics; assessment of C-findings; liver and spleen imaging; and skin photography (through Cycle 17). The local investigator will assess response per modified IWG-MRT-ECNM response criteria, using local pathology and using baseline C-findings when present (Appendix 7 and Appendix 9). Additionally, patients with myeloid AHN will be assessed by the local investigator for AHN response using the criteria outlined in Appendix 11.

Blood sampling to determine plasma concentrations of avapritinib will occur on Day 1 of Cycles 1, 2, 3, and 5 as well as on C1D15 in all patients. In addition, in a subset of up to 15 patients, more intensive PK sampling will be performed.

In addition to local investigator assessment of response, response will also be adjudicated by central committees. For patients in Cohort 1, adjudicated ORR will be assessed using modified IWG-MRT-ECNM consensus response criteria by the SSC, using central pathology. AHN response will also be adjudicated by the SSC for all patients with an AHN component. Cutaneous disease will be assessed in all patients with baseline mastocytosis in skin using standardized photography with response determined by an independent Skin Assessment Committee (through Cycle 17 only).

Patients demonstrating an SM response of CR/CRh, PR, and CI will be confirmed 12 weeks (± 4 weeks) after initial response by the assessments referred to above. For patients with PD due to SM, progression of disease will be confirmed 4 weeks after initial documentation by the same assessments, unless the patient has clinical progression which, in the opinion of the Investigator, requires an immediate change in therapy. If criteria for SM PD are not confirmed, the patient will not be considered to have progressed and may remain on study. Criteria for CR/CRh, PR, CI, SD, and PD are in Appendix 7 and Appendix 9.

For patients with AHN, AHN response will be assessed at the same time points as SM response using the criteria outlined in Appendix 11. Disease progression will be confirmed 4 weeks after initial documentation by the same assessments referred to above unless the patient has clinical progression that, in the opinion of the Investigator, requires an immediate change in therapy. Patients requiring treatment of AHN will be discontinued from study.

The AdvSM-SAF will be collected daily from Screening C1D-7 to ensure at least 7 days of baseline data, through Cycle 17 (ie, 71 weeks) or until the patient discontinues from the study, if before Cycle 17. The [redacted] will be collected at each scheduled study visit through Cycle 17 and at end-of-treatment (EOT), if EOT is at or before Cycle 17.

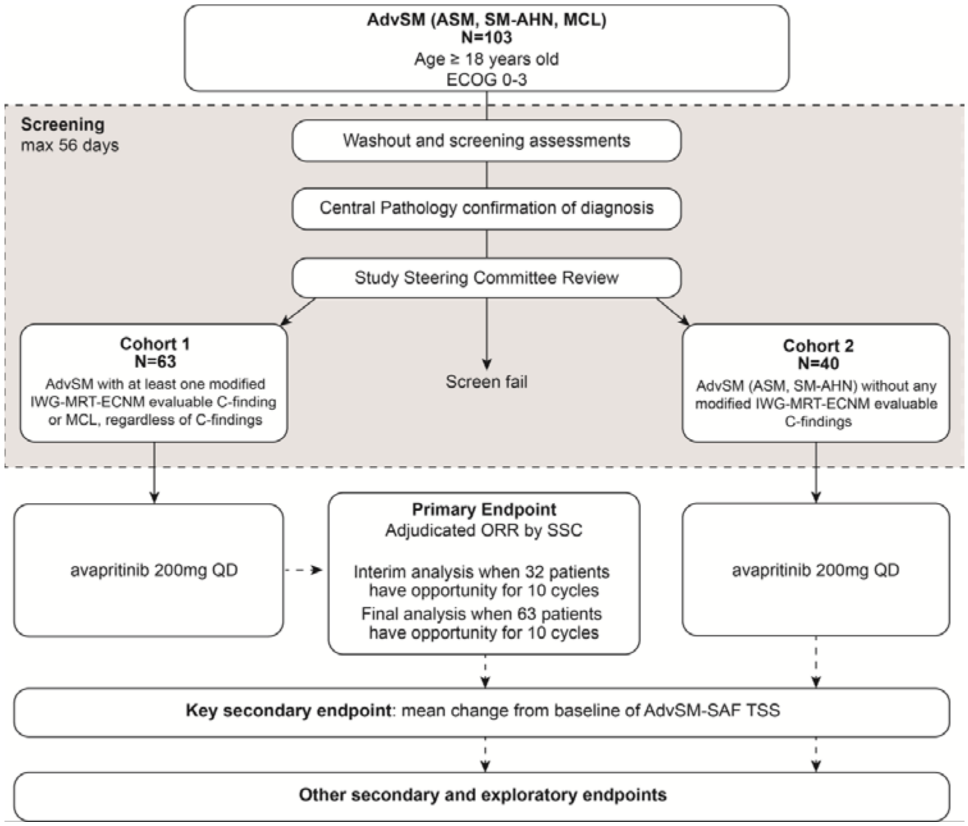
End-of-Treatment and Follow-up: All patients are to have an EOT visit 14 days after discontinuation of study treatment. Patients who discontinue from the study drug for reasons other than confirmed PD or initiation of other cytoreductive therapy will have response assessments (including BM biopsy, liver and spleen imaging, and laboratory and other C-finding assessments) performed at the EOT visit unless the assessments were performed within the preceding 24 weeks (or preceding 16 weeks if EOT is before Cycle 11), in which case they need not be repeated. Thereafter, all patients discontinued from the study drug without confirmed PD or initiation of other cytoreductive therapy will be followed every 24 weeks for assessment of response status until PD or initiation of other cytoreductive therapy. Patients who experience PD or initiate another cytoreductive therapy during follow-up for PD will subsequently be followed every 12 weeks for OS.

All patients will have a Safety follow-up 30 days after discontinuation of study drug.

Patients who discontinue study drug due to confirmed PD will be followed with telephone calls every 12 weeks to determine OS unless the reason for discontinuation is death, withdrawal of consent, loss to follow-up, or closure of the study by Sponsor.

A study schematic is in Figure 6. All assessments and their timing are detailed in the schedule of assessments (Appendix 1) and the PK sampling schedule (Appendix 2).

Figure 6: Study Schematic



Abbreviations: AdvSM = Advanced Systemic Mastocytosis; ASM = aggressive systemic mastocytosis; ECOG = Eastern Cooperative Oncology Group; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MCL = mast cell leukemia; ORR = overall response rate;QD = once daily; SAF = Symptom Assessment Form; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm; SSC = Study Steering Committee; TSS = total symptom score.

4.1.1 Study Steering Committee

An SSC composed of SM experts will determine patient eligibility based on confirmation of AdvSM diagnosis. The SSC will confirm the presence or absence of at least 1 evaluable C-finding attributable to SM per modified IWG-MRT-ECNM criteria. Confirmation of SM diagnosis and subtyping will be based on Central Pathology Laboratory review of screening BM biopsy and presence of WHO B- and C-findings. Patients with at least 1 SSC-confirmed modified IWG-MRT-ECNM evaluable C-finding or MCL (regardless of C-findings) will be assigned to Cohort 1. Patients with AdvSM without modified IWG-MRT-ECNM C-findings, as confirmed by the SSC, will be assigned to Cohort 2, with the exception of MCL.

For patients in Cohort 1, the SSC will adjudicate SM ORR using modified IWG-MRT-ECNM criteria and rules as agreed to by the SSC. Adjudicated responses will be based on algorithmic determination of each response criterion by the Sponsor statistician using data from every study visit for assessment of CI (eg, laboratory tests [hematology and chemistry], serum tryptase, evaluations of other baseline C-findings [eg, frequency of paracentesis]), and data from visits where BM biopsy and liver and spleen imaging are performed centrally for assessment of CR/CRh and PR. For Cohorts 1 and 2, associated hematologic neoplasm response also will be assessed by the SSC, using local data, including local cytogenetics data, and BM and PB reports from Central Pathology Review.

4.1.2 Central Laboratories and Review Committees

Central laboratories will be used for the measurement of serum tryptase and *KIT* D816V mutant allele burden and other mutations in PB and BM. *KIT* D816V status will be determined locally for SSC assessment of study eligibility during the Screening period.

An independent Central Pathology Laboratory will be responsible for review of the following:

- All baseline BM biopsies and aspirates and PB samples for assessment of AdvSM diagnosis and subclassification.
- All on-study BM biopsies and aspirates and PB samples for determination of AHN response.
- All on-study BM biopsies and aspirates and PB samples for determination of SM response.
- Any baseline and on-study extracutaneous (eg, GI tract, liver, lymph node) biopsies for MC infiltrates and determination of response.

Screening SM biopsies, aspirates and PB samples must be taken within 56 days of C1D1 and must be shipped to the central pathology lab with adequate time to allow for sample preparation, central pathological review and SSC review of eligibility. Shipment of samples at least 21 days before planned C1D1 is ideal, but shorter review windows are permissible with written approval of the Sponsor, Central pathologist and SSC chair (or designee).

All other laboratory assessments, including BM cytogenetics, will be performed locally.

An independent central radiology vendor will review all magnetic resonance imaging (MRI) and computed tomography (CT) scans of the liver and spleen to assess volume at Screening and all postbaseline time points.

An independent Skin Assessment Committee, composed of dermatologists with expertise in SM-related skin disease, will review all skin photographs at all pre- and post-treatment time points to determine mastocytosis in skin response in patients with cutaneous disease at baseline.

4.2 Justification of the Study Design

The study is designed as an open-label, single-arm efficacy and safety study of avapritinib in patients with AdvSM. Patients with AdvSM, including those diagnosed with ASM, SM-AHN, and MCL, with and without prior SM treatment, who meet all study eligibility criteria as confirmed by the SSC will be enrolled and begin dosing with avapritinib. Eligible patients will continue to receive BSC for management of MC mediator-related symptoms throughout the duration of the study. Please refer to Section 1.3, Study Rationale, for further justification of the study design.

4.2.1 Use of Modified IWG-MRT-ECNM Response Criteria

The primary endpoint of this study will be adjudicated ORR assessed by modified IWG-MRT-ECNM criteria in patients who are confirmed by the SSC to have an evaluable C-finding attributable to SM (Cohort 1). In consultation with AdvSM experts, regulatory authorities, and authors of the published IWG-MRT-ECNM consensus response criteria for AdvSM, the published criteria will be modified for this study to address some issues that were not considered when the original criteria were drafted. Notably, this is the first Phase 2 or 3 study of any drug to prospectively employ these criteria. Challenges in the application of the published criteria were noted in the Phase 1 BLU-285-2101 study; hence, modifications to the criteria, agreed to by the SSC, will be employed in this study. These modifications are summarized in Table 7. The rationale for each modification is provided below the table.

Table 7: Comparison of Original and Modified IWG-MRT-ECNM Criteria

Assessment	Original Criteria	Modified Criteria
Evaluable C-findings		
Symptomatic splenomegaly	Patient endorses symptoms of discomfort and/or early satiety	Symptoms not required
Splenomegaly	> 5 cm below left costal margin	≥ 5 cm below left costal margin
Response Criteria		
Pretreatment bone marrow MCs required for valid response criterion	NA	≥ 5%
CRh category of response	NA	Included
Duration for Confirmation of PD	8 weeks	4 weeks

Abbreviations: CRh = CR with partial recovery of peripheral blood counts; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MC = mast cells; NA = not applicable; PD = progressive disease.

- Definition of splenomegaly as an evaluable C-finding: Inclusion of patients with and without symptomatic splenomegaly as an evaluable C-finding and definition of splenomegaly as ≥ 5 cm (versus > 5 cm).

  Rationale: Measurement of spleen size by palpation is imprecise; 5 cm cannot be differentiated from slightly > 5 cm. Therefore, the criteria will be modified to define patients with palpable splenomegaly ≥ 5 cm as an evaluable C-finding. Additionally, many patients with enlarged spleen do not complain of discomfort or early satiety. This may occur when the spleen has been enlarged for some time and the patient has become accustomed to it. Also, different patients experience discomfort differently, and patients with SM may have poor appetites and not notice early satiety because they are eating small quantities of food. Therefore, this subjective criterion has been removed from the C-finding definition for splenomegaly.

- A category of CRh has been added, defined as meeting all CR criteria but with partial recovery of PB counts with minimum thresholds for absolute neutrophil count (ANC; $\geq 0.5 \times 10^9$/L), platelets ($\geq 50 \times 10^9$/L), and hemoglobin (≥ 8.0 g/dL) required.

  Rationale: When the IWG-MRT-ECNM response criteria were published in 2013, the advent of effective TKI therapy for AdvSM, and its attendant myelosuppression, was not anticipated. Data from the ongoing Phase 1 study of avapritinib in patients with AdvSM (BLU-285-2101) clearly indicate that patients may demonstrate a CR in their BM but continue to have only partial recovery of PB counts, not meeting the criteria for CR (preliminary analysis indicates CR and CRh rates of 11% and 5%, respectively). As other disease (eg, AML and acute lymphocytic leukemia [ALL]) response criteria have included CRh criteria where CR was otherwise demonstrated but with only partial recovery of PB counts, the Sponsor and SSC believe it is appropriate to include CRh criteria in AdvSM response assessment criteria.

- A criterion for pretreatment BM MCs has been added for PR response criteria such that BM MCs are only valid as a response criterion if the pretreatment BM MCs are ≥ 5% (ie, if pretreatment BM MCs are < 5%, BM MCs will not be considered in evaluation of PR). Partial remission will be based on achievement of serum tryptase and CI finding criteria only.

  Rationale: As with serum tryptase, which is not valid as a response criterion per IWG-MRT-ECNM criteria if the pretreatment serum tryptase level is < 40 ng/mL, BM MC response cannot be reliably assessed for ≥ 50% reduction when pretreatment MC burden is low (< 5%). Therefore, this criterion is not valid for assessment of PR. When pretreatment BM MCs are < 5%, this criterion will be omitted for assessment of PR, with only serum tryptase and C-findings being assessed for PR. Complete remission/CRh can still be assessed when pretreatment BM MCs are < 5% as the criterion for CR requires no (ie, absence of) compact neoplastic MC aggregates in the BM.

- Confirmation of PD will be performed at 4 weeks rather than 8 weeks.

  Rationale: The Sponsor and SSC are concerned that 8 weeks is too long to delay initiation of alternative cytoreductive therapy in patients with confirmed PD.

Partial response in the spleen will be based on reduction in spleen volume by imaging. This is not a modification but rather an option, as allowed by published IWG-MRT-ECNM criteria. The criterion for CI is defined as ≥ 35% reduction in volume in patients with baseline splenomegaly, as was defined in prior trials of midostaurin in AdvSM (Gotlib, et al., 2016) and ruxolitinib in myelofibrosis (Verstovsek, et al., 2012). A spleen and liver CR is defined based on lack of palpation (as allowed by published IWG MRT ECNM criteria), since there are no accepted criteria for normal spleen or liver volume.

Additionally, to expand the knowledge base of response of the AHN component to SM treatment, criteria will be employed, based on those published by Savona et al (Savona, et al., 2015) for assessment of myelodysplastic /myeloproliferative neoplasm response to treatment. These criteria are most applicable to the AHN of chronic myelomonocytic leukemia (CMML) and myelodysplastic/myeloproliferative neoplasms, unclassifiable (MDS/MPN-U). Other criteria may be used retrospectively to assess response in other types of AHN.

4.2.2 Use of a Study Steering Committee and Other Central Review Committees

To ensure that only patients with a confirmed diagnosis of AdvSM per WHO criteria are enrolled, eligibility will be prospectively determined by an SSC. The SSC will also prospectively evaluate whether patients either have or do not have an evaluable C-finding attributable to SM per modified IWG-MRT-ECNM response criteria. Patients confirmed by the SSC to have an evaluable C-finding attributable to SM per modified IWG-MRT-ECNM criteria or MCL, regardless of C-findings, will be assigned to Cohort 1, and those confirmed by the SSC to have ASM and SM-AHN, but not to have an evaluable C-finding attributable to SM per modified IWG-MRT-ECNM criteria, will be assigned to Cohort 2.

For patients assigned to Cohort 1, the SSC will adjudicate SM ORR based on algorithmic determination of each response criterion by the Sponsor statistician, as outlined in the modified IWG-MRT-ECNM response criteria.

To standardize assessments, BM and other extracutaneous tissue biopsies will be read by a Central Pathology Laboratory with expertise in MC pathology, and liver and spleen volume will be assessed using standardized procedures with imaging read by a Central Radiology Review Committee. As many patients with AdvSM suffer from mastocytosis in skin (often UP), a Skin Assessment Committee composed of dermatologists with SM expertise will evaluate cutaneous response (change from baseline) to treatment using serial photography of the skin.

4.2.3 Key Secondary Endpoint of Symptom Improvement Using a Patient-Reported Outcome Tool

Many, if not most, patients with AdvSM suffer from symptoms attributable to MC burden and/or release of MC mediators including pruritus, flushing, nausea, vomiting, diarrhea, abdominal pain, and fatigue. Improvement in symptoms, as well as objective responses to treatment, is critical to a patient's wellbeing. As such, the Sponsor has developed a PRO tool (AdvSM-SAF; Appendix 15) that assesses symptoms specific to AdvSM. Symptoms will be assessed daily using this PRO on an electronic diary (eDiary). Change in symptoms from baseline during treatment with avapritinib will be a key secondary endpoint of this study, which would be applicable to patients regardless of whether they are evaluable by modified IWG-MRT-ECNM criteria. Additional QoL measures, including the [redacted], will further characterize QoL during treatment with avapritinib.

4.3 Rationale for the Dose Selected

Preliminary data have shown avapritinib to be well tolerated at once-daily doses of 30 to 400 mg in patients with AdvSM and other myeloid malignancies, as well as in patients with advanced GIST. In the Phase 1 study of patients with AdvSM and other myeloid malignancies (BLU-285-2101), the MTD was not reached. However, among the 7 patients treated at 400 mg, 1 patient exhibited a dose-limiting toxicity of Grade 4 vomiting and most patients required dose reductions. Based on overall tolerability and the frequency of dose reductions at 400 mg, 300 mg was selected as the RP2D for further evaluation. However, with additional patients treated at 300 mg QD, and a longer duration of observation, patients have required dose interruptions and reductions to manage AEs. For patients with the prescribed dose of 300 mg QD, the average daily dose received was 224 mg. Therefore, a dose of 200 mg QD will be used in this study.

Avapritinib plasma concentrations at once-daily doses of $\geq$ 200 mg are significantly greater than plasma concentrations achieved in the patient-derived mouse xenograft model, which were active against resistance mutations in that model (refer to Section 1.1 for information regarding the activity of avapritinib against resistant *KIT* mutations). Since AdvSM is an aggressive disease, the Investigator will be permitted to increase the dose to 300 mg QD after 8 weeks of treatment at 200 mg QD, in the absence of toxicity (ie, criteria requiring dose reduction per Table 9), for suboptimal response.

5 POPULATION

5.1 Number of Patients

Approximately 103 patients will be enrolled in this study, including approximately 63 patients in Cohort 1 and up to 40 patients in Cohort 2.

5.2 Inclusion Criteria

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

1. Patients who are ≥ 18 years of age.
2. Patients must have 1 of the following diagnoses as confirmed by WHO diagnostic criteria (Appendix 4, Appendix 5, and Appendix 6). Before enrollment, the SSC must confirm the diagnosis of AdvSM (based on Central Pathology Laboratory assessment of BM).
    - ASM.
    - SM-AHN.
        - The AHN must be myeloid, with the following exceptions that are excluded:
            - AML.
            - Myelodysplastic syndrome that is very high- or high-risk, as defined by the International Prognostic Scoring System for Myelodysplastic Syndromes (Greenberg, et al., 2012).
            - A myeloid AHN with ≥ 10% BM or PB blasts.
            - Philadelphia chromosome-positive malignancies.
        - Incidental indolent, low-grade lymphoid AHNs (eg, chronic lymphocytic leukemia) not requiring treatment are eligible.
    - MCL, including diagnoses with an AHN component.
3. Patients with SM-AHN should have received prior treatment for the AHN component of disease if, in the opinion of the Investigator, such therapy was appropriate.
4. Patient must have a BM biopsy taken within 56 days of C1D1, assessed by the Central Pathology Laboratory.

5. Cohort 1 only: Patient must have at least 1 of the following measurable C-findings, per modified IWG-MRT-ECNM criteria, attributed to SM (Appendix 6, unless diagnosis is MCL, which does not require a C-finding). Laboratory abnormality C-findings should not be assessed until the required washout period from last cytoreductive therapy has been met. If a C-finding improves during the Screening period, prior to dosing, and no longer meets criteria for evaluability, it can no longer be counted as a C-finding. In addition,

   - Patients must have documented evidence of mast cell aggregates in the bone marrow or other extracutaneous organ based on central pathology.
   - Patient must be willing to have follow up biopsies of affected organ(s) to document response.

   Measurable C-findings:

   - Cytopenias:
     - ANC < 1.0×10^9/L *or*
     - Hemoglobin < 10 g/dL *or*
     - Platelet count < 75×10^9/L.

     NOTE: Cytopenias attributable to prior cytoreductive therapy or causes other than SM may not be used as C-findings.

   - Symptomatic ascites or pleural effusion requiring medical intervention such as:
     - Use of diuretics (Grade 2) *or*
     - ≥ 2 therapeutic paracenteses or thoracenteses (Grade 3) at least 28 days apart over the 12 weeks before C1D-8 and 1 of the procedures is performed during the 6 weeks before C1D-8.

   - ≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × upper limit of normal [ULN]), aspartate aminotransferase (AST; > 3.0 × ULN), alanine aminotransferase (ALT; > 3.0 × ULN), or alkaline phosphatase (> 2.5 × ULN) with 1 of the following present:
     - Ascites *or*
     - Clinically relevant portal hypertension *or*
     - Liver MC infiltration that is biopsy-proven *or*

    - No other identified cause of abnormal liver function.
  - ≥ Grade 2 hypoalbuminemia (< 3.0 g/dL).
  - A spleen that is palpable ≥ 5 cm below the left costal margin.
  - Transfusion-dependent anemia defined as:
    - Transfusion of ≥ 6 units packed red blood cells (PRBCs) in the 12 weeks before C1D-8 *and*
    - Most recent transfusion occurring during the 4 weeks before C1D-8 *and*
    - Transfusion administered for hemoglobin ≤ 8.5 g/dL *and*
    - Reason for transfusion is not bleeding, hemolysis, or therapy-related.

6. Patient must have a serum tryptase ≥ 20 ng/mL.
7. Patients receiving cytoreductive therapy within the preceding 12 weeks must have discontinued therapy due to disease progression, refractory disease, lack of efficacy, or intolerance.
8. Patient's non-antineoplastic SM therapies (ie, BSC; eg, H1 and H2 blockers) must be stable (same dose, no new medications for SM) for ≥ 14 days C1D-8. This criterion is not applicable if a patient has progressive disease and it is in the patient's best interest to enroll in the study rapidly with Medical Monitor approval.
9. If the patient is receiving corticosteroids, the dose must be ≤ 20 mg/d prednisone or equivalent and dose must be stable for ≥ 14 days before C1D-8. This criterion is not applicable if the patient has progressive disease, and it is in the patient's best interest to enroll in the study rapidly with Medical Monitor approval.
10. Patient has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 3.
11. Patient must be able to give written informed consent.

5.3 Exclusion Criteria

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

1. Patient has received prior treatment with avapritinib.
2. Patient has received any cytoreductive therapy (including midostaurin and other TKIs, hydroxyurea, azacitidine) or an investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy (eg, brentuximab vedotin) less than 28 days before obtaining screening BM biopsy

for this study. If the patient has progressive disease and it is in the patient's best interest to enroll in the study rapidly, cytoreductive therapy may be discontinued 1 day before the screening BM biopsy with approval from the Medical Monitor. Cytoreductive therapy may not be restarted during Screening or while on study.

3. Patient has received prior radiotherapy within 14 days before the screening BM biopsy, unless given to palliate specific sites of disease (eg, bone lesion).

4. Patient received any hematopoietic growth factor within 14 days of screening BM biopsy.

5. Patient requires therapy with a concomitant medication that is a strong inhibitor, strong inducer, or moderate inducer of CYP3A4 (Appendix 13).

6. Patient has had a major surgical procedure within 14 days of the first dose of study drug. Surgical procedures such as central venous catheter placement, BM biopsy, and feeding tube placement are considered minor surgical procedures.

7. Patient is a candidate for allogeneic hematopoietic stem cell transplantation for treatment of SM, in the opinion of the Investigator.

8. Patient has eosinophilia and known positivity for the *FIP1L1-PGDFRA* fusion, unless the patient has demonstrated relapse or PD on prior imatinib therapy. Patients with eosinophilia ($> 1.5 \times 10^9$/L), who do not have a detectable *KIT* D816 mutation, must be tested for a *PDGFRA* fusion mutation by fluorescence in situ hybridization (FISH) or PCR.

9. Patient has history of another primary malignancy that has been diagnosed or required therapy within 3 years before the first dose of study drug. The following are exempt from the 3-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.

10. Patient meets any of the following laboratory criteria:

    - AST or ALT > 3.0 × ULN; no restriction if due to suspected liver infiltration by MCs.

    - Bilirubin > 1.5 × ULN; no restriction if due to suspected liver infiltration by MCs or Gilbert's disease. (In the case of Gilbert's disease, a direct bilirubin > 2.0 × ULN would be an exclusion.)

    - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 or creatinine> 1.5 × ULN.

    - Platelet count < 50,000/µL (within 4 weeks of the first dose of study drug) or receiving platelet transfusion(s)

11. Patient has a QT interval corrected using Fridericia's formula (QTcF) > 480 msec.

12. Patient has a history of a seizure disorder (eg, epilepsy) or requirement for antiseizure medication.

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

14. Patient has a known risk or recent history (12 months before the first dose of study drug) of intracranial bleeding (eg, brain aneurysm, concomitant vitamin K antagonist use).

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

16. Patient has clinically significant, uncontrolled cardiovascular disease, including Grade III or IV congestive heart failure according to the New York Heart Association classification; myocardial infarction or unstable angina within the previous 6 months; clinically significant, uncontrolled arrhythmias; or uncontrolled hypertension.

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

18. Female patients who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception from the first dose of study drug and for at least 6 weeks after the last dose of study drug. Men who are unwilling, if not surgically sterile, to abstain from sexual intercourse or employ highly effective contraception from the first dose of study drug and for at least 6 weeks after the last dose of study drug. Refer to Section 9.6.1 for acceptable methods of contraception.

19. Female patients who are pregnant, as documented by a serum beta human chorionic gonadotropin (β-hCG) pregnancy test consistent with pregnancy obtained within 15 days before 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 approval of the Sponsor after pregnancy has been excluded. Women of nonchildbearing potential (ie, women who are postmenopausal or have undergone hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) do not require a serum β-hCG pregnancy test.

20. Women who are breast feeding.

21. Patient has a prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the opinion of the Investigator, 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.

22. Hypersensitivity to avapritinib or to any of the excipients.

23. Patient is participating in another interventional study.

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 (refer to Section 5.2 and Section 5.3) have been satisfied.

Upon identification of an eligible patient, study centers will register the patient using the Interactive Voice/Web Response System (IXRS). Additional information on patient registration will be provided in the Study Manual. All eligibility criteria must be entered into the electronic case report form (eCRF) as per the timepoints indicated in Appendix 3 to allow sufficient time for review and determination of eligibility by the SSC.

The SSC will confirm eligibility for all patients before enrollment and administration of the first dose of study drug. Only patients deemed eligible per SSC review will be enrolled.

5.5 Study Completion

It is anticipated that patients will receive at least 1 cycle of avapritinib. After Cycle 1, patients may continue to receive study drug until precluded by toxicity, confirmed disease progression, noncompliance, pregnancy, withdrawal of consent, death, physician decision, or closure of the study by the Sponsor. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.

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

5.6 Patient Withdrawal Criteria

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

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

- Study drug-related intracranial bleeding of any grade.
- Withdrawal of consent.
- Pregnancy.
- Death.
- Confirmed SM PD (4 weeks after initial documentation).
- Confirmed AHN PD (4 weeks after initial documentation) requiring the initiation of other cytoreductive therapy.

- SM or AHN clinical progression (ie, not meeting modified IWG-MRT-ECNM criteria for confirmed progression) requiring alternative cytoreductive treatment.
- Initiation of other cytoreductive therapy.
- Investigator decision.
- Termination of study by Sponsor.

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

- AEs.
- Protocol deviation.
- Noncompliance.
- Investigator decision.
- Loss to follow-up.

When a patient discontinues study drug and/or withdraws from the survival follow-up part of the study, the primary reason(s) for discontinuation or withdrawal must be recorded in the appropriate sections of the electronic case report form (eCRF) and all efforts will be made to complete and report final study observations as thoroughly as possible. Patients who withdraw consent from study treatment participation but consent to survival follow-up will be contacted by phone as defined in Appendix 1.

All AEs potentially related to avapritinib should be monitored until they are resolved, have stabilized, have returned to pre-exposure baseline, are determined to be due to another illness, or until a subsequent therapy is initiated. For AEs considered not related to study drug, similar monitoring guidelines will only be required through 30 days after the last dose of study drug. If the patient withdraws from treatment because of an AE, every effort must be made to perform protocol-specified safety follow-up procedures, as outlined in Section 7.6.

If there is a medical reason for withdrawal, the patient will remain under the supervision of the Investigator or designee until the condition has returned to baseline or stabilized.

6 STUDY CONDUCT

6.1 General Conduct

The study will be conducted at multiple centers in the United States, Canada, and Europe.

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

The schedule of assessments is in Appendix 1.

The minimum duration of patient participation is expected to be approximately 16 weeks, including a Screening period to assess study eligibility of up to 8 weeks; a treatment period of at least 1 cycle (28 days); an EOT visit at least 14 ± 7 days after the last dose of study drug; and a Safety Follow-up visit by telephone for resolution of any AEs 30 days (± 7 days) after the last dose of study drug. Thereafter, patients without confirmed PD or those who have not initiated a new cytoreductive therapy are to be assessed for response every 24 weeks until the development of PD or initiation of another cytoreductive therapy. All patients with confirmed PD at EOT, PD during Follow-Up for PD, or who initiate another cytoreductive therapy will be followed for OS every 12 weeks, unless they discontinue from the study due to death, withdrawal of consent, loss to follow-up, or closure of the study by Sponsor.

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

The expected enrollment period is approximately 12 months. The expected duration of the study is approximately 54 months.

6.2 Early Termination

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

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

- Determination of unexpected, significant, or unacceptable risk to patients.
- Insufficient adherence to protocol requirements.
- Plans to modify, suspend, or discontinue the development of study drug.
- Failure to enroll patients at an acceptable rate after exhausting all efforts to improve enrollment.
- Other administrative reasons.

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

6.3 Dose and Administration

Avapritinib will be administered at 200 mg orally QD, continuously in 28-day cycles. Avapritinib can worsen baseline cytopenias, and Grade 3 thrombocytopenia, in particular, may be a risk factor for intracranial bleeding. Therefore, the 200 mg starting dose of avapritinib may be adjusted based on the degree of a patient's cytopenia at baseline, before starting avapritinib. Prespecified dose modification recommendations for AEs related to avapritinib, including thrombocytopenia, intracranial bleeding, and cognitive effects are described in Section 6.3.1.

In addition, CBC should be monitored carefully for worsened thrombocytopenia upon initiation of avapritinib, particularly within the first 2 cycles. Avapritinib dose should be modified as indicated below in Section 6.3.1. Additional unscheduled CBCs may be needed until platelet count is stable. Any coagulopathy at baseline or on study should be corrected and monitored at every study visit. Investigators should increase monitoring of thrombocytopenia and coagulopathy in the setting of progressive disease.

The dose of avapritinib may be reduced for toxicity, or may be increased, at the discretion of the Investigator, up to 300 mg QD if, after at least 8 weeks of treatment at 200 mg QD, in the absence of toxicity requiring dose reduction, the patient has had a suboptimal response, defined as no better than SD. Dose may be increased to 300 mg QD earlier than 8 weeks if there is evidence of progressive disease and with written permission of Sponsor. In addition, alternate dose scheduling, such as dosing every other day, may be considered with written permission of the Sponsor.

Patients will be dispensed the appropriate number of Sponsor-packaged, labeled bottles on Day 1 of each cycle to allow dosing until the next scheduled visit, which is expected to be within 28 days (through C3D1), 2 months (from Cycle 3 to Cycle 11), or 3 months (after Cycle 11). Patients must return all unused tablets (or the empty bottles) at each scheduled visit.

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

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

If the patient typically takes avapritinib in the evening and forgets to take his/her evening dose, he/she should take the study drug dose by 12 am (midnight) that day. If the dose has not been taken by the specified time, that dose should be omitted, and the patient should resume treatment with the next scheduled dose in the evening.

If the patient switches from a regular morning dose schedule to an evening dose schedule, he/she should ensure the doses are taken at least 8 hours apart.

If a patient vomits during or after taking avapritinib, redosing is not permitted until the next scheduled dose.

6.3.1 Dose Modification Recommendations

Avapritinib can commonly lead to cytopenias, most often anemia and thrombocytopenia, particularly in patients with baseline cytopenias. Prolonged Grade 3 thrombocytopenia is a risk factor for intracranial bleeding. Specific dose reductions for thrombocytopenia are summarized in Table 8.

Dose modification guidelines for other toxicities assessed as related to avapritinib are also summarized in Table 9. These guidelines should be followed by Investigators. Dose modifications, different from those listed in Table 9, may be considered based on the clinical circumstances and must be documented and communicated with the Sponsor.

Guidance for re-escalation after resolution of adverse drug reactions is in Section 6.3.2.

In general, dose reductions at doses above 100 mg QD should occur in 100 mg decrements. At 100 mg QD, patients may dose reduce to 50 mg QD. At 50 mg QD, patients may dose reduce to 25 mg QD, the lowest permitted dose in this study. Patients requiring a dose reduction at 25 mg QD should interrupt or permanently discontinue study treatment. Doses may be interrupted for study drug-related toxicities for up to 56 days. In general, if a nonhematologic study drug-related toxicity does not resolve to ≤ Grade 2 or has not returned to baseline after a dose interruption of more than 56 days (8 weeks), the patient should be discontinued from study treatment. If a hematologic study drug-related toxicity does not resolve to ≤ Grade 2 or has not returned to baseline after a dose interruption of more than 56 days, the Sponsor’s medical monitor must be contacted.

Guidelines for dose modification for new or worsening cognitive effects assessed as related to avapritinib should be followed; however, the Investigator should carefully assess whether these cognitive effects were present at baseline and if they are more appropriately attributed to AdvSM, or another cause, before making dose adjustments.

During dose interruptions, study sites should continue to observe the study schedule as planned. Retiming/clock-stop has resulted in significant delays in disease assessments that are critical for monitoring patient safety and efficacy. As specified in Section 6.3, the study drug is to be administered continuously in 28-day cycles. Therefore, the cycle count begins with Day 1 of any given cycle starting with Cycle 1 Day1 and continues uninterrupted as a 28-day cycle, regardless of dosing interruptions and midcycle dosing restarts, with allowances only for the allowable visit windows, as specified in the Schedule of Assessments (Appendix 1).

A temporary discontinuation (up to 56 days) in avapritinib dosing is allowed for patients who require an interruption (eg, for surgery or another procedure, or for toxicity) during the treatment period. Avapritinib may be discontinued 48 hours before any planned procedure and resumed at least 48 hours after the procedure is completed.

The Sponsor's medical monitor must be contacted for dose interruptions of more than 56 days for any reason; a longer recovery period is permitted with written approval by the Sponsor.

Table 8: Dose Modification and Re-Escalation Guidelines for Thrombocytopenia

Platelet count	Modification	Re-Escalation
≥ 75,000/µL	• Monitor CBC at least every 28 days • No dose modification required	
50,000/µL - < 75,000/µL	• Monitor CBC at least every 14 days • No dose modification required	

<50,000/µL
 	
At discretion of local investigator, platelet count may be repeated once, within a week, to confirm trend, before modifying dose.
	• Interrupt dosing
	• Monitor CBC at least every 14 days
	• If platelet count is ≥ 50,000/µL without transfusion or growth factor support, then resume at reduced dose (see below). Discuss with medical monitor if not improved to ≥ 50,000/µL in 2 weeks.
	• Occurrence at dose ≥ 200 mg QD:
	  o Resume treatment by reducing the dose by 100 mg less than the current dose
	• Occurrence at 100 mg QD:
	  o Resume treatment by reducing the dose to 50 mg QD
	• Occurrence at 50 mg QD:
	  o Resume treatment by reducing the dose to 25 mg QD
	• Occurrence at 25 mg QD:
	  o Discontinue avapritinib
	• If in the opinion of the Investigator it is believed to be in the best interest of the patient to resume treatment without platelet improvement, contact the medical monitor to discuss restarting treatment with growth factor or platelet transfusion support.
		• Platelets improved to ≥ 50,000 for 4 weeks with or without supportive therapy (eg, hematopoietic growth factors, transfusions)

< 25,000/µL	• Consider platelet transfusion • Interrupt and modify dose as above	

Abbreviations: QD = once daily.

Table 9: Dose Modification and Re-Escalation Guidelines for Avapritinib-Related Toxicity

Avapritinib-Related Toxicity	Modification	Re-Escalation
Nonhematologic and Hematologic Toxicity (except thrombocytopenia)		
Grade 1 or Grade 2	• No dose modification required	
Grade 3 or Grade 4 of any duration	• Occurrence at dose ≥ 200 mg QD: o Interrupt until event is ≤ Grade 2, or has returned to baseline, then resume treatment by reducing the dose by 100 mg less than the current dose • Occurrence at 100 mg QD: o Interrupt until event is ≤ Grade 2, or has returned to baseline, then resume treatment by reducing the dose to 50 mg QD • Occurrence at 50 mg QD: o Interrupt until event is ≤ Grade 2, or has returned to baseline, then resume treatment by reducing the dose to 25 mg QD • Occurrence at 25 mg QD: o Discontinue avapritinib	• Nonhematologic toxicities have recovered to ≤ Grade 2 or baseline for at least 2 weeks • Hematologic toxicities have recovered to ≤ Grade 2 or baseline and are manageable with supportive therapy (eg, hematopoietic growth factors, transfusions)
Increased Alkaline Phosphatase		
Up to Grade 4, within 8 weeks of treatment initiation, with no other evidence of liver dysfunction, or determined to be of bone origin by fractionation	• No dose modification required	
Cognitive Effects[a]		
Grade 1	• No dose modification required	

Avapritinib-Related Toxicity	Modification	Re-Escalation

Grade 2	• Interrupt dosing for a minimum of 7 days
	• Occurrence at dose ≥ 200 mg:
	  o When event is ≤ Grade 1, or has returned to baseline (unless, in the opinion of Investigator, it is believed to be in the best interest of the patient to resume treatment earlier), resume treatment with a reduction in dose 100 mg less than the current dose
	• Occurrence at 100 mg:
	  o When event is ≤ Grade 1, or has returned to baseline (unless, in the opinion of the Investigator, it is believed to be in the best interest of the patient to resume treatment earlier), resume treatment at 50 mg QD
	• Occurrence at 50 mg:
	  o When event is ≤ Grade 1, or has returned to baseline (unless, in the opinion of Investigator, it is believed to be in the best interest of the patient to resume treatment earlier), resume treatment at 25 mg QD
	• Occurrence at 25 mg:
	  o Discontinue avapritinib
		Toxicities attributed to avapritinib have recovered to ≤ Grade 1 or baseline for at least 2 weeks

Grade 3 or Grade 4 of any duration	• Interrupt dosing for a minimum of 14 days • Occurrence at ≥ 200 mg: o When event is ≤ Grade 1, or has returned to baseline (unless, in the opinion of the Investigator, it is believed to be in the best interest of the patient to resume treatment earlier), resume treatment with reduction in dose by 100 mg less than the current dose	Toxicities attributed to avapritinib have recovered to ≤ Grade 1 or baseline for at least 2 weeks

Avapritinib-Related Toxicity	Modification	Re-Escalation

	• Occurrence at 100 mg:
	  ○ When event is ≤ Grade 1, or has returned to baseline (unless, in the opinion of the Investigator, it is believed to be in the best interest of the patient to resume treatment earlier), resume treatment with reduction in dose to 50 mg QD
	• Occurrence at 50 mg QD:
	  ○ When event is ≤ Grade 1, or has returned to baseline (unless, in the opinion of Investigator, it is believed to be in the best interest of the patient to resume treatment earlier), resume treatment at 25 mg QD
	• Occurrence at 25 mg QD:
	  ○ Discontinue avapritinib	

Intracranial Bleeding		
Any grade	• Permanently discontinue study drug	

Abbreviations: ICP = intracranial pressure; QD = once daily; QOD = every other day; SM = systemic mastocytosis.

[a] Cognitive effects requiring dose modification include changes in cognition, memory, attention, mood, or speech that are more severe than at baseline and assessed as related to study treatment (ie, not due to systemic mastocytosis or other cause).

6.3.2 Dose Re-Escalation after Resolution of Adverse Drug Reactions

Avapritinib doses may be re-escalated from the reduced dose level to the immediate previously administered dose level based on the criteria detailed in Table 9.

Patients may receive step-wise avapritinib dose re-escalations up to the starting dose (eg, 100 mg QD to 200 mg QD), with each dose level being administered for 1 cycle before escalation to the next higher dose level if the above criteria continue to be met. Dose escalation should not occur unless the prior dose was well-tolerated by the patient (eg, no Grade 3 or 4 AEs). In no circumstances should a patient receive a daily dose higher than 300 mg.

If a patient experiences study drug-related intracranial bleeding of any grade, study drug must be permanently discontinued.

6.3.3 Dose Escalation for Suboptimal Response

The Investigator will be permitted to increase the dose of avapritinib up to 300 mg QD, in the absence of toxicity (ie, criteria requiring dose reduction per Table 9), for suboptimal response or loss of response. Suboptimal response is defined as no better than stable disease by C3D1 or later per modified IWG-MRT-ECNM response criteria. The dose may be increased up to 300 mg QD earlier than 8 weeks if there is evidence of PD and with permission of Sponsor.

6.4 Prior and Concomitant Therapy

All concomitant medications and procedures should be recorded in the eCRF beginning with the signing of informed consent, including all BSC medications used to manage SM symptoms.

All prior treatments for AdvSM and AHN should be recorded into the eCRF as well.

All transfusions, including RBC and platelet transfusions, administered within the 12 weeks before C1D-8, as well as all transfusions received from C1D-7 through study participation, will be recorded. Details will include number of units transfused, pretransfusion hemoglobin and platelet count, and reason for RBC transfusion.

All treatments, including diuretics, paracentesis, and thoracentesis, administered for ascites and/or pleural effusions within the 12 weeks before C1D-8, as well as all treatments received from C1D-7 through study participation, will be recorded.

6.4.1 Prohibited Concomitant Therapy

The following medications and procedures are prohibited during the Screening period:

- Cytoreductive therapy (including midostaurin and other TKIs) or an investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy less than 28 days, before the screening BM biopsy. If the patient has progressive disease and it is in the patient's best interest to enroll in the study rapidly, cytoreductive therapy may be discontinued 1 day before the screening BM biopsy with approval from the Medical Monitor.

- Hematopoietic growth factors less than 14 days before the screening BM biopsy.

- Radiotherapy less than 14 days before the screening BM biopsy, unless local radiotherapy to treat a localized bone lesion, and the radiation field does not include the BM biopsy site.

- Major surgical procedures less than 14 days before the first dose of study drug. Surgical procedures such as central venous catheter placement, BM biopsy, and feeding tube placement are considered minor.

The following medications and procedures are prohibited during the study:

- Strong CYP3A4 inhibitors and strong and moderate CYP3A4 inducers. Refer to Appendix 13 for a list of prohibited medications and foods.
- Any investigational agent or device other than avapritinib, including commercially available agents that are investigational for the treatment of the patient's underlying malignancy.
- Any antineoplastic treatment (including kinase inhibitors and chemotherapy) other than avapritinib; however, local radiotherapy to treat localized bone lesions is permitted.
- Patients requiring antiseizure medication are not eligible. However, if a patient develops an AE requiring antiseizure medication during study participation, the medication is allowed.

6.4.2 Pharmacokinetic Drug-Drug Interactions

In vitro, avapritinib is a reversible inhibitor of CYP2C9 and CYP3A4/5 at clinically relevant concentrations ([I]/Ki >0.1). Avapritinib also demonstrated time-dependent inhibition of CYP3A4/5 in vitro with an estimated K_{inact} and K_I of 0.0301 min^{-1} and 12.3 µM, respectively. In vitro, avapritinib, at concentrations of 0.3 to 3 µM, induced CYP3A4 mRNA expression with a maximal 3.25-fold induction observed at 3 µM. Therefore, clinical drug-drug interactions with comedications for which CYP2C9- or CYP3A-mediated metabolism constitutes the primary mechanism of clearance are likely. In vitro, avapritinib is an inhibitor of P-gp, BCRP, BSEP, MATE1, and MATE2K. Therefore, avapritinib may have the potential to increase plasma concentrations of coadministered 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 14 for a list of these medications.

The oxidative metabolism of avapritinib is primarily mediated by CYP3A4 and to a lesser extent by CYP2C9. Preliminary unaudited data are available from a clinical drug-drug interaction study, BLU-285-0104, in healthy adult subjects. Coadministration of a single 200 mg dose of avapritinib with itraconazole 200 mg QD (a strong CYP3A inhibitor) increased avapritinib C_{max} and $AUC_{0\text{-}inf}$ by 1.4- and 4.2-fold, respectively, compared to a 200 mg dose of avapritinib administered alone. The concomitant use of strong CYP3A inhibitors should be avoided (refer to Appendix 13). Moderate CYP3A inhibitors may also increase avapritinib exposure and should be used with caution (refer to Appendix 14). Coadministration of a single 400 mg dose of avapritinib with rifampin 600 mg QD (a strong CYP3A inducer), decreased avapritinib C_{max} and $AUC_{0\text{-}inf}$ by 74% and 92%, respectively, compared to a 400 mg dose of avapritinib administered alone. The concomitant use of strong and moderate inducers of CYP3A should be avoided (refer to Appendix 13).

As the absorption of avapritinib may be affected by gastric pH, antacids should not be taken within 3 hours before or after avapritinib administration, and proton-pump inhibitors should be avoided if possible. H_2-receptor antagonists are frequently required as part of standard therapy for patients with SM; therefore, the use of H_2-receptor antagonists is not restricted.

6.4.3 Other Precautions

Patients should be advised to use clothing and sunscreen to avoid direct sun exposure.

6.4.4 Permitted Concomitant Therapy

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

Best supportive care medications should be optimized during the Screening period, ideally no later than 14 days before C1D-8; however, this may not be possible in the setting of progressive disease. Best supportive care may include the following classes of agents: H1 and H2 blockers; proton pump inhibitors; osteoclast inhibitors; leukotriene inhibitors; corticosteroids (dose not to exceed 20 mg of prednisone or equivalent); cromolyn sodium and other MC stabilizers; and the anti-IgE antibody, omalizumab. Dose (and schedule) of BSC medications should not exceed approved doses and should not be increased during the study (if possible) but may be reduced if symptoms improve.

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. Anti-diarrhea medications may also be used after documented diarrhea has occurred, at the Investigator's discretion.

Hematopoietic growth factors may be used at the Investigator's discretion and in accordance with the American Society of Clinical Oncology guidelines or equivalent for the treatment of neutropenia and/or anemia.

Moderate CYP3A inhibitors may increase avapritinib exposure and should be used with caution (refer to Appendix14).

Caution is advised for patients taking antiplatelet or antithrombotic therapies, particularly in combination with severe thrombocytopenia. Patients with baseline platelet counts below 50,000/µL that require anti-platelet or antithrombotic medications are excluded from the study. Patients enrolled on the study who are taking antiplatelet or antithrombotic medications should interrupt those medications when their platelet counts drop below 50,000/µL and until their platelet count recovers.

7 DESCRIPTION OF STUDY PROCEDURES

7.1 Screening

After informed consent is provided, all patients will undergo screening procedures to determine eligibility within 56 days before dosing on C1D1. Screening may occur across multiple days but should be completed by C1D-8 in order to give the SSC 7 days to review the eligibility data. The SSC may take less than 7 days to review and the patient may start treatment as soon as SSC approval is given. All screening results required for confirmation of AdvSM diagnosis and determination of eligibility should be entered into the eCRF for transmittal to the SSC by C1D-8. Screening time windows for study eligibility are summarized in Appendix 3. In addition, patients may be rescreened with the approval of the Sponsor. If a patient is rescreened, all screening assessments must be repeated unless specifically defined in the protocol as archival samples/assessments that are allowed when done within the defined window.

The following procedures will be performed during the Screening period:

- Review of inclusion and exclusion criteria. Review may be repeated at baseline, before the first dose of study drug, based on local requirements. Patients must be excluded from the study if they no longer meet the inclusion and exclusion criteria at this point.

- Obtain demographic data, including sex, age, race, and ethnicity.

- Optimize and stabilize BSC medications ideally no later than 14 days before C1D-8. Best supportive care medications, including those used to treat osteoporosis, and all other concomitant therapies are to be recorded from signing of the informed consent form through the Safety Follow-up assessment. This is not applicable if a patient has progressive disease, and it is in the patient's best interest to enroll in the study rapidly with Medical Monitor approval.

- Complete medical history, including a complete medical and surgical history, as well as a targeted history of mastocytosis and/or other malignancies, prior SM/AHN treatments, including corticosteroids, the duration of and response to each treatment and reason for discontinuation, if available, and concurrent illnesses. Review of medical history may be repeated at baseline, before the first dose of study drug, based on local requirements. Patients meeting ASM criteria with a sole C-finding of large lytic lesions will need to provide radiology reports with lesion measurements for SSC review. Patients who met WHO criteria for AdvSM in the past but may have lost criteria to due to therapy (ie, midostaurin improved weight loss, or splenectomy fixed hypersplenism) will need to provide historical medical documentation of WHO C-findings for SSC review if they are critical for AdvSM diagnosis.

- Assessment of evaluable C-findings per modified IWG-MRT-ECNM criteria (Appendix 6) and their attribution to SM at least 8 days before C1D1 (ie, on C1D-8), observing required washout periods for prior therapies (refer to Section 6.4.1). Eligibility assessments must be made ≥ 28 days after the patient's last dose of cladribine, interferon alpha, pegylated interferon, or any antibody therapy and ≥ 14 days after the last dose of TKIs, including midostaurin, other cytoreductive therapies, and investigational agents. If a patient has progressive disease and it is in the patient's best interest to enroll rapidly in the study, this washout period may be reduced to 1 day after discussion with the Medical Monitor.

  - Obtain history of RBC and platelet transfusions including dates, number of units transfused, pretransfusion hemoglobin and/or platelet counts, and reasons for RBC transfusion in the 12 weeks before C1D-8 (refer to Section 7.2.3.3.6).

  - For patients with symptomatic ascites and/or pleural effusions at baseline, dates and number of paracenteses and/or thoracenteses within the 12 weeks prior to C1D-8, as well as all diuretics for management of ascites and/or pleural effusions 12 weeks before C1D-8, will be recorded (refer to Section 7.2.3.3.1).

  - Clinical laboratory assessments (hematology, coagulation, serum chemistry, and urinalysis). Safety assessments (including serum chemistry and liver function tests) may be repeated within 7 days of C1D1 and can be performed on C1D1, prior to dose, based on local requirements. During screening, patients with any degree of thrombocytopenia must repeat a CBC with differential approximately 28 days before study drug initiation and again within 7 days before study drug initiation.

  - Complete physical examination including evaluation of the skin, head and neck, lymph nodes, heart, lungs, abdomen (including measurement of liver and spleen size by palpation), musculoskeletal and neurological systems, including ECOG PS (Appendix 12).

- Obtain blood samples for serum tryptase and send to Central Laboratory by C1D-21.

- Document patient's *KIT* D816V mutation status with archival test or local testing during Screening and enter into eCRF by C1D-8.

- Obtain screening BM biopsy and aspirate with PB smear. Samples must be obtained within 56 days of C1D1. Archival samples may be used if they fit within the 56-day windows to C1D1 and were obtained after washout (if needed).

    - Samples must be obtained ≥ 28 days after the last dose of cladribine, interferon alpha, pegylated interferon, or any antibody therapy and ≥ 14 days after the last dose of TKIs, including midostaurin, other cytoreductive therapies, and investigational agents. If a patient has progressive disease and it is in the patient's best interest to enroll in the study, this washout period may be reduced to 1 day after discussion with the Medical Monitor.
    - Samples should be sent to the study site's local laboratory for:
        - Local assessment of MC infiltrates (to serve as baseline for future local assessment of response).
        - Cytogenetics.
    - A second set of samples will be obtained and processed according to the Study Laboratory Manual, and shipped to the Central Pathology Laboratory preferably no later than C1D-21 for:
        - Confirmation of AdvSM diagnosis and subclassification.
        - Quantification of BM MC infiltrates.
- Biopsy of other suspected or known areas of SM involvement (optional); completed and shipped to the Central Pathology Laboratory by C1D-21.
- Imaging of liver and spleen for assessment of volume (MRI [preferred] or CT). Refer to Section 7.2.3.3.4 and to the Study Manual for details.
- Assessment of mastocytosis in skin by photography. Refer to the Study Manual for details.
- Serum pregnancy test (women of childbearing potential only).
- Vital signs including weight, height, temperature, pulse, and systolic/diastolic blood pressure.
- 12-lead ECG to be conducted after 5 minutes in a recumbent or semi-recumbent position.
- DXA scan for the evaluation of bone density.
- Imaging of brain by MRI (preferred) or CT scan without contrast. An earlier imaging study performed up to 8 weeks before signing the ICF may be used if no clinically significant neurological events have occurred and the platelet count has remained entirely above 50,000/µL from the time of the scan to signing the ICF.
- Record AEs from the date of the informed consent signature through the Safety Follow-up Assessment.

- Instruct patient on collection of AdvSM-SAF data on eDiary during Screening to ensure at least 7 days of baseline data before C1D1. Sites should verify that the devices function, are transmitting data properly, and that the patient is using the eDiary correctly on a daily basis during the Screening period. Patients who are unable to consistently and accurately use the AdvSM-SAF due to disability, non-fluency in the available languages, or another reason may still enroll with written permission of the Sponsor.

- Obtain SSC determination of eligibility (refer to Section 7.1.1).

7.1.1 Confirmation of AdvSM Diagnosis and Evaluable C-Findings by Study Steering Committee

Confirmation of the diagnosis of AdvSM by WHO criteria is to be made by the SSC before study enrollment. Data required for the SSC to confirm the diagnosis of AdvSM include BM biopsy, BM aspirate, PB smear and corresponding CBC obtained during the Screening period, serum tryptase from the central laboratory, *KIT* D816V mutation status from archival or local testing, and documentation of all C-findings per modified IWG-MRT-ECNM criteria and relevant clinical data to assess attribution of C-finding to SM (eg, prior cytoreductive therapies). Historical documentation of WHO C-findings and radiology reports of lytic lesions may be required. Bone marrow and other extracutaneous tissue samples must be sent to the Central Pathology Laboratory. If Central Pathology Review concludes the central BM samples are inadequate for confirmation of AdvSM diagnosis or for quantification of MCs, the local BM sample must be shipped to the Central Pathology Laboratory and review must be completed by the Central Pathology Laboratory and SSC to confirm AdvSM diagnosis before confirmation of eligibility. Subclassification based on BM histopathology may be performed retrospectively. Local cytogenetics and molecular data will be used by Central Pathology Review to subclassify AHN.

Data required by the SSC to confirm presence or absence of evaluable C-findings attributable to SM, include prior cytoreductive therapies; CBCs; chemistries; documentation of splenomegaly and/or hepatomegaly by palpation; presence of ascites and/or pleural effusions and treatments including paracenteses, thoracenteses, and diuretics; and RBC and platelet transfusions administered during the 12 weeks before C1D-8. After review of the data, the SSC will assign patients with an evaluable C-finding attributable to SM per modified IWG-MRT-ECNM criteria or MCL, regardless of C-findings, to Cohort 1. Patients with AdvSM (ASM and SM-AHN) without an evaluable C-finding attributable to SM per modified IWG-MRT-ECNM criteria will be assigned to Cohort 2.

7.2 Efficacy Assessments

7.2.1 Systemic Mastocytosis Response

Systemic mastocytosis response to avapritinib will be assessed by both the Investigator and the SSC (Cohort 1 only) according to the modified IWG-MRT-ECNM criteria listed in Appendix 7 at the time points outlined in Appendix 1. Modified IWG-MRT-ECNM criteria are based on findings from BM biopsy and aspirate, and PB smear; BM cytogenetics; other extracutaneous tissue biopsies (when available); liver and spleen imaging; and other clinical and laboratory parameters. In addition, abnormal clinical and laboratory findings will undergo an attribution determination by the Investigator and SSC to assess whether the abnormalities are due to SM at baseline, or whether the worsening of the abnormalities on study is due to progressive SM.

The response for each individual parameter, as well as the Investigator's overall assessment of response, at each assessment time point per Appendix 1, should be entered into the eCRF, independent of duration, for all patients on study. For BM, the Investigator's response will be based on locally read BM biopsies; serum tryptase results will come from Central Laboratory testing. Resolution of modified IWG-MRT-ECNM C-findings should be used in determining response, when present at baseline. Responses should be confirmed 12 weeks (+4 weeks) after first documentation of response. For patients meeting PD criteria, progression of disease should be confirmed 4 weeks later, before the patient is discontinued from the study. Patients without confirmed progression may continue on study.

For patients in Cohort 1, the SM ORR will be adjudicated by the SSC based on algorithmic determination of each response criterion by the Sponsor statistician using data from every study visit for assessment of CI and SD (eg, laboratory tests [hematology and serum chemistry], serum tryptase, and evaluations of other baseline C-findings [eg, frequency of paracentesis]), and data from visits where BM biopsy and liver and spleen imaging are performed for assessment of CR/CRh and PR. The SSC ORR assessment will use local laboratory data (eg, CBC and liver function tests); clinical data on ascites and pleural effusions; transfusion requirements; serum tryptase data from the Central Laboratory; BM and other extracutaneous biopsy data from the Central Pathology Laboratory; and liver and spleen volume data provided by the Central Radiology Review Committee.

7.2.2 Associated Hematologic Neoplasm Response

At the same time points at which the SM response is assessed by modified IWG-MRT-ECNM criteria, AHN response for patients with SM-AHN will be assessed by both the Investigator and the SSC using the criteria in Appendix 11. Assessment will be completed locally by the Investigator and centrally, as for SM response, and adjudicated by the SSC by using the same samples and data available to assess SM response. Responses should be confirmed 12 weeks (+4 weeks) after initial documentation of response. Local cytogenetic data will be used in the determination of PD for patients with SM-AHN. For patients meeting PD criteria for AHN, progression of disease should be confirmed 4 weeks later, before the patient is discontinued from study. Patients with confirmed AHN PD but not confirmed SM PD per modified IWG-MRT-ECNM criteria will only be discontinued from study treatment if they require immediate alternative cytoreductive treatment.

7.2.3 Response Assessment Measures

7.2.3.1 Bone Marrow and Other Extracutaneous Biopsies

Bone marrow biopsy and aspirate and a PB smear will be obtained at the time points outlined in Appendix 1 for SM response assessment according to modified IWG-MRT-ECNM criteria (Appendix 7) and for AHN response assessment (Appendix 11). Patients with a confirmed CR/CRh based on Central Pathology Review (confirmed 12 weeks after the first CR/CRh; ie, 2 consecutive BM biopsies demonstrating absence of neoplastic MCs) are not required to have subsequent BM biopsy unless loss of response is suspected. Unless CR/CRh is confirmed by Central Pathology Review on 2 consecutive BM biopsies separated by at least 12 weeks, BM biopsies will continue to be required.

Bone marrow response assessment will be performed both at the local study site and by Central Pathology Review <u>using separate biopsy cores, aspirates, and PB smears</u> obtained at same time points. As the central response assessment is the primary objective of the trial, please send the more optimal biopsy and aspirate to the central pathology laboratory, rather than to the local laboratory. Instructions regarding the acquisition of BM samples will be provided in a laboratory manual.

Patients with suspected MC infiltrates in other extracutaneous organs may have those organs biopsied to document MC infiltrates during Screening. Patients with screening extracutaneous tissue biopsies may have those organs biopsied at the same time points as BM biopsies are performed postbaseline to determine response in MC infiltrates. If this biopsy is performed at Screening, it should be repeated to assess response at Cycle 3, and then as indicated to confirm response. Extracutaneous organ biopsies should be guided by patient symptoms and laboratory abnormalities, but may include GI tract, liver, or lymph nodes. All screening and postbaseline extracutaneous tissue biopsies will be shipped to the Central Pathology Laboratory for assessment of response. Instructions regarding the processing and shipment of extracutaneous tissue samples will be provided in a laboratory manual.

7.2.3.2 Serum Tryptase

Blood samples will be collected at the time points outlined in Appendix 1 to characterize the change from baseline in serum tryptase concentration during treatment with avapritinib. Samples will be analyzed in a Central Laboratory.

7.2.3.3 Organ Damage (C-Findings)

Criteria for evaluable C-findings per modified IWG-MRT-ECNM criteria and criteria for response are outlined in Appendix 6. C-findings must be attributed by the Investigator to SM or other etiology. A patient must have at least 1 C-finding, evaluable by modified IWG-MRT-ECNM response criteria and attributable to SM, to be eligible for enrollment into Cohort 1, (unless they have MCL, which does not require the presence of a C-finding). Only C-findings attributed to SM are evaluable for response. C-findings evaluable for response include ascites and/or pleural effusions, liver function test abnormalities, hypoalbuminemia, splenomegaly, cytopenias (ANC, platelets, and hemoglobin), and transfusion-dependent anemia and thrombocytopenia. All C-findings must be confirmed by the SSC. C-findings may change in attribution over time due to additional medical issues, AEs, and progression of AHN disease components. If worsening of a baseline C-finding attributable to SM is primarily attributable due to another cause (ie, gastric bleeding leading to worsened baseline anemia), that C-finding will be considered unevaluable until that other cause is no longer considered to be clinically significant.

7.2.3.3.1 Ascites and Pleural Effusions

Patients with symptomatic ascites and/or pleural effusions (ie, symptomatic and requiring medical intervention; refer to Appendix 6) at baseline will be evaluated for response throughout the study. Dates and number of paracenteses and/or thoracenteses (or taps from an indwelling drain) within the 12 weeks prior to C1D-8 will be recorded. All paracenteses and thoracenteses performed through EOT, as well as medications, such as diuretics, used to treat effusions, will be recorded.

7.2.3.3.2 Liver Function Test Abnormalities

Liver function will be assessed by measurement of direct bilirubin, ALT, AST, and alkaline phosphatase. Patients with ≥ Grade 2 abnormalities in any of these tests at baseline are evaluable for response, if attributed to SM and if they also have baseline ascites, clinically relevant portal hypertension, or biopsy-proven MC infiltration of the liver or no other cause of the abnormalities is identified. Response in the abnormal test (reversion to normal range) will be assessed during treatment at time points outlined in Appendix 1.

7.2.3.3.3 Hypoalbuminemia

Albumin will be assessed at baseline and during treatment at the time points outlined in Appendix 1 (refer to serum chemistry). Hypoalbuminemia ≥ Grade 2 at baseline is an evaluable C-finding if attributed to SM. These patients will be assessed for improvement to normal range.

7.2.3.3.4 Liver and Spleen Volume Imaging

Assessment of liver and spleen volume will be performed using serial imaging (MRI [preferred] or CT) at the time points outlined in Appendix 1. Patients who are not candidates for MRI (eg, patients with pacemakers, implanted metal clips, claustrophobia), or patients at sites where an MRI is not readily available, may be evaluated by CT to measure liver and spleen volume. The same modality (MRI or CT) must be used for a given patient throughout the study unless a new contraindication for the originally selected method develops. Liver and spleen imaging should be performed according to guidelines provided in the Study Manual. Study Steering Committee response assessments of liver and spleen volume will be based on Central Radiology Review. Response is defined as ≥ 35% reduction in spleen volume (PR) or resolution of palpable splenomegaly/hepatomegaly (CR).

7.2.3.3.5 Cytopenias

The presence of ANC ≥ Grade 3 (ANC < 1.0×10^9/L), platelet count ≥ Grade 2 (platelets < 75×10^9/L) or hemoglobin ≥ Grade 2 (hemoglobin < 10 g/dL) at baseline is an evaluable C-finding, if attributed to SM. Response, as defined in Appendix 5, will be assessed at all postbaseline time points outlined in Appendix 1.

7.2.3.3.6 Transfusion-Dependent Anemia and Thrombocytopenia

Red blood cell and platelet transfusion data for the 12 weeks before C1D-8 will be collected during Screening and all transfusions during the treatment period will be collected to determine response in patients with transfusion-dependent anemia and/or thrombocytopenia at baseline. The date and number of units of PRBCs and/or platelet transfusions must be recorded. Pretransfusion hemoglobin and platelet counts are required, as well as the reason for PRBC transfusion (eg, hemolysis, bleeding, treatment-related, SM-related, other).

7.2.3.4 Skin Photographs

Patients who present with mastocytosis in skin at Screening and who consent to the optional procedures, may have standardized skin photographs taken at time points specified in Appendix 1 at Screening and during treatment (until Week 71/Cycle 17) to assess improvement in cutaneous disease. Patients may opt out of photography assessments at any time if they have any concerns. Photographs will be assessed by a Skin Assessment Committee for response to treatment.

7.2.3.5 KIT D816 Allele Burden

Bone marrow aspirate and PB samples will be collected to characterize the *KIT* D816V MAF and other *KIT* mutations at baseline and at the postbaseline time points outlined in Appendix 1. For the purposes of confirmation of AdvSM diagnosis by WHO criteria, a sample tested locally, or an archival sample will be used. Baseline and post-treatment samples for assessment of response will be analyzed at a Central Laboratory. This will allow for the assessment of changes in MAF during treatment and at the time of disease progression. Sequencing for other *KIT* mutant alleles may allow identification of acquired *KIT* resistance mutations and other mutations at the time of disease progression and their correlation with response and progression.

7.2.3.6 Other Mutations

Bone marrow aspirate and PB samples will be collected to characterize other mutations (eg, *TET2, SRSF2, ASXL1, RUNX1*) present at baseline and at the postbaseline time points outlined in Appendix 1. Samples will be analyzed at a Central Laboratory. This will allow for the assessment of new mutations during treatment and at progression and their correlation with response and progression.

7.2.3.7 Cytogenetics for Associated Hematologic Neoplasm Disease Progression

Bone marrow aspirate will be collected to assess cytogenetic abnormalities in the myeloid hematopoietic cells. Samples will be obtained at baseline and at the time points specified in Appendix 1. This analysis will be performed at each study site's local laboratory. All abnormal cytogenetic findings present at baseline and postbaseline will be recorded in the eCRF. These data will be used by the Investigator and the SSC to subclassify AHN and to determine progression of the AHN component of disease.

7.2.3.8 Bone Density by Bone Densitometry/DXA Scan

Dual-energy x-ray absorptiometry scan for evaluation of bone density will be performed at Cycle 11, and then repeated at the end of every 12 cycles to assess improvement in bone density. Both lumbar spine and hip will be assessed at each time point.

7.2.3.9 Best Supportive Care Medication Use

Medications that are used to manage symptoms of SM will be optimized and stabilized during the baseline period. Optimized doses are not to exceed approved doses of each medication. Medications include H1 and H2 blockers, proton pump inhibitors, leukotriene inhibitors, corticosteroids (dose not to exceed 20 mg prednisone or equivalent), cromolyn sodium, omalizumab, and osteoclast inhibitors. These medications may ameliorate symptoms related to MC mediators but do not reduce MC burden. Based on patient symptoms, as assessed by the Investigator, doses of drugs may be reduced during treatment with avapritinib. Dose and schedule of each agent administered at baseline will be assessed at each postbaseline visit.

7.2.3.10 Patient-Reported Outcomes (AdvSM-SAF)

The AdvSM-SAF (Appendix 15) will be employed for daily PRO assessment at baseline and through Cycle 17 or until the patient discontinues the study, if earlier than Cycle 17.

The AdvSM-SAF is a 10-item questionnaire that assesses symptoms and functional domains specific to AdvSM. Individual symptom scores, domain scores (skin, GI, and other), and TSS are generated based on average scores for each 7-day period. Eight symptoms are scored on a scale of 0 to 10 for severity and 2 symptoms (vomiting and diarrhea) are scored for number of episodes. Recall period is 24 hours. Patients will complete the AdvSM-SAF daily using an eDiary during Screening, completing at least 7 days before the first dose of study drug through C17D28, inclusive.

If a patient is unable to consistently and accurately use the AdvSM-SAF due to disability, non-fluency in the available languages, or another reason, the patient may still enroll with written permission of the Sponsor.

7.2.3.11 [redacted]

[redacted]

[redacted]

[redacted]

7.3 Pharmacokinetic Assessment

Blood samples will be collected before and after study drug dosing to determine circulating plasma concentrations of avapritinib, as outlined in the PK sampling schedule in Appendix 2. All patients will have standard PK sampling. A subset of approximately 15 patients, identified by study site ability and patient willingness, will undergo more intensive PK sampling, also outlined in Appendix 2.

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

7.4 Biomarker Analysis

Blood samples will be collected at the time points outlined in Appendix 1 to measure [redacted]

7.4.1 Exploratory Analyses

Blood samples will be collected at the time points outlined in Appendix 1 for exploratory biomarker research focused on developing new genetic and mechanistic biomarkers to assess the effects of avapritinib in patients with cancer. Additionally, biomarker research may be performed using residual samples and material derived from PK, serum tryptase and/or *KIT* D816V samples. Further details will be provided in a laboratory manual.

7.5 Safety Assessments

The schedule of safety assessments is described in Appendix 1. Additional safety assessments may be performed when clinically indicated, at the Investigator's discretion, and based on local requirements.

All clinical and laboratory safety assessments will be assessed by the Investigator for clinical significance. New clinically significant findings or worsened AEs from baseline in severity of medical history events will be reported as AEs.

7.5.1 Eastern Cooperative Oncology Group Performance Status

Determination of ECOG PS will be performed at the time points outlined in Appendix 1. Refer to Appendix 12 for ECOG PS scoring.

7.5.2 Clinical Laboratory Testing

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

Clinical laboratory evaluations will be conducted at the time points outlined in Appendix 1. In addition, all clinically significant laboratory abnormalities, as assessed by the Investigator, will be followed by repeat testing and further investigated according to the judgement of the Investigator.

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

Hematology:	Hemoglobin, hematocrit, RBC count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), RBC distribution width (RDW), reticulocyte count, white blood cell count (WBC) with differential (including ANC), and platelet count.
Coagulation:	Prothrombin time (PT) or international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen.
Serum chemistry:	Sodium, potassium, blood urea nitrogen or urea, bicarbonate (venous), creatinine, calcium, chloride, magnesium, phosphorus, albumin, AST, ALT, alkaline phosphatase, gamma glutamyl transferase, total and direct bilirubin, lactate dehydrogenase, uric acid, and glucose. Creatinine clearance or eGFR will be measured at Screening only.
Urinalysis (dipstick):	pH, specific gravity, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, protein, and urobilinogen.
Serum or urine pregnancy[a]:	β-hCG.

[a] A serum pregnancy test should be performed for women of childbearing potential at Screening, on C1D1, and at EOT. A serum or urine pregnancy test should be performed locally when study visits are less frequent than every 4 weeks.

In addition, a platelet aggregation assay for newly enrolling patients with a platelet count > 150, 000/µL or for patients on study with a platelet count > 150,000/µL, even if no baseline value was assessed, is to be performed locally on fresh blood samples as indicated in Appendix 1 at selected sites.

7.5.3 Vital Signs

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

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

7.5.4 Electrocardiograms

Twelve-lead ECGs will be obtained for all patients at the time points outlined in Appendix 1.

Twelve-lead ECGs are to be conducted after 5 minutes in a recumbent or semi-recumbent position.

7.5.5 Brain Imaging

An MRI (preferred) or CT scan of the brain will be performed during Screening to serve as a baseline for comparison. An earlier imaging study performed up to 8 weeks before signing the ICF may be used if no clinically significant neurological events have occurred and the platelet count has remained entirely above 50,000/µL from the time of the scan to signing the ICF. Postbaseline scans will only be obtained, as warranted, based on patient symptoms. Patients with abnormalities indicative of risk for hemorrhage, or prior, recent, or current hemorrhage, are excluded from the study.

7.5.6 Physical Examination

Physical examinations will be performed as outlined in Appendix 1. Targeted examinations will focus on evaluating changes from Screening and previous physical examinations, and AEs. All physical examinations (complete and targeted) should include measurement by palpation of liver and spleen size and a focal neurological exam.

7.5.7 Adverse Events, Concomitant Medications, and Therapeutic Procedures

Each patient must be carefully monitored for the development of AEs throughout the study from the time of signing the consent form to 30 days after the last dose of avapritinib. In addition, all SAEs that occur > 30 days after the last dose are to be reported.

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

The dose, frequency, and route of administration of all concomitant medications, including all BSC medications, administered from the signing of informed consent through the Safety Follow-up visit will be recorded in the eCRF.

Concomitant diuretic medications, any paracenteses and/or thoracenteses, and transfusions of PRBCs and/or platelets should be recorded from 12 weeks before C1D1 through the EOT visit.

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

All patients will have the EOT visit after discontinuation of study drug (refer to Appendix 1 for a description of EOT assessments). Patients who discontinue from the study drug for reasons other than confirmed PD or initiation of other cytoreductive therapy will have response assessments (including BM biopsy and aspirate, PB smear, liver and spleen imaging, and laboratory and other C-finding assessments) performed at the EOT visit unless the assessments were performed within the preceding 24 weeks (or preceding 16 weeks if EOT is before Cycle 11). These same procedures will be repeated every 24 weeks (± 14 days) until PD or initiation of other cytoreductive therapy.

A Safety Follow-up visit will be conducted by telephone to assess resolution of any ongoing AEs 30 days (± 7 days) after the last dose of study drug, or earlier if the patient initiates another cytoreductive therapy.

All patients who experience confirmed PD at EOT, PD during Follow-up for PD, or initiate another cytoreductive therapy will be followed for OS, unless they discontinue from the study due to death, withdrawal of consent, or loss to follow-up, or the study is closed by the Sponsor. Overall survival assessments will begin at the EOT visit for patients who discontinue study drug before the EOT visit, or after follow-up for PD is complete.

7.7 Sample Processing, Storage, and Shipment

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

8 STUDY DRUG MANAGEMENT

8.1 Description

The investigational drug, avapritinib, will be administered during this study.

8.2 Formulation

Avapritinib will be administered as an immediate release tablet for oral administration. The drug substance and drug product are manufactured and formulated following current Good Manufacturing Practices.

Each white avapritinib tablet is blended with pharmacopeial excipients. The formulation blend is roller compacted, compressed into round tablets, and aesthetically film coated. Avapritinib tablets are prepared as 25 and 100 mg in strength. The 25 mg strength tablet is intended for patients whose dose is 25 or 50 mg.

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

8.3 Storage

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

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

8.4 Packaging and Shipment

Avapritinib tablets will be supplied to the study center, packaged in 60 cc wide-mouth, high-density polyethylene bottles. Each bottle will be capped with a tamper-evident, child-resistant closure.

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

8.5 Accountability

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

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

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

Patients will receive instructions for home administration of avapritinib.

All unused and used study drug should be retained at the center until they are 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 center per the center's Standard Operating Procedures and documented. All material containing avapritinib will be treated and disposed of as hazardous waste in accordance with governing regulations.

8.6 Compliance

Patients will be dispensed the appropriate number of study drug bottles to allow for dosing for a full cycle, or until the next scheduled visit. Patients are to return all unused tablets (or the empty bottles) on Day 1 of each treatment cycle or at the next scheduled visit. Compliance with the dosing regimen will be assessed based on return of unused drug (or empty bottles).

8.7 Overdose

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

If the overdose incident resulted in 1 or more AEs, the AE(s) must be reported in accordance with the instructions in Section 9 (AEs) or Section 10 (SAEs) of this protocol.

The highest dose of avapritinib studied clinically is 600 mg QD; there is no known antidote for avapritinib overdose. In the event of a suspected overdose, avapritinib dosing should be held, supportive care instituted, and the patient should be observed until clinical stabilization.

9 ADVERSE EVENTS

Monitoring of AEs will be conducted throughout the study. Adverse events, SAEs, and serious pretreatment events (refer to Section 9.2 and Section 10) will be recorded in the eCRF from the time of signing informed consent through 30 days after the last study drug dose. In addition, all SAEs that occur > 30 days post-treatment will also be reported. All study drug-related AEs should be monitored until they are resolved, have stabilized, have returned to pre-exposure baseline, are determined to be due to another illness, or until a subsequent therapy is initiated. For AEs considered not related to study drug, similar monitoring guidelines will only be required through 30 days after the last dose of study drug.

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 (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgement about causality. An AE can arise from any use of the drug (eg, off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. Overdose includes any dose higher than 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 AE that is not clearly caused by something other than avapritinib.

9.1.3 Unexpected Adverse Event

An unexpected AE is one for which the nature or intensity of the event is not consistent with the applicable product information (eg, information found in 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 nonleading questions (eg, "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

All AEs (serious and nonserious) 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 an 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 1 comprehensive event.

9.3 Assessment of Severity

Severity of all AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE), Version5.0. Adverse events not listed in the NCI 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 clearly caused by something other than avapritinib.
- Related: The AE does not meet the criteria for "Not Related."

9.5 Pretreatment Events

A pretreatment event is any untoward occurrence that occurs before administration of any study drug in a patient who has signed informed consent to participate in the study. The event 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 (eg, spontaneous abortion, which may qualify as an SAE).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient or partner of a male patient occurring while the patient is 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 the avapritinib 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 avapritinib to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately using the Pregnancy Report Form. The Investigator must follow up and document the course and outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished. The female patient or partner of a male patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. Monitoring should continue until conclusion of the pregnancy.

All outcomes of pregnancy must be reported by the Investigator to the Sponsor or Medical Monitor on a Pregnancy Outcome Report form within 30 days after he/she has gained knowledge of the delivery or elective abortion.

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

9.6.1 Contraception Requirements

Women of childbearing potential must agree to use a highly effective method of contraception from the first dose of study drug until at least 6 weeks after the last dose of avapritinib (CTFG, 2014). Women are considered to be of childbearing potential after menarche until becoming postmenopausal (defined as no menses for at least 12 months without an alternative medical cause), unless permanently sterile. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy (CTFG, 2014). Because avapritinib is a potential CYP3A4 inducer, women should use hormonal contraception with caution and supplement with other highly effective methods.

Males with partners who are female and of reproductive potential must agree that they will use condoms, and their partners must use a highly effective contraceptive method from the first dose of study drug and for 6 weeks after the last dose of avapritinib.

Highly effective forms of contraception are defined as:

- Combined (estrogen and progestogen containing) hormonal contraceptives that inhibit ovulation, including oral, intravaginal, and transdermal products.
- Progestogen-only hormonal contraceptives that inhibit ovulation, including oral, injectable, and implantable products.
- Intrauterine devices (IUD) and intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion (women).
- Male partner vasectomy or other method of surgical sterilization provided that the partner is the sole sexual partner of the trial participant and the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence (men and women), which is refraining from heterosexual intercourse during the entire period of risk associated with study treatment. Periodic abstinence (such as calendar, symptothermal and postovulation methods), withdrawal (coitus interruptus), and the lactational amenorrhea method are not acceptable methods of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: (CTFG, 2014).

The following methods of contraception are not considered highly effective:

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

Source: (CTFG, 2014).

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 EVENTS

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 (ie, 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 an AE (eg, 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 'nonserious' 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 patient who received study treatment.

- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based on appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

    - Intracranial bleeding events.

    - 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.

All intracranial bleeding events must be reported as SAEs.

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 Pharmaceutical Product Development (PPD), LLC. 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 avapritinib. 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 intensity of the event and relationship to study drug. Follow-up information on the SAE may be requested by the Sponsor or Medical Monitor.

Contact Information:

Pharmaceutical Product Development (PPD), LLC

globalsaeinbox@blueprintmedicines.com

or

USA eFAX: 1 800-878-5719

UK eFAX: 44-203-031-1056

(Refer to the study manual for international numbers)

If there are serious, unexpected adverse drug reactions associated with the use of study drug, 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, that occur after signing the informed consent through 30 days after 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 avapritinib, 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. Refer to Section 9.2 for additional details.

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 (refer to Section 9.3 for definitions).
- Relationship of the event to study treatment (refer to Section 9.4 for definitions).
- Action taken: none; change in the study drug administration (eg, temporary interruption in dosing); drug treatment required; nondrug treatment required; hospitalization or prolongation of hospitalization required (complete SAE page); diagnostic procedure performed; patient discontinued from treatment (complete End-of-Treatment visit).
- Outcome: patient recovered without sequelae; patient recovered with sequelae; event ongoing; patient died (notify the Medical Monitor immediately and complete the SAE report form).

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.

Safety, efficacy, PK, and pharmacodynamic evaluations will be assessed in the appropriate populations. Data presentations will be for all AdvSM patients, as well as by subgroups (ie, patients with ASM, SM-AHN, MCL; patients with and without prior cytoreductive therapy (midostaurin vs other); patients with and without *KIT* D816 mutation), as appropriate.

All data will be provided in by-patient listings.

One interim analysis (IA) for superiority will be performed at approximately 50% of the information fraction (ie, the first 32 patients enrolled in Cohort 1 are evaluable for response). See Section 11.5 for details.

11.2 Sample Size Estimation

The primary objective of this study is to determine adjudicated ORR (CR/CRh + PR + CI) based on modified IWG-MRT-ECNM criteria in patients with AdvSM treated with avapritinib and enrolled in Cohort 1. Assuming the null hypothesis ORR of 28% versus the alternative hypothesis ORR of 50%, and a 1-sided type I error rate of 0.025, a sample size of 63 patients in the modified IWG-MRT-ECNM evaluable cohort (Cohort 1) will have 93.5% power using the exact 1-sample binomial test. Enrollment of the SM-AHN subgroup will be capped at approximately 70% of the 63 Cohort 1 patients (ie, maximum of 45 patients) to ensure the study population reflects the general AdvSM patient population.

This sample size will also allow statistical testing of the key secondary objective of patients with symptom reduction based on AdvSM-SAF TSS. Assuming the null hypothesis is the mean change of TSS ≥ 0, versus the alternative hypothesis of the mean change of TSS is ≤ -10 with avapritinib treatment, the standard deviation of mean change of TSS is assumed to be 20, and a 1-sided type I error rate of 0.025, all treated patients in the modified IWG-MRT-ECNM evaluable cohort and the non-modified IWG-MRT-ECNM evaluable cohort will be included in the analysis. A sample size of 63 patients will have > 90% power using a 1 sample t-test. Testing for this key secondary endpoint will be sequential to ensure control of the study-wise type I error rate (ie, it will only be performed when the null hypothesis for the primary objective is rejected).

The non-modified IWG MRT-ECNM evaluable cohort will enroll approximately additional 40 patients, for a total of 103. With 103 patients, there is about 88% probability of observing at least 1 AE at 2% frequency, instead of 3.5% frequency with 60 patients.

11.3 Analysis Populations

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

- Response-Evaluable Population: The response-evaluable population will include all patients who receive at least 1 dose of study drug, have a diagnosis of AdvSM, and are evaluable per modified IWG-MRT-ECNM criteria at baseline as assessed by SSC review, and have at least 2 complete postbaseline response assessments (inclusive of BM and/or other involved tissue biopsy and liver and spleen imaging) and had been on study for at least 6 cycles (28 × 6 = 168 days), or had end of study visit. In addition to the primary efficacy analysis, the response-evaluable population will be used for all secondary efficacy analyses related to response, such as objective response, TTR, DOR, PFS, CI rate, and clinical benefit rate.

- Safety Population: The safety population will include all patients who receive at least 1 dose of study drug. The safety population will be used for the key secondary analysis and all safety analyses, PRO analyses, and efficacy analyses that are not based on modified IWG-MRT-ECNM response criteria.

11.4 Statistical Methods

11.4.1 Disposition

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

11.4.2 Demographic and Baseline Characteristics

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

11.4.3 Primary Efficacy Analysis

The primary efficacy analysis will include all patients in the response-evaluable population. Overall Response is defined as confirmed CR/CRh, PR, or CI per SSC review, after algorithmic determination of response for each individual criterion by the Sponsor statistician using modified IWG-MRT-ECNM consensus response criteria, with pathology components confirmed by Central Pathology Review. A confirmed response is a response confirmed ≥ 12 weeks after the originally documented response. Hypothesis testing against the null hypothesis of ORR ≤ 28% will be performed using exact 1-sample binomial test. There is 1 interim analysis that will include the first 32 patients (with the SM-AHN subgroup capped at approximately 70%) enrolled in the modified IWG-MRT-ECNM-evaluable cohort and are evaluable for response, as defined in Section 11.3. If the 1-sided p-value is < 0.00625, the null hypothesis will be rejected, and avapritinib will be deemed effective in treating patients with AdvSM and the interim analysis will be used to support a marketing application; however, the trial will remain open for full enrollment. If the 1-sided p-value is ≥ 0.00625 at the interim analysis, the final analysis will be used to support a marketing application. The final analysis of the primary efficacy endpoint will occur after all 63 patients (with the SM-AHN subgroup capped at approximately 70%) are enrolled in the modified IWG-MRT-ECNM-evaluable cohort and have had the opportunity to receive avapritinib treatment for at least 10 cycles or have discontinued treatment earlier. The final primary efficacy analysis will be tested at 1-sided alpha level of 0.02178 (See Section 11.5).

11.4.4 Secondary Analyses

11.4.4.1 Key Secondary Endpoint

AdvSM-SAF TSS is calculated as the summation of AdvSM-SAF questions 1 to 6, 8, and 10 (up to 80 points) for any given assessment timepoint if all questions are answered. Each question contributes to the TSS equally. The 7-day average of TSS is calculated as the average TSS of the 7 consecutive prior assessment days if at least 4 TSS scores exist during the 7-day period of time. A 7-day average of the AdvSM-SAF TSS will be used to compare the change from baseline to a postbaseline assessment. Change in AdvSM-SAF TSS is calculated from Baseline to C11D1 for patients on treatment for more than

10 cycles. The last observation carried forward method will be used for patients who end treatment before completing 10 cycles. Mean change will be calculated for all patients in the safety population and tested against the null hypothesis of ≥ 0 in TSS. If the 1 sample t-test p-value is < 0.025, the null hypothesis will be rejected, and avapritinib will be deemed effective in reducing symptoms in patients with AdvSM.

11.4.4.2 Other Secondary Endpoints

11.4.4.2.1 Efficacy

Confirmed and unconfirmed CR/CRh + PR rate, unconfirmed response rate (CR/CRh + PR + CI), and clinical benefit rate (CR/CRh + PR + CI + SD) will be reported. Response rate and 95% confidence intervals within the subgroups of the response-evaluable population (ie, patients with ASM, SM-AHN, or MCL) will be reported separately, but no statistical testing will be performed for the subgroups.

Time-to-event outcomes include TTR, DOR, PFS, and OS:

- Time-to-Response: TTR is defined as the time from first dose to the time of initial evaluation of CI or better.
- Duration of Response: DOR is defined as the time from initial documentation of a CI or better to the time of initial documentation of confirmed PD or death due to any cause, whichever occurs first. For responders who have not progressed or died at the time of analysis, DOR will be censored at the last response assessment that is SD or better.
- Progression-Free Survival: PFS is defined as time from first dose to the time of initial documentation of confirmed PD or death due to any cause, whichever occurs first. Patients who have not progressed or died at the time of analysis will be censored at the last response assessment that is SD or better.
- Overall Survival: OS is defined as time from first dose to the time of death due to any cause. Patients who are known to be alive or are lost to follow-up will be censored at the last time point they were known to be alive.

Duration of response will be analyzed descriptively for the responders (CR/CRh + PR + CI) and (CR/CRh + PR) in the response-evaluable population. Time to response and PFS will be analyzed using the Kaplan-Meier method in the response-evaluable population, and OS will be analyzed using the Kaplan-Meier method in the safety population.

For patients excluded from the response-evaluable population solely due to unevaluable BM for response, the rate of CI will be reported with 95% confidence intervals. Clinical improvement rate in subgroups of these patients (ie, patients with ASM, SM-AHN, or MCL) will also be reported separately.

11.4.4.2.2 Individual Measures of Mast Cell Burden

Assessment of individual measures of MC burden (BM MCs, serum tryptase, *KIT* D816 mutation burden in PB and BM, and liver and spleen volume by imaging) will include absolute change and percent change from baseline at each time point, as well as maximum percent reduction from baseline. The proportion of patients with BM CR or PR (ie, absence of neoplastic MC aggregates in the BM and ≥ 50% reduction in BM MCs, respectively), serum tryptase CR or PR (ie, serum tryptase < 20 ng/mL and ≥ 50% reduction, respectively), *KIT* D816 mutation burden CR or PR (ie, undetectable and ≥ 50% reduction, respectively), and spleen or liver CR or PR by imaging (ie, ≥ 35% reduction in spleen volume and normal spleen and liver length, respectively) will be presented. Analyses will only include patients with minimum MC burden at Screening for each respective measure (ie, ≥ 5% BM MCs per Central Pathology Review, serum tryptase ≥ 40 ng/mL, enlarged spleen or liver per Central Radiology Review) and at least 1 postbaseline assessment in the safety population.

11.4.4.2.3 [redacted]

[redacted]

[redacted]

11.4.4.2.4 Pharmacokinetics

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

Mean and individual subject predicted avapritinib exposure parameters (C_{max}, AUC_{0-24}, and C_{trough} [lowest concentration reached by a drug before the next dose is administered]) from the population PK model will be summarized, as appropriate.

11.4.4.2.5 Exposure and Safety

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 summarized. Reasons for dose modifications will be listed by patient and summarized.

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

Concomitant medications will be listed by patient and summarized.

All safety data will be listed by patient and summarized.

<u>Adverse Events</u>

Summary tables and listings for AEs will include treatment-emergent AEs (TEAE), where a TEAE is defined as any AE that occurred between the first dose of a study drug through 30 days after the last dose of any study drug. The incidence of TEAEs (new or worsening from baseline) will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and/or preferred term, intensity (based on NCI CTCAE, Version 5.0 grading, as assessed by the Investigator), seriousness, and relationship to study treatment. Similar terms may be presented together as 1 cluster term. The following summaries will be produced:

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

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

Laboratory Abnormalities

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

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

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

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

Other Safety Data

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

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

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

Additional safety analyses may be performed, as necessary.

11.4.5 [redacted]

[redacted]

[redacted]

11.5 Interim Analysis

An interim analysis for efficacy stopping will be conducted to determine whether continuation until study completion is warranted. ORR (CR/CRh, PR, or CI) based on modified IWG-MRT-ECNM consensus response criteria per SSC review will be used as the endpoint for the interim analysis. The interim analysis will be performed at approximately 50% of the information fraction; it will include the first 32 patients (with the SM-AHN subgroup capped at approximately 70%) enrolled in the modified IWG-MRT-ECNM- evaluable cohort, once they are considered evaluable for response as defined in Section 11.3. This interim analysis is expected to occur approximately 18 months after the first patient is enrolled. Regardless of the results of the interim analysis, enrollment will continue to completion.

If the testing for ORR is not statistically significant at the interim analysis, the ORR testing will be conducted again at the final analysis when 63 patients (with the SM-AHN subgroup capped at approximately 70%) have been enrolled in the modified IWG-MRT-ECNM evaluable cohort and have had the opportunity to receive avapritinib treatment for at least 10 cycles or have discontinued treatment earlier. The final analysis is expected to occur approximately 24 months after the first patient is enrolled.

To establish the statistical monitoring guideline to control the overall Type I error rate at 0.025 (1-sided), critical values for the interim and final analyses of ORR is determined using power error spending function with parameter $\rho=2$. The interim analysis will be considered positive if the observed p value is less than 0.00625 (1-sided) at the interim analysis. The final analysis will be tested at 1-sided alpha level of 0.02178.

If the testing for ORR is statistically significant at the interim analysis, the key secondary endpoint will be tested in all treated patients with alpha level of 0.025 (1-sided). Other secondary endpoints related to response will be summarized in all response-evaluable patients. All safety analyses, PRO analyses, and efficacy analyses that are not based on modified IWG-MRT-ECNM response criteria will be summarized in all safety population patients.

12 ETHICS AND RESPONSIBILITIES

12.1 Good Clinical Practice

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

12.2 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 wellbeing of the patients. The study will only be conducted at study centers where IRB/IEC approval has been obtained. The protocol, IB, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC. The IRB/IEC is to be notified of any amendment to the protocol in accordance with local requirements. Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

12.3 Informed Consent

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

After the study has been fully explained, written informed consent will be obtained from the patient before 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).

12.4 Records Management

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

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

12.5 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.

12.6 Study Files and Record Retention

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

12.7 Liability and Insurance

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

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. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

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

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

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

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 judgement 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 and Blueprint Medicines and its authorized representatives are allowed full access to the records.

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

18 REFERENCES

[redacted]

Arias M, Villalba C, Requena I, Vazquez-Veiga H, Sesar A, and Pereiro I. Acute spinal epidural hematoma and systemic mastocytosis. *Spine (Phila Pa 1976).* 2004;29(8):E161-3.

Barete S, Lortholary O, Damaj G, Hirsch I, Chandesris MO, Elie C, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. *Blood.* 2015;126(8):1009-16; quiz 1050.

Chabot B, Stephenson DA, Chapman VM, Besmer P, and Bernstein A. The proto-oncogene c-kit encoding a transmembrane tyrosine kinase receptor maps to the mouse W locus. *Nature.* 1988;335(6185):88-9.

Cohen SS, Skovbo S, Vestergaard H, Kristensen T, Moller M, Bindslev-Jensen C, et al. Epidemiology of systemic mastocytosis in Denmark. *Br J Haematol.* 2014;166(4):521-8.

CTFG. Recommendations related to contraception and pregnancy testing in clinical trials [Online]. C.T.F. Group, ed. 2014.

EMA. European public assessment report (EPAR) for Rydapt [Online]. 2017. https://www.ema.europa.eu/en/medicines/human/EPAR/rydapt.

FDA. Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers [Online]. USFDA, ed. 2016. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Garcia-Montero AC, Jara-Acevedo M, Teodosio C, Sanchez ML, Nunez R, Prados A, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood.* 2006;108(7):2366-72.

Glivec SmPC. Summary of Product Characteristics. Dublin, Ireland: Novartis Europharm Limited.

Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. *N Engl J Med.* 2016;374(26):2530-41.

Gotlib J, Pardanani A, Akin C, Reiter A, George T, Hermine O, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. *Blood.* 2013;121(13):2393-401.

Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood.* 2012;120(12):2454-65.

Kantarjian H, Giles F, List A, Lyons R, Sekeres MA, Pierce S, et al. The incidence and impact of thrombocytopenia in myelodysplastic syndromes. *Cancer.* 2007;109(9):1705-14.

Lennartsson J, and Ronnstrand L. Stem cell factor receptor/c-Kit: from basic science to clinical implications. *Physiol Rev.* 2012;92(4):1619-49.

Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood.* 2009;113(23):5727-36.

Nixon A, Doll H, Kerr C, Burge R, and Naegeli AN. Interpreting change from patient reported outcome (PRO) endpoints: patient global ratings of concept versus patient global ratings of change, a case study among osteoporosis patients. *Health Qual Life Outcomes.* 2016;14:25.

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

Rydapt. Package Insert. 2017a. East Hanover, New Jersey: Novartis.

Rydapt. Summary of Product Characteristics. 2017b. Camberley, UK: Novartis Europharm Limited.

Savona MR, Malcovati L, Komrokji R, Tiu RV, Mughal TI, Orazi A, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. *Blood.* 2015;125(12):1857-65.

Sucker C, Mansmann G, Steiner S, Gattermann N, Schmitt-Graeff A, Loncar R, et al. Fatal bleeding due to a heparin-like anticoagulant in a 37-year-old woman suffering from systemic mastocytosis. *Clin Appl Thromb Hemost.* 2008;14(3):360-4.

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th Edition. Volume Volume 2. Lyon, France: IARC Press. 2017.

Theoharides TC, Valent P, and Akin C. Mast Cells, Mastocytosis, and Related Disorders. *N Engl J Med.* 2015;373(19):1885-6.

Valent P. Mastocytosis: a paradigmatic example of a rare disease with complex biology and pathology. *Am J Cancer Res.* 2013;3(2):159-72.

Valent P, Akin C, and Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood.* 2017;129(11):1420-1427.

Valent P, Sperr WR, and Akin C. How I treat patients with advanced systemic mastocytosis. *Blood.* 2010;116(26):5812-7.

Verstovsek S. Advanced systemic mastocytosis: the impact of KIT mutations in diagnosis, treatment, and progression. *Eur J Haematol.* 2013;90(2):89-98.

Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366(9):799-807.

19 APPENDICES

19.1 Appendix 1: Schedule of Assessments

Refer to the Description of Study Procedures (Section 7) for additional details regarding each assessment.

Schedule of Assessments

Study Activities	**Screening**		**Study Treatment**							**EOT[a]**	**Safety F/U**	**F/U for PD[g]**	**F/U for OS[b]**
Time Period/Cycle			**C1**		**C2**	**Every 2 months C3 to C11**		**Every 3 months after C11[c]**					
						C3, C7, C11 (S&E)	**C5, C9 (S)**	**C14, C20, etc. (S)**	**C17, C23, etc. (S&E)**				
Study Day	**-56 to -8**	**-7 to -1**	**Baseline D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**14 days post last dose**	**30 days post last dose**	**Every 6 months**	**Every 3 months**
Window (Days)		**+ 3**		**± 2**	**± 3**	**± 7**	**± 7**	**+ 14**	**+ 14**	**± 7**	**± 7**	**± 14**	**± 14**
Informed consent[d]	X												
Inclusion/exclusion criteria	X												
Demographics	X												
Medical history[e]	X												
RBC and platelet transfusion data collection[f]	X					X						X[g]	
Paracenteses and thoracenteses and diuretics[h]	X					X						X[g]	
Height	X												

Study Activities	Screening		Study Treatment							EOT[a]	Safety F/U	F/U for PD[g]	F/U for OS[b]
Time Period/Cycle			C1		C2	Every 2 months C3 to C11		Every 3 months after C11[c]					
						C3, C7, C11 (S&E)	C5, C9 (S)	C14, C20, etc. (S)	C17, C23, etc. (S&E)				
Study Day	-56 to -8	-7 to -1	Baseline D1	D15	D1	D1	D1	D1	D1	14 days post last dose	30 days post last dose	Every 6 months	Every 3 months
Window (Days)		+ 3		± 2	± 3	± 7	± 7	+ 14	+ 14	± 7	± 7	± 14	± 14
Weight	X		X	X	X	X	X	X	X	X		X[g]	
Physical examination[i]	X		X	X	X	X	X	X	X	X			
Vital signs[j]	X		X	X	X	X	X	X	X	X			
Serum pregnancy (β-hCG) test[k]	X		X							X			
Urine or serum pregnancy test[k]	X				X								
ECOG PS	X		X	X	X	X	X	X	X	X			
AdvSM-SAF[l]	X	X	X (through C17D28)										
12-lead ECG[m]	X		X	X	X	X	X	X	X	X			
Complete blood count[n,aa]	X	X[n]		X	X	X[aa] (q28d)	X[aa] (q28d)	X[aa] (q28d)	X[aa] (q28d)	X		X[g]	
Serum chemistry[n]	X			X	X	X	X	X	X	X		X[g]	
Coagulation[n]	X		X	X	X	X	X	X	X	X			
Urinalysis[n]	X									X			

Study Activities			**Study Treatment**							**EOT[a]**	**Safety F/U**	**F/U for PD[g]**	**F/U for OS[b]**
						Every 2 months C3 to C11		**Every 3 months after C11[c]**					
Time Period/Cycle	**Screening**		**C1**		**C2**	**C3, C7, C11 (S&E)**	**C5, C9 (S)**	**C14, C20, etc. (S)**	**C17, C23, etc. (S&E)**				
			Baseline										
Study Day	**-56 to -8**	**-7 to -1**	**D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**14 days post last dose**	**30 days post last dose**	**Every 6 months**	**Every 3 months**
Window (Days)		+ 3		± 2	± 3	± 7	± 7	+ 14	+ 14	± 7	± 7	± 14	± 14
Blood sample for local platelet aggregation assay			At selected sites only: for newly enrolling patients with a platelet count >150,000/µL, this assay is to be performed locally on fresh blood samples at baseline, C2D1, C3D1, and C7D1 or at any applicable time point for patients on study with a platelet count >150,000/µL, if no baseline value was assessed.										
SSC determination of eligibility		X											
Study drug administration			X										
Blood sample for exploratory biomarkers[o]			X		X	X[q]			X[q]	X[q]			
Blood sample for serum tryptase[o]	X			X	X	X[q]			X[q]	X[q]		X[g]	
Blood sample for *KIT* D816V mutant allele burden and other mutations[o,p]	X		X	X	X	X[q]			X[q]	X[q]		X[g]	
BM aspirate for *KIT* D816V mutant allele burden and other mutations[o,p]	X					X[q]			X[q]	X[q]		X[g]	

Study Activities			**Study Treatment**							**EOT[a]**	**Safety F/U**	**F/U for PD[g]**	**F/U for OS[b]**
Time Period/Cycle	**Screening**		**C1**		**C2**	**Every 2 months C3 to C11**		**Every 3 months after C11[c]**					
						C3, C7, C11 (S&E)	**C5, C9 (S)**	**C14, C20, etc. (S)**	**C17, C23, etc. (S&E)**				
Study Day	**-56 to -8**	**-7 to -1**	**Baseline D1**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**14 days post last dose**	**30 days post last dose**	**Every 6 months**	**Every 3 months**
Window (Days)		**+ 3**		**± 2**	**± 3**	**± 7**	**± 7**	**+ 14**	**+ 14**	**± 7**	**± 7**	**± 14**	**± 14**
Blood sampling for PK			Refer to Section 19.2 (Appendix 2) for detailed PK sampling schedule										
BM biopsy, aspirate, and PB smear collection[o,r,s]	X					X[q]			X[q]	X[q]		X[g]	
BM aspirate for cytogenetics for local analysis	X					X			X[q]	X[q]		X[g]	
Biopsy of other suspected or known areas of SM involvement[o,t]	X					X			X			X[g]	
Organ damage C-findings	X			X	X	X	X	X	X	X		X[g]	
Response per modified IWG-MRT-ECNM criteria				X	X	X[q]			X[q]	X[q]		X[g]	
PI attribution per mIWG criteria	X		X	X	X	X	X	X	X	X			
PI SM response assessment						X			X				

Study Activities			Study Treatment							EOT[a]	Safety F/U	F/U for PD[g]	F/U for OS[b]
Time Period/Cycle	Screening		C1		C2	Every 2 months C3 to C11		Every 3 months after C11[c]					
						C3, C7, C11 (S&E)	C5, C9 (S)	C14, C20, etc. (S)	C17, C23, etc. (S&E)				
Study Day	-56 to -8	-7 to -1	Baseline D1	D15	D1	D1	D1	D1	D1	14 days post last dose	30 days post last dose	Every 6 months	Every 3 months
Window (Days)		+ 3		± 2	± 3	± 7	± 7	+ 14	+ 14	± 7	± 7	± 14	± 14
SM-AHN response				X	X	X[q]			X[q]	X[q]		X[g]	
Liver and spleen imaging[u,v]	X					X[q]			X[q]	X[q]		X[g]	
DXA scan[w]	X					X (C11)			X (q48wk)				
Brain imaging[v]	X												
Skin assessment[x]	X					X			X (C17 only)				
[redacted]													
Assessment of OS													X[b]
AE monitoring	X												
SAE monitoring	X												
Concomitant medications and optimization of BSC	X[z]	X											

Abbreviations: AdvSM = Advanced Systemic Mastocytosis; AdvSM-SAF = Advanced Systemic Mastocytosis Symptom Assessment Form; AE = adverse event; AHN = associated hematologic neoplasm; BM = bone marrow; BSC = best supportive care; C = cycle; CBC = complete blood count; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; CT = computed tomography; D = day; DXA = dual-energy x-ray absorptiometry; ECG =electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EDC = electronic data capture; [redacted]; EOT = end-of-treatment; F/U = Follow-up; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; *KIT* = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MC mast cell; MRI = magnetic resonance imaging; OS = overall survival; PB = peripheral blood; PD = progressive disease; [redacted]; PI = principal investigator; PK = pharmacokinetic(s); PR = partial remission; q28d = every 28 days; q48wk = every 48 weeks; RBC = red blood cell; S = safety assessment; S&E = safety and efficacy assessment; SAE = serious adverse event; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm; SSC = Study Steering Committee.

[a] Patients terminating the study for reasons other than PD or initiation of other cytoreductive therapy will have response assessments (including BM biopsy and aspirate, PB smear, and liver and spleen imaging, and laboratory and other C-finding assessments) performed at the EOT visit unless procedures have been performed within the preceding 24 weeks after Cycle 11, or within the preceding 16 weeks if patient EOT is within the first 11 cycles of the study, in which case they need not be repeated.

[b] Overall survival assessments will be conducted by telephone contact every 3 months (± 14 days) to determine OS for patients who discontinue study drug due to PD or initiate another cytoreductive therapy. For patients who discontinue study drug for a reason other than PD, OS assessments will begin after follow-up for PD is complete, unless the reason for discontinuation is death, withdrawal of consent, loss to follow-up, or closure of the study by Sponsor.

[c] Safety (C14, C20, etc.) and response assessment (C17, C23, etc.) visits will continue to alternate every 3 months.

[d] Informed consent may be obtained within 8 weeks (Days -56 to -15) before the first dose of study drug. Patients will be evaluated by the study site for eligibility during a Screening period of up to 7 weeks (Day -56 to -8).

[e] A complete medical and surgical history, as well as a targeted history of mastocytosis, other malignancies, and prior SM/AHN treatments will be collected at the Screening visit.

[f] Data on all RBC and platelet transfusions will be collected for the 12 weeks before C1D-8 and through EOT. For patients discontinuing without documentation of PD or initiation of other cytoreductive therapy, these data will continue to be collected until PD is documented and/or other cytoreductive therapy is initiated.

[g] Patients who discontinue without confirmed PD or initiation of new cytoreductive therapy will be assessed for response using modified IWG-MRT-ECNM criteria (including BM biopsy and liver and spleen imaging) every 24 weeks (± 14 days) until the development of confirmed PD, initiation of another cytoreductive therapy, death, or loss to follow-up.

[h] For patients with symptomatic ascites and/or pleural effusions at baseline, dates and number of paracenteses and/or thoracenteses within the 12 weeks before C1D-8, as well as all diuretics used to treat effusions during the 12 weeks before C1D-8, will be recorded. All paracenteses and thoracenteses performed through EOT, as well as diuretics used to treat effusions, will be recorded. For patients discontinuing without documentation of PD or initiation of other cytoreductive therapy, these data will continue to be collected until PD is documented and/or other cytoreductive therapy is initiated.

[i] A complete physical examination will be performed at the Screening visit, including evaluation of skin, head and neck, lymph nodes, heart, lungs, abdomen (including measurement of liver and spleen size by palpation), musculoskeletal, and neurological systems, including focal neurological history. Subsequent physical examinations may be targeted but must include measurement of liver and spleen size by palpation and a focal neurological history and exam.

[j] Vital signs include temperature, pulse, and systolic/diastolic blood pressure. Blood pressure and pulse assessments should be conducted while the patient is seated or supine.

[k] To be performed for women of childbearing potential. A serum pregnancy test will be obtained within 15 days (preferably within 8 days) before the first dose of study drug. When study visits are less frequent than every 4 weeks, a local serum or urine pregnancy test should be done every 4 weeks.

[l] AdvSM-SAF will be collected daily starting in Screening to ensure at least 7 days of baseline data and through Cycle 17 or until the patient discontinues from the study, if earlier than Cycle 17. Sites are encouraged to provide the devices and begin data collection at the time of ICF. Patients who are unable to

consistently and accurately use the AdvSM-SAF due to disability, non-fluency in the available languages, or another reason may still enroll with written permission of the Sponsor.

[m] Twelve-lead ECGs are to be conducted after 5 minutes in a recumbent or semi-recumbent position.

[n] Safety assessments (including CBC with differential, serum chemistry, and liver function tests) may be repeated within 7 days of C1D1 and can be performed on C1D1, prior to dose, based on local requirements. Patients with any degree of thrombocytopenia must repeat CBC with differential about 28 days before C1D1 and again within 7 days before dosing.

[o] Screening samples should be obtained at the site and shipped to the Central Laboratory (blood samples for serum tryptase, *KIT* D816V mutation and other mutations, and biomarkers) or Central Pathology Laboratory (BM biopsy and aspirate with PB smear and other extracutaneous biopsies). In addition to Screening, blood and bone marrow sampling for other mutations should be performed at C3D1, C7D1, and C11D1 and then every 6 cycles, as well as at EOT and at the time of PD. Also performed 12 weeks (± 4 weeks) after documentation of CR or PR to confirm response and 4 weeks after SM and/or AHN PD or clinical progression to confirm PD.

[p] Archival or local test for *KIT* D816V mutation must be performed and entered into EDC before C1D-8.

[q] Performed at C3D1, C7D1 and C11D1 and then every 6 cycles. Also performed 12 weeks (± 4 weeks) after documentation of CR or PR to confirm response and 4 weeks after SM and/or AHN PD or clinical progression to confirm PD. Performed at EOT if patient discontinues for reasons other than PD or initiation of alternative cytoreductive therapy (unless procedures have been performed within the preceding 24 weeks after Cycle 11, or within the preceding 16 weeks if EOT is within the first 11 cycles of the study, in which case they do not need to be repeated). Additional assessments may be performed at Investigator discretion.

[r] Patients with a confirmed CR/CRh (confirmed 12 weeks after the first CR/CRh) per Central Pathology review are not required to have subsequent BM biopsies unless loss of response is suspected.

[s] A baseline BM core biopsy, aspirate, and PB smear must be obtained within 56 days of C1D1 during Screening for Central Pathology Laboratory diagnosis of SM and subclassification and MC quantification. At baseline and all subsequent time points, 2 sets of BM biopsies, aspirates and PB smears will be collected—1 for shipment to the Central Pathology Laboratory, and 1 for local assessment. In case of a "dry tap," BM touch prep slides may be submitted in place of the BM aspirate slides. If separate BM core and/or aspirate cannot be obtained for the Central Pathology Laboratory, local samples should be submitted to the Central Pathology Laboratory in place of the Central specimens. Archival BM sample can be sent to the Central Pathology Laboratory, if it was taken within 56 days of C1D1, and it meets washout criteria.

[t] If biopsy of another extracutaneous site of disease is performed at Screening and positive for neoplastic mast cell aggregates, it should be repeated (if considered safe by the investigator), to assess response at C3D1, C7D1 and C11D1 and then every 6 cycles until documentation of a confirmed CR (2 consecutive biopsies negative for mast cell aggregates at least 12 weeks apart). Additional assessments may be performed at Investigator discretion. Archival samples may be used as screening sample if obtained within 56 days prior to C1D1 and obtained after washout (if needed) and upon approval of the Medical Monitor.

[u] Performed for assessment of volume with digital scans transferred to Central Radiology Laboratory. Patients with confirmed CR/CRh (confirmed 12 weeks after the first CR/CRh) per Central Pathology review are not required to have liver and spleen imaging unless loss of response is suspected (eg, palpable spleen).

[v] Imaging is by MRI or CT scan; MRI is preferred. Historical neuroimaging within 8 months may be used with permission of the Sponsor.

[w] DXA scan for evaluation of bone density of lumbar spine and hip/femoral neck will be performed at Screening, at Cycle 11, and then repeated at the end of every 12 cycles. Historical DXA within 6 months may be used with the permission of the Sponsor.

[x] For patients with mastocytosis in skin at Screening, standardized skin photographs may be taken during Screening and postbaseline at Cycles 3, 7, 11, and 17. Patients must consent to the photographs and may opt out at any time.

[y] Completed at each visit through Cycle 17 and at EOT, if EOT is before or at Cycle 17.

[z] Medications for management of MC-mediated symptoms will be optimized and stabilized during Screening. These medications (BSC) should be optimized no later than 14 days before C1D-8. BSC doses should not be increased during study participation unless patient experiences increased symptoms.

[aa] CBCs must be obtained approximately every 28 days (±7 days) and may be performed at a local lab if a study visit at the site is not scheduled. Laboratory test results must be reported to the study site, which should dose modify in accordance with guidance in Table 8 and Table 9.

19.2 Appendix 2: Pharmacokinetic Sampling Schedules

Refer to the Description of Study Procedures (Section 7.3) for additional details regarding which patients will have standard PK sampling and which patients will undergo intensive PK sampling.

Pharmacokinetic Sampling Schedule – Standard Sampling for All Patients

Study Activities	Study Treatment				
Time Period/Cycle	C1		C2	C3	C5
Study Day	D1	D15	D1	D1	D1
Window (Days)		± 2	± 3	± 7	± 7
Time Point					
Predose	X	X	X	X	X
1 hour postdose (± 5 minutes)	X	X	X	X	X
4 hours postdose (± 10 minutes)		X			
6 to 8 hours postdose (± 10 minutes)		X			

Abbreviations: C = cycle; D = day.
Note: Investigators may also obtain blood samples for pharmacokinetic analysis at the time(s) significant drug-related adverse events and serious adverse events occur.

Refer to the Description of Study Procedures (Section 7.3) for additional details regarding which patients will have standard PK sampling and which patients will undergo intensive PK sampling.

Pharmacokinetic Sampling Schedule – Intensive Sampling for a Subset of 15 Patients

<table>
<tr><th>Study Activities</th><th colspan="9">Study Treatment</th></tr>
<tr><th>Time Period/Cycle</th><th colspan="6">C1</th><th>C2</th><th>C3</th><th>C5</th></tr>
<tr><th>Study Day</th><th>D1</th><th>D2</th><th>D3</th><th>D15</th><th>D16</th><th>D17</th><th>D1</th><th>D1</th><th>D1</th></tr>
<tr><th>Window (Days)</th><th></th><th></th><th></th><th>± 2</th><th></th><th></th><th>± 3</th><th>+ 7</th><th>+ 7</th></tr>
<tr><td colspan="10">Time Points</td></tr>
<tr><td>Predose</td><td>X</td><td rowspan="7">C1D2 dose will not be administered to allow for collection of the 48-hour postdose sample on C1D3</td><td></td><td>X</td><td rowspan="7">C1D16 dose will not be administered to allow for collection of the 48-hour postdose sample on C1D17</td><td></td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>0.5 hours postdose (± 5 minutes)</td><td>X</td><td></td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 hour postdose (± 5 minutes)</td><td>X</td><td></td><td>X</td><td></td><td rowspan="4">At any 1 time point between 6-8 hours postdose</td><td rowspan="4">At any 1 time point between 6-8 hours postdose</td><td rowspan="4">At any 1 time point between 6-8 hours postdose</td></tr>
<tr><td>2 hours postdose (± 5 minutes)</td><td>X</td><td></td><td>X</td><td></td></tr>
<tr><td>4 hours postdose (± 10 minutes)</td><td>X</td><td></td><td>X</td><td></td></tr>
<tr><td>8 hours postdose (± 10 minutes)</td><td>X</td><td></td><td>X</td><td></td></tr>
<tr><td>10 hours postdose (± 15 minutes)</td><td>X</td><td></td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>24 hours postdose (± 1 hour)</td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>48 hours postdose (± 1 hour)</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
</table>

Abbreviations: C = cycle; D = day.

19.3 Appendix 3: Assessment of Eligibility before Cycle 1 Day 1 Dosing

Screening Assessment	Collection Timeframe		Action to be Taken
	Start	Finish	
Screening Assessments Required for SSC Review			
BM biopsy, aspirate, and PB **for confirmation of AdvSM diagnosis and quantification of MC burden**	Completion of washout[a]	C1D-21	Send 1 set of samples to Local Pathology Laboratory and a second set of samples to Central Pathology Laboratory
Bone marrow cytogenetics	Signature of ICF	C1D-21	Process at local laboratory and entered results into eCRF no later than C1D-21
Biopsy of other suspected/known areas of SM involvement – optional	Signature of ICF	C1D-21	Send to Central Pathology Laboratory
Hematology and serum chemistry	Completion of washout[a]	C1D-21	Perform locally and enter results into eCRF no later than C1D-21
Serum tryptase to Central Laboratory	Signature of ICF	C1D-21	Send to Central Laboratory; enter into eCRF no later than C1D-8
Archival result or test for *KIT* D816V locally during Screening[b]	Signature of ICF	C1D-8	Enter results into eCRF no later than C1D-8
C-finding measurement and attribution	Completion of washout[a]	C1D-8	Enter data into eCRF no later than C1D-8
Documentation of splenomegaly and/or hepatomegaly by palpation	Signature of ICF	C1D-8	Enter into eCRF no later than C1D-8
For patients with symptomatic ascites/pleural effusion: collect data and number of paracenteses, thoracenteses, and diuretic use for ascites/pleural effusion	Data collection timeframe begins 12 weeks before C1D-8		Enter into eCRF no later than C1D-8
Obtain history of RBC and platelet transfusions (dates, number of units transfused, pretransfusion hemoglobin and/or platelet counts) and reason(s) for RBC transfusion	Data collection timeframe begins 12 weeks before C1D-8		Enter into eCRF no later than C1D-8
Other screening assessments: physical examination, collection of demographic data, medical history (including mastocytosis history), prior mastocytosis therapies and procedures	Signature of ICF	C1D-21	Enter into eCRF no later than C1D-21

Screening Assessment	Collection Timeframe		Action to be Taken
	Start	Finish	
Screening Assessments Not Requiring Central Review for Eligibility			
Optimize BSC – BSC dose must be stable for ≥ 14 days before C1D8	Signature of ICF	C1D-15	
For patients with mastocytosis in skin, standardized skin photographs will be taken	Signature of ICF	C1D-8	Send to Canfield (central repository for skin photography) as soon as available
Imaging of liver and spleen for assessment of volume[c]	Signature of ICF	C1D-8	Upload to central imaging vendor immediately, once image is available
DXA scan for evaluation of bone density[c]	Signature of ICF	C1D-8	Perform locally and enter findings into eCRF as soon as available
Brain MRI or CT without contrast[d]	Signature of ICF	C1D-8	Perform locally and enter findings into eCRF
Other screening assessments: vital signs, ECOG PS, ECG	Signature of ICF	C1D-8	Enter into eCRF as soon as available
AdvSM-SAF collected daily by eDiary to establish baseline symptoms C1D-7 to C1D-1	C1D-7	C1D-1 for Baseline, then through Cycle 17	Collect electronically
Screening sample for *KIT* D816V for Central Laboratory testing	Signature of ICF	C1D1 predose	Ship to Central Laboratory

Abbreviations: AdvSM = advanced mastocytosis; AdvSM-SAF = AdvSM Symptom Assessment Form; BM = bone marrow; BSC = basic supportive care; C = cycle; CBC = complete blood count; CT = computed tomography; D = day; DXA = dual-energy x-ray absorptiometry; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; ICF = informed consent; KIT = V-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MC = mast cell; MRI = magnetic resonance imaging; PB = peripheral blood; PS = performance status; RBC = red blood cell; SM = systemic mastocytosis; SSC = study steering committee.

[a] Fourteen-day washout required for tyrosine kinase inhibitors (eg, midostaurin), cytoreductive therapy, investigational agents, radiotherapy, and hematopoietic growth factors. Twenty-eight-day washout required for cladribine, interferon alpha, pegylated interferon, and any antibody therapy. If a patient has progressive disease and it is in the patient's best interest to enroll rapidly in the study, this washout period may be reduced to 1 day after discussion with the Medical Monitor.

[b] There is no time restrictions on archival test results.

[c] DXA scan for evaluation of bone density can be performed earlier with permission of the Sponsor, as long as it is within 6 months.

[d] MRI is preferred. An earlier imaging study performed up to 8 weeks before signing the ICF may be used if no clinically significant neurological events have occurred and the platelet count has remained entirely above 50,000/µL from the time of the scan to signing the ICF.

19.4 Appendix 4: World Health Organization Criteria for Diagnosis of Systemic Mastocytosis

Diagnosis of SM: Requires 1 Major + 1 Minor Criterion *or* 3 Minor Criteria	
Major Criteria	**Minor Criteria**
Multifocal dense infiltrates of mast cells (≥ 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)	In biopsy sections of bone marrow or other extracutaneous organs, • > 25% of all mast cells in the infiltrate are spindle-shaped or have atypical morphology or > 25% of all mast cells in bone marrow aspirate smears are immature or atypical • Detection of an activating point mutation at codon 816 of *KIT* in the bone marrow, blood, or another extracutaneous organ • Mast cells in bone marrow, blood, or other extracutaneous organ express CD25 with or without CD2 in addition to normal mast cell markers[a] • Baseline total serum tryptase is persistent > 20 ng/mL[a], unless there is an associated myeloid neoplasm, in which case this parameter is not valid

Abbreviations: CD2 = cluster of differentiation 2; CD25 = cluster of differentiation 25; *KIT* = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; SM = systemic mastocytosis.

[a] CD25 is the more sensitive marker by both flow cytometry and immunohistochemistry.

Source: (Swerdlow, et al., 2017).

19.5 Appendix 5: World Health Organization Criteria for Variants of Advanced Systemic Mastocytosis

WHO Diagnosis	Additional Criteria (to those listed in Appendix 4)
SM with an associated hematologic neoplasm (SM-AHN)	Meet the criteria for an associated hematological neoplasm (ie, a myelodysplastic syndrome, myeloproliferative neoplasm, acute myeloid leukemia, lymphoma or another hematological neoplasm classified as a distinct entity in the WHO classification)
Aggressive SM (ASM)	≥ 1 C-finding: • Bone marrow dysfunction caused by neoplastic mast cell infiltration, manifested by ≥ cytopenia: ANC <1.0 × 10^9/L or Hgb < 10g/dL or platelet count <100 × 10^9/L • Palpable hepatomegaly with impaired liver function[a], ascites and/or portal hypertension • Palpable splenomegaly with hypersplenism[b] • Malabsorption with weight loss due to gastrointestinal mast cell infiltrates[c] • Skeletal involvement, with large osteolytic lesions with or without pathological fractures[d] • Does not meet the criteria for MCL
Mast cell leukemia (MCL)	≥ 20% mast cells in bone marrow aspirate smear

Abbreviations: ANC = absolute neutrophil count; SM = systemic mastocytosis; WHO = World Health Organization.
Note: World Health Organization C-findings are applicable to diagnosis of Advanced SM only; they are not to be used to determine if patient meets criteria for an evaluable C-finding, which is based on International Working Group-Myeloproliferative Neoplasms Research and Treatment criteria (refer to Appendix 6).
[a] Signs of impaired liver function include elevated transaminases and/or bilirubin levels and/or hyperalbuminemia (with or without ascites or portal hypertension.
[b] Hypersplenism is defined as splenomegaly in association with a cytopenia, as defined by a C-finding (eg, platelets < 100 × 10^9/L).
[c] Malabsorption with weight loss is defined as hypoalbuminemia or weight loss > 10% with a 6-month period.
[d] Large osteolytic lesions are defined as ≥ 2 cm.
Source: (Swerdlow, et al., 2017).

19.6 Appendix 6: Modified IWG-MRT-ECNM Definition of Evaluable C-Findings

Nonhematologic C-findings	
Ascites or pleural effusions	Symptomatic ascites or pleural effusion requiring medical intervention such as: (1) Use of diuretics (Grade 2) or (2) ≥ 2 therapeutic paracenteses *or* thoracenteses (Grade 3) at least 28 days apart over 12 weeks before C1D-8 with 1 procedure performed during the 6 weeks before C1D-8
Liver function abnormalities	• ≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × ULN), AST (> 3.0 × ULN), ALT (> 3.0 × ULN) or AP (> 2.5 × ULN) in the presence of: o Ascites *and/or* o Clinically relevant portal hypertension, *and/or* o Liver MC infiltration that is biopsy-proven *or* o No other identified cause of abnormal liver function
Hypoalbuminemia	≥ Grade 2 hypoalbuminemia (< 3.0 g/dL)
Marked splenomegaly	A spleen that is palpable ≥ 5 cm below the left costal margin
Hematologic C-findings	
ANC	≥ Grade 3 ANC (< 1.0 × 10^9/L)
Anemia (transfusion-independent)	≥ Grade 2 Hgb (< 10 g/dL)
Anemia (transfusion-dependent)	• Transfusion of ≥ 6 units PRBCs in the 12 weeks before C1D-8 *and* • Most recent transfusion occurring during the 4 weeks before C1D-8 *and* • Transfusions administered for Hgb ≤ 8.5 g/dL *and* • Reason for transfusions is not bleeding, hemolysis, or therapy-related
Thrombocytopenia (transfusion-independent)	≥ Grade 2 thrombocytopenia (< 75 × 10^9/L)
Thrombocytopenia (transfusion-dependent)	• Transfusion of ≥ 6 units of apheresed platelets (or ≥ 6 pools of random donor or buffy coat) 12 weeks before C1D-8 *and* • ≥ 2 units transfused 4 weeks before C1D-8 *and* • Transfusions administered for platelet count < 20 × 10^9/L

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AP = alkaline phosphatase; AST = aspartate aminotransferase; C1D1 = Cycle 1 Day 1; Hgb = hemoglobin; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment; MC = mast cell; PBRC = packed red blood cell; ULN = upper limit of normal.
Notes: One or more C-findings is required for eligibility. Grade is based on the Common Terminology Criteria for Adverse Events, Version 5.0.
Source: Adapted from (Gotlib, et al., 2013).

19.7 Appendix 7: Modified IWG-MRT-ECNM Consensus Response Criteria in Advanced Systemic Mastocytosis

<table>
<tr><th>Response</th><th colspan="2">Criteria for Response</th></tr>
<tr><td>Complete remission (CR)[a]</td><td colspan="2">Requires all 4 of the following criteria, and response duration must be ≥ 12 weeks:
• No presence of compact neoplastic MC aggregates in the BM or other biopsied extracutaneous organ
• Serum tryptase level < 20 ng/mL[b]
• Peripheral blood count remission defined as:
  ○ ANC ≥ 1 × 10^9/L with normal differential (absence of neoplastic MCs and blasts < 1%) and
  ○ Platelet count ≥ 100 × 10^9/L and
  ○ Hgb level ≥ 11 g/dL
• Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (C-findings)[c]</td></tr>
<tr><td>CR with partial recovery of peripheral blood counts (CRh)[a]</td><td colspan="2">Requires all criteria for CR be met and response duration must be ≥ 12 weeks; however, patient may have residual cytopenias. The following minimum recovery of peripheral blood counts is required:
• ANC > 0.5 × 10^9/L with normal differential (absence of neoplastic MCs and blasts < 1%) and
• Platelet count > 50 × 10^9/L and
• Hgb level > 8.0 g/dL</td></tr>
<tr><td>Partial remission (PR)[a]</td><td colspan="2">Requires all 3 of the following criteria, and response duration must be ≥ 12 weeks, in the absence of CR/CRh and PD:
• Reduction by ≥ 50% in neoplastic MCs in the BM[d] and/or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage
• Reduction of serum tryptase level by ≥ 50%[b]
• Resolution of 1 or more biopsy-proven or suspected SM-related organ damage (C-finding[s])[c]</td></tr>
<tr><td>Clinical improvement (CI)[a]</td><td colspan="2">Response duration must be ≥ 12 weeks
Requires 1 or more of the nonhematologic and/or hematologic response criteria to be fulfilled (refer to Appendix 9) in the absence of CR, CRh, PR, or PD</td></tr>
<tr><td>Stable disease (SD)</td><td colspan="2">Not meeting criteria for CR/CRh, PR, CI, or PD</td></tr>
<tr><td rowspan="6">Progressive disease (PD)[e]</td><td colspan="2">Requires at least 1 element from the criteria below; duration must be ≥ 4 weeks:</td></tr>
<tr><td>Baseline</td><td>Postbaseline</td></tr>
<tr><td>Any Grade 2 nonhematologic organ damage</td><td>• Worsening by 1 grade and
• Minimum 100% increase (doubling) of laboratory abnormality</td></tr>
<tr><td>≥ Grade 2 albumin</td><td>• Worsening by 1 grade and
• Decrease by ≥ 0.5 g/dL</td></tr>
<tr><td>≥ Grade 3 nonhematologic organ damage</td><td>Minimum 100% increase (doubling) of laboratory abnormality</td></tr>
<tr><td>≥ Grade 2 transfusion-independent anemia or thrombocytopenia</td><td>New transfusion dependence for an 8-week period of ≥ 4 units of PRBCs or platelets</td></tr>
</table>

Response	Criteria for Response	
	Transfusion-dependent anemia or thrombocytopenia	• ≥ 100% increase in the average transfusion frequency for an 8-week period compared with the 12-week pretreatment period
	≥ Grade 3 neutropenia	• > 50% decrease in neutrophil count *and* • Absolute decrease of neutrophil count of ≥ 0.25 x 10^9/L *and* • Grade 4 (< 0.5 x 10^9/L)
	Baseline spleen size of not palpable or < 5 cm	• Development of at least 10 cm palpable symptomatic splenomegaly *or* • Increase in spleen volume ≥ 25%
	Splenomegaly ≥ 5 cm	• > 50% worsening *and* • Development of ≥ 10 cm of palpable symptomatic splenomegaly compared with the baseline value *or* • Increase in spleen volume ≥ 25%
Loss of response (LOR)	Loss of a documented CR/CRh, PR, or CI that must be for ≥ 8 weeks. Downgrading of CR/CRh to PR or PR to CI is considered as such but is not considered a loss of response unless CI is also lost for a minimum of 8 weeks. The baseline value for LOR is the pretreatment measurement(s) and not the nadir values during response.	

Abbreviations: ANC = absolute neutrophil count; BM = bone marrow; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; CT = computed tomography; Hgb = hemoglobin; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment; LOR = loss of response; MC = mast cells; MRI = magnetic resonance imaging; PBRCs = packed red blood cells; PD = progressive disease; PR = partial remission; SD = stable disease; SM = systemic mastocytosis.

Note: Guidelines for assessing response are as follows: (A) Only disease-related ≥ Grade 2 organ damage is evaluable as a primary endpoint. (B) Response assessments of CR, CRh, PR, SD, PD, and LOR should only be applied to these ≥ Grade 2 organ damage findings in the context of trials. (C) Disease status at the time of patient removal from the study singularly relates to the updated status of initial ≥ Grade 2 organ damage finding(s). (D) Exclusion of drug-related toxicity and/or other clinical issues (eg, gastrointestinal tract bleeding in the case of worsening anemia/transfusion-dependence) should be undertaken before assigning the designation PD or LOR in a patient with worsening of baseline ≥ Grade 2 organ damage.

[a] Responses that are not maintained for a period of at least 12 weeks do not fulfill criteria for CR/CRh, PR, or CI; however, both maintained and unmaintained (< 12 weeks duration) responses should be recorded in the electronic case report form each time they are observed in order to measure duration of response.

[b] Only valid as a response criterion if the pretreatment serum tryptase level is ≥ 40 ng/mL (ie, if pretreatment serum tryptase is < 40 ng/mL, it will not be considered as a criterion in evaluation of response).

[c] Biopsy of organ(s) in addition to the bone marrow to evaluate for SM-related organ damage may be considered.

[d] Only valid as a response criterion if the pretreatment BM MCs are ≥ 5% (ie, if pretreatment BM MCs are < 5%, BM MCs will not be considered as a criterion in evaluation of response).

[e] Preservation of at least 1 CI finding permits a patient to maintain the response of CI if 1 or more CI findings are lost but none meet criteria for PD. However, if 1 or more of the CI findings become PD, then the CI finding assignment is lost and the patient meets criteria for PD. The baseline value for evaluating PD is the pretreatment measurement(s). The PD findings must be considered related to the underlying disease and not to other clinical factors. Progression of an underlying chronic myeloid neoplasm to acute myeloid leukemia is also considered PD.

Source: Adapted from (Gotlib, et al., 2013).

19.8 [redacted]

[redacted]

19.9 Appendix 9: Modified IWG-MRT-ECNM Clinical Improvement Criteria for Response

Criteria	Baseline criteria	Criteria for response
Nonhematologic		
Ascites or pleural effusions	(1) Symptomatic ascites or pleural effusion requiring medical intervention such as use of diuretics (Grade 2) or (2) ≥ 2 therapeutic paracenteses or thoracenteses at least 28 days apart over 12 weeks before C1D-8 (Grade 3) and 1 of the procedures is performed 6 weeks before C1D-8	(1) Complete resolution of symptomatic ascites or pleural effusion (including trace or minimal on radiographic imaging) and no longer in need of diuretics for ≥ 12 weeks and no longer in need of diuretics for ≥ 12 weeks or (2) No therapeutic paracenteses or thoracentesis for ≥ 12 weeks
Liver function test abnormalities	≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × ULN), AST (> 3.0 × ULN), ALT (> 3.0 × ULN) or AP (> 2.5 × ULN) in the presence of: ascites and/or clinically relevant portal hypertension and/or liver MC infiltration that is biopsy-proven or other causes of abnormal liver function are not identified	Reversion of ≥ 1 LFTs to normal range for ≥ 12 weeks
Hypoalbuminemia	≥ Grade 2 hypoalbuminemia (< 3.0 g/dL)	Reversion of albumin to normal range for ≥ 12 weeks
Marked splenomegaly	A spleen that is palpable ≥ 5 cm below left costal margin	≥ 35% reduction in spleen volume based on 3D MRI or CT scan for ≥ 12 weeks
Hematologic		
ANC	≥ Grade 3 ANC (< 1.0×10^9/L)	≥ 100% increase and an absolute increase ≥ 0.5×10^9/L for ≥ 12 weeks
Anemia (transfusion-independent)	≥ Grade 2 Hgb (< 10 g/dL)	An increase in Hgb ≥ 2 g/dL that is maintained for ≥ 12 weeks
Anemia (transfusion-dependent)	Transfusion of ≥ 6 units PRBCs in the 12 weeks before C1D-8 *and* Most recent transfusion occurring in the 4 weeks before C1D-8 *and* Transfusions administered for Hgb ≤ 8.5 g/dL *and* Reason for transfusions is not bleeding, hemolysis or therapy-related	Transfusion independence for ≥ 12 weeks and maintenance of Hgb ≥ 8.5 g/dL at the end of the 12-week period of response duration
Thrombocytopenia (transfusion-independent)	≥ Grade 2 thrombocytopenia (< 75×10^9/L)	≥ 100% increase and an absolute increase ≥ 50×10^9/L and no need for platelet transfusion for ≥ 12 weeks

Criteria	Baseline criteria	Criteria for response
Thrombocytopenia (transfusion-dependent)	(1) Transfusion of ≥ 6 units of apheresed (or ≥ 6 pools of random donor or buffy coat) platelets during the 12 weeks before C1D-8, and (2) ≥ 2 units transfused in the 4 weeks before C1D-8, and (3) Transfusions given for platelet count < 20 × 10^9/L	Transfusion independence for ≥ 12 weeks and maintenance a platelet count ≥ 20 × 10^9/L

Abbreviations: 3D = 3 dimension; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AP = alkaline phosphatase; AST = aspartate aminotransferase; CT = computed tomography; Hgb = hemoglobin; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MC = mast cell; MRI = magnetic resonance imaging; LFT = liver function test; PRBC = packed red blood cell; ULN = upper limit of normal.
Note: Toxicity grading is based on Common Terminology Criteria for Adverse Events, Version 5.0.
Source: Adapted from (Gotlib, et al., 2013).

19.10 Appendix 10: Comparison of C-Finding Criteria per WHO and Modified IWG-MRT-ECNM

	WHO	**IWG-MRT-ECNM**
Purpose	**Diagnosis of AdvSM**	**Establish baseline and response**
Time points assessed	Screening only	Screening and all postbaseline timepoints
ANC	$< 1.0 \times 10^9$/L	$< 1.0 \times 10^9$/L
Hemoglobin	< 10 g/dL	< 10 g/dL
Platelet count	$< 100 \times 10^9$/L	$< 75 \times 10^9$/L
Transfusion-dependent anemia	NA	• Transfusion of ≥ 6 units PRBCs in the 12 weeks before C1D-8 *and* • Most recent transfusion occurring during the 4 weeks before C1D-8 *and* • Transfusions administered for hemoglobin ≤ 8.5 g/dL *and* • Reason for transfusions is not bleeding, hemolysis, or therapy-related
Transfusion-dependent thrombocytopenia	NA	• Transfusion of ≥ 6 units of apheresed platelets (or ≥ 6 pools of random donor or buffy coat) during the 12 weeks before C1D-8 *and* • ≥ 2 units transfused during the 4 weeks before C1D-8 *and* • Transfusions administered for platelet count $< 20 \times 10^9$/L
Spleen	Palpable splenomegaly **with hypersplenism** (eg, as documented by thrombocytopenia ie, platelets <100 x 10^9/L)	A spleen that is palpable **≥ 5 cm** below the left costal margin
Ascites or pleural effusions	NA	Symptomatic ascites or pleural effusion requiring medical intervention such as: • Use of diuretics (Grade 2) *or* • ≥ 2 therapeutic paracenteses or thoracenteses (Grade 3) at least 28 days apart over 12 weeks before C1D-8 with 1 procedure performed during the 6 weeks before C1D-8

Purpose	WHO Diagnosis of AdvSM	IWG-MRT-ECNM Establish baseline and response
Liver function	Hepatomegaly with impaired liver function – ie, elevated transaminases and/or bilirubin levels and/or hypoalbuminemia (with or without ascites or portal hypertension)	≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × ULN), AST (> 3.0 × ULN), ALT (> 3.0 × ULN), or AP (> 2.5 × ULN) in the presence of: • Ascites *and/or* • Clinically relevant portal hypertension, *and/or* • Liver MC infiltration that is biopsy-proven *or* • No other unidentified causes of abnormal liver function
Hypoalbuminemia	Malabsorption with hypoalbuminemia	Albumin < 3.0 g/dL
Skeletal involvement	Skeletal involvement with large osteolytic lesions and/or pathologic fractures	NA

Abbreviations: AdvSM = Advanced systemic mastocytosis; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AP = alkaline phosphatase; AST = aspartate aminotransferase; C1D1 = Cycle 1 Day 1; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment; MC = mast cell; NA = not applicable; PRBC = packed red blood cell; ULN = upper limit of normal; WHO = World Health Organization.
Notes: One or more WHO C-finding is required for confirmation of diagnosis of AdvSM and 1 or more C-finding per modified IWG-MRT-ECNM criteria is required for eligibility (confirmation of an evaluable C-finding for response assessment). Grade is based on the Common Terminology Criteria for Adverse Events, Version 5.0.
Source: Adapted from (Gotlib, et al., 2013) and (Swerdlow, et al., 2017).

19.11 [redacted]

[redacted]

[redacted]

19.12 Appendix 12: Eastern Cooperative Oncology Group Performance Status

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

Source: (Oken, et al., 1982).

19.13 Appendix 13: Excluded Medications and Foods

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

Abbreviation: CYP3A4 = cytochrome P450 3A4.
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 via inhibition or induction or are moderate CYP3A4 inducers; appropriate medical judgement is required. Please contact Blueprint Medicines with any queries you have on this issue.

19.14 Appendix 14: Medications to be Used with Caution

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

Abbreviations: BCRP = Breast Cancer Resistance Protein; CYP3A4 = Cytochrome P450 3A4; CYP2C9 = Cytochrome P450 2C9.
Source: (FDA, 2016).

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

19.15 [redacted]

[redacted]

[redacted]

19.16 [redacted]

[redacted]

19.17 [redacted]

[redacted]

[redacted]

19.18 Appendix 18: Confidentiality and Investigator Statement

BLU-285-2202

An Open-label, Single Arm, Phase 2 Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

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

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

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

______________________________ ______________________________

Principal Investigator Name (printed) Signature

____

Date