CLINICAL STUDY PROTOCOL

CGT9486-20-201

A PHASE 2 OPEN-LABEL, MULTICENTER CLINICAL STUDY OF THE SAFETY, EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC PROFILES OF CGT9486 AS A SINGLE AGENT IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS

Study Sponsor:
Cogent Biosciences, Inc.
275 Wyman Street, 3rd Floor
Waltham, MA 02451 USA
Telephone: 617-945-5576

Responsible Medical Officer:
Jessica Sachs, MD
Chief Medical Officer
Telephone: 617-945-5576
E-mail: jessica.sachs@cogentbio.com

EudraCT: 2021-001010-10

NCT: NCT04996875

Protocol History:
Date (Version)

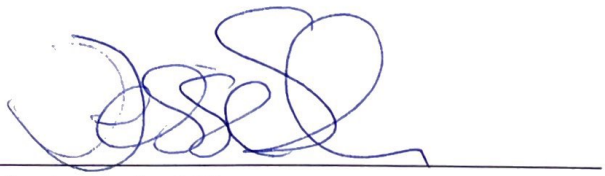
11 February 2021 Original (Version 1)
15 March 2021 Amendment 01 (Version 2)
16 April 2021 Amendment 02 (Version 3)
06 May 2021 Amendment 03 (Version 4)
20 December 2021 Amendment 04 (Version 5)
20 December 2022 Amendment 05 (Version 6)

CONTACT INFORMATION

Sponsor:	Cogent Biosciences, Inc 275 Wyman Street, 3rd Floor Waltham, MA 02451 USA Telephone: 617-945-5576
24-Hour Serious Adverse Event (SAE) Reporting	To report an SAE: Fax: 1-800-878-1719 E-mail: APEX_Safety_Reporting@cogentbio.com

SPONSOR PROTOCOL APPROVAL

I have read the clinical protocol for Study CGT9486-20-201 Amendment 05 (Version 6) (dated 20 December 2022) and approve the design of this study:



21 Dec 2022

Jessica Sachs, MD
Chief Medical Officer
Cogent Biosciences, Inc.

Date (DD Month YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for bezuclastinib. I have read the clinical protocol for Study CGT9486-20-201 Amendment 05 (Version 6) (dated 20 December 2022) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guidelines on Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and all applicable local regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Cogent Biosciences, Inc.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD Month YYYY)

SYNOPSIS

Name of Sponsor/Company: Cogent Biosciences, Inc.

Name of Study Drug Product(s): Bezuclastinib (CGT9486)

Name of Active Ingredients: Bezuclastinib

Study Title:

A Phase 2 Open-Label, Multicenter Clinical Study of the Safety, Efficacy, Pharmacokinetic, and Pharmacodynamic Profiles of CGT9486 as a Single Agent in Patients With Advanced Systemic Mastocytosis

Protocol Identifier:

CGT9486-20-201
NCT: NCT04996875
EudraCT: 2021-001010-10

Phase of Development: 2

Study Center(s):

Approximately 55 centers in North America, Europe, and other international locations

Study Duration:

The total duration of the study is expected to be approximately 7 years.

Screening Period: Up to 42 days

Treatment Period: From the initiation of therapy through the End of Treatment Visit following the last cycle of bezuclastinib. Subjects will continue to receive treatment with bezuclastinib until disease progression, intolerable toxicity, Investigator decision, withdrawal of consent, or other protocol-specified reason for discontinuation of study drug.

Long-term Follow-up Period: Subjects will be followed for at least 2 years following discontinuation of study drug to assess survival.

The study will continue until all subjects have completed at least 2 years of follow up for overall survival, withdrawn from study participation, been lost to follow-up, or died, whichever occurs first.

Number of Subjects (planned):

The total number of planned subjects with advanced systemic mastocytosis (AdvSM) enrolled in the study is up to approximately 120 and includes:

Part 1: Dose Optimization will enroll approximately 28 subjects, including up to 4 subjects who are non-evaluable based on the modified International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis (IWG-MRT-ECNM) response criteria

Part 2: Expansion will enroll approximately 75 subjects who are evaluable based on the modified IWG-MRT-ECNM response criteria, and up to approximately 15 additional subjects who are non-evaluable based on the modified IWG-MRT-ECNM response criteria

Objectives and Endpoints:

	Objectives	Endpoints
Part 1: Dose Optimization		
Primary	To identify a clinically active and tolerable systemic	• Safety assessments (incidence of adverse events [AEs], serious adverse events [SAEs], changes

	exposure range of bezuclastinib in subjects with AdvSM	from baseline in laboratory results) and dose modifications • Pharmacokinetics (PK) and pharmacodynamic assessments • Overall response rate (ORR) based on the modified IWG-MRT-ECNM response criteria per Central Response Review Committee (CRRC)
Part 2 Stage 1: Dose Confirmation		
Primary	To confirm the optimal dose of bezuclastinib in subjects with AdvSM	• Safety assessments (incidence of AEs, SAEs, changes from baseline in laboratory results) and dose modifications • PK and pharmacodynamic assessments • ORR based on the modified IWG-MRT-ECNM response criteria per CRRC
Part 2 Stage 2: Expansion		
Primary	To determine the efficacy of bezuclastinib at the selected optimal dose in subjects with AdvSM who are evaluable based on the modified IWG-MRT-ECNM response criteria	ORR defined as the percentage of subjects classified as confirmed responders (complete response [CR], CR with incomplete hematologic recovery [CRh], partial response [PR], and clinical improvement [CI]) according to modified IWG-MRT-ECNM response criteria as assessed by CRRC
Part 1 and Part 2		
Secondary	To characterize the safety and tolerability of bezuclastinib in subjects with AdvSM	Incidence of AEs, SAEs, AEs leading to dose modifications, and changes from baseline in laboratory results
	To evaluate additional efficacy parameters with bezuclastinib in subjects with AdvSM	Duration of response (DOR), defined as the date of the first documented response (CR, CRh, PR, or CI) to date of first documented disease progression or loss of response, or death from any cause, whichever occurs first, based on modified IWG-MRT-ECNM response criteria
		Time to response (TTR), defined as the date of randomization/first dose of study drug to the date of the first documented response (CR, CRh, PR, or CI) based on modified IWG-MRT-ECNM response criteria
		Progression-free survival (PFS), defined as the date of randomization/first dose of study drug to the date of first documented disease progression, or death from any cause, whichever occurs first

		Overall survival (OS), defined as the date of randomization/first dose of study drug to the date of death from any cause
		Pure Pathologic Response (PPR), including complete remission, complete remission with partial hematologic recovery, molecular complete remission, and partial remission (Gotlib et al, 2020)
		Changes in spleen and liver size assessed by magnetic resonance imaging (MRI)
	To determine the effects of bezuclastinib on serum tryptase	Changes in the levels of serum tryptase
	To determine the effects of bezuclastinib on *KIT* D816V mutation allele burden	Changes in the levels of *KIT* D816V mutation allele burden in blood and bone marrow
	To evaluate histopathologic response in the blood and bone marrow	Change in pathologic findings in the blood and bone marrow, including mast cell infiltration, monocytosis, and eosinophilia
	To assess the PK of bezuclastinib in subjects with AdvSM	Plasma concentrations and PK parameters (eg, area under the plasma concentration-time curve [AUC] and maximum observed plasma concentration [C_{max}]) of bezuclastinib
	To assess patient-reported outcomes in subjects with AdvSM	Patient Global Impression of Change (PGIC) scale and change and percent change from baseline in the following patient-reported outcome measures: Patient Global Impression of Severity (PGIS) scale, Mastocytosis Quality of Life Questionnaire (MC-QoL), and Mastocytosis Activity Score (MAS) where appropriate translations are available (Siebenhaar et al, 2018; Siebenhaar et al, 2016)
	To explore the effect of bezuclastinib in subjects with AdvSM who are non-evaluable based on the modified IWG-MRT-ECNM response criteria	• Incidence of AEs, SAEs, AEs leading to dose modifications, and changes from baseline in laboratory results • PPR, including complete remission, complete remission with partial hematologic recovery, molecular complete remission, and partial remission (Gotlib et al, 2020)
Exploratory	To explore various pharmacodynamic markers and their relationship with clinical safety and efficacy	Blood and bone marrow obtained at various timepoints throughout the trial to determine the effects of bezuclastinib on pharmacodynamic markers including *KIT* D816V mutation allele burden and myeloid mutation profile as a measure of pharmacodynamic activity

	To explore the PK/pharmacodynamic relationships	Assessing the relationships between bezuclastinib PK and pharmacodynamic markers including *KIT* D816V mutation allele burden
	To explore changes in cutaneous lesions in subjects with baseline mastocytosis in skin	Change in number or pigmentation of cutaneous lesions by standardized photographs
	To explore changes in C-findings	Proportion of subjects with resolution of C-findings, including resolution of hypoalbuminemia and changes in size of skeletal lesions

Study Rationale:

Systemic mastocytosis (SM) encompasses a variety of mast cell disorders characterized by accumulation and expansion of abnormal neoplastic mast cells in various organs including the bone marrow, gastrointestinal tract, skin, liver, and spleen (Shomali et al, 2018). Mast cells play a role in immunoglobulin E-mediated immune responses, inflammation, and immune responses to infection. Accumulation of abnormal mast cells can lead to hematologic and non-hematologic organ damage. SM is characterized by mast cell infiltration of 1 or more extracutaneous organs with or without skin involvement (Shomali et al, 2018) and encompasses a spectrum of diagnoses that can range from a nonadvanced course to a more advanced course. AdvSM is an aggressive and life-threatening form of the disease. The molecular pathogenesis of SM is driven by activation of the KIT receptor. In 95% of cases, a *KIT* D816V mutation in exon 17 can be identified (Garcia-Montero et al, 2006; Jara-Acevedo et al, 2015; Vaes et al, 2017).

Two targeted therapies against KIT, midostaurin and avapritinib, have been approved in some regions for the treatment of patients with AdvSM. Severe safety and tolerability issues have limited the use of both products in AdvSM such that the National Comprehensive Cancer Network guidelines include clinical trial enrollment as an appropriate first-line therapy (RYDAPT SmPC, 2021; AYVAKIT SmPC, 2021; NCCN Systemic Mastocytosis, Version 3.2021).

Bezuclastinib is an inhibitor of KIT with potent activity against *KIT* exon 17 and 18 activation-loop mutations. It has been evaluated in a Phase 1/2 study in patients with gastrointestinal stromal tumors (GIST) as a single agent, and in combination with sunitinib (Trent et al, 2020; Wagner et al, 2018). The dose levels to be evaluated in this study are expected to provide exposures below those achieved at the recommended Phase 2 dose identified in patients with GIST. Once the optimal dose is confirmed, an expansion period will be conducted in patients with AdvSM.

Study Design and Methodology:

This is a 2-part study of the KIT inhibitor bezuclastinib in subjects with AdvSM. Part 1 will determine a clinically active and tolerable exposure range of bezuclastinib for subjects with AdvSM using the original bezuclastinib formulation (Formulation A). A modified formulation of bezuclastinib (Formulation B) has been developed with higher bioavailability. Formulation B will be introduced in Part 2, which will be conducted with a 2-stage design: Stage 1 will confirm the optimal dose of bezuclastinib Formulation B, and Stage 2 will consist of an expansion period. Patient eligibility will be reviewed and enrollment approved by an Eligibility Committee (EC) during the Screening Period. In addition, eligibility will be reviewed and confirmed by a retrospective EC, and disease response will be adjudicated by the CRRC. The Study Steering Committee (SSC) and the Sponsor will review all available data, including safety, efficacy, PK/pharmacodynamic, and dose modification data, from Part 1 after all subjects in Part 1 have been enrolled and completed at least 2 cycles of bezuclastinib Formulation A and from Part 2 Stage 1 after all subjects have been enrolled and completed at least 2 cycles of bezuclastinib Formulation B.

Throughout the study, oral bezuclastinib will be administered daily as a single agent. Each 28-day period is 1 cycle. Treatment will be continuous; there will be no gaps between cycles.

Part 1: Dose Optimization

In Part 1 of the study, approximately 28 subjects will be randomized to 1 of 4 dose cohorts of bezuclastinib Formulation A, including up to 4 subjects who are non-evaluable per modified IWG-MRT-ECNM response criteria based on lack of evaluable organ damage per modified IWG-MRT-ECNM criteria. Subjects will be randomized in a 1:1:1:1 (50 mg twice a day [BID]:100 mg BID:200 mg BID:400 mg once daily [QD]) manner. Randomization will be stratified by evaluability per modified IWG-MRT-ECNM response criteria (ie, evaluable vs non-evaluable). Bezuclastinib Formulation A should be taken with food and water. Subjects will receive bezuclastinib at their assigned dose until confirmed disease progression, intolerable toxicity, Investigator decision, withdrawal of consent, or other protocol-specified reason for discontinuation of study drug. Once the optimal dose level of bezuclastinib Formulation B is confirmed in Part 2 Stage 1, subjects receiving Formulation A may be transitioned to receive Formulation B. Additional blood samples for PK may be collected following the transition from Formulation A to Formulation B.

Part 2: Expansion

Part 2 will be conducted with a 2-stage design: Stage 1 will confirm the optimal dose of bezuclastinib Formulation B, and Stage 2 will consist of an expansion period.

In Stage 1, approximately 20 subjects who are evaluable per modified IWG-MRT-ECNM response criteria will be randomized 1:1 to receive 150 mg QD or 300 mg QD of bezuclastinib Formulation B. Randomization will be stratified by prior treatment with a tyrosine kinase inhibitor (TKI) (ie, yes vs no). Based on available data from Part 1, bezuclastinib Formulation B at 150 mg QD is predicted to result in systemic exposure associated with clinical activity and acceptable safety and tolerability. A higher dose level of bezuclastinib, 300 mg QD, will also be explored to determine if an increased dose results in increased clinical activity with acceptable safety and tolerability. The totality of clinical data from Part 1 and Part 2 Stage 1 will be used to confirm the optimal dose of bezuclastinib Formulation B in subjects with AdvSM. Subjects in Part 2 Stage 1 may have their dose adjusted once the optimal dose of bezuclastinib Formulation B is confirmed.

Once approximately 20 subjects have been enrolled in Part 2 Stage 1, enrollment may continue until the dose for Part 2 Stage 2 is confirmed. Following enrollment of 20 subjects in Part 2 Stage 1 and prior to analysis of Part 2 Stage 2 data, enrolled subjects will receive either 150 mg and/or 300 mg based on ongoing review of available data and following IDMC approval. Of the additional subjects who may be enrolled, those who receive the dose selected for Part 2 Stage 2 will contribute to the Stage 2 analysis population.

In Stage 2, approximately 55 subjects who are evaluable per modified IWG-MRT-ECNM response criteria will be enrolled to receive bezuclastinib Formulation B at the selected optimal dose. Up to approximately 15 additional subjects who are non-evaluable per modified IWG-MRT-ECNM response criteria based on lack of evaluable organ damage per modified IWG-MRT-ECNM criteria may be enrolled.

To ensure the study population reflects the general AdvSM patient population, enrollment of the SM with an associated hematologic neoplasm (SM-AHN) subtype will be capped at approximately 80% (Jawhar et al, 2019).

Bezuclastinib Formulation B will be orally administered on an empty stomach, at least 1 hour before or 2 hours after a meal. Subjects will receive bezuclastinib at the selected Part 2 dose until confirmed disease progression, intolerable toxicity, physician decision, withdrawal of consent, or other protocol-specified reason for discontinuation of study drug.

Response Assessments

A bone marrow assessment will be performed on Cycle (C)3 Day 1 to document initial response. Bone marrow assessments will be performed every 3 cycles (approximately every 12 weeks) from Cycle 6 until Cycle 12 (Day 1 of C6, C9, C12), and then every 6 cycles (C18, C24, etc) thereafter. If an initial response (CR, CRh, PR, or CI) is achieved on or after C12, a repeat bone marrow assessment will be performed 12 weeks after the initial documented response to confirm response per modified IWG-MRT-ECNM response criteria.

Safety Assessments

Safety will be assessed by AEs, physical examinations, vital signs, hematology and chemistry laboratories, and electrocardiograms (ECGs). AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the time of database creation and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 or higher.

Pharmacokinetic and Pharmacodynamic Assessments

Blood samples will be collected for determination of bezuclastinib PK. Blood and bone marrow will be collected for analysis of the clinical and pharmacodynamic effects of bezuclastinib.

Criteria for Dose Modifications in Part 1 and Part 2

When treatment-related toxicities are observed, dosing with bezuclastinib may be interrupted until recovery from the observed treatment-related toxicities, and to consider if dose reductions are appropriate for continued therapy with bezuclastinib. Please refer to the Bezuclastinib Dose Table below for dose modification guidance for Formulation A and Formulation B. Repeated dose reductions are permitted; however, doses below 50 mg QD are not allowed. Subjects who are unable to tolerate bezuclastinib 50 mg QD will be discontinued from treatment. Subjects who require a dose reduction due to a treatment-related toxicity may have their bezuclastinib dose re-escalated if they are on the reduced dose for more than 28 days without recurrence of the observed toxicity and with no new treatment-related events requiring dose modification. If another treatment-related event requiring a dose reduction occurs, the subject will not be allowed to re-escalate the dose again unless it is in the best interest of the subject per the Investigator and agreed to by the Sponsor.

	Bezuclastinib Dose Table					
	Formulation A (Part 1)				**Formulation B (Part 2)**	
	Dose Cohort 1	**Dose Cohort 2**	**Dose Cohort 3**	**Dose Cohort 4**		
Initial dose	50 mg BID	100 mg BID	200 mg BID	400 mg QD	150 mg QD	300 mg QD
First dose reduction	50 mg QD	50 mg BID	100 mg BID	200 mg QD	100 mg QD	150 mg QD
Second dose reduction	NA	50 mg QD	50 mg BID	100 mg QD	50 mg QD	100 mg QD
Third dose reduction	NA	NA	50 mg QD	50 mg QD	NA	50 mg QD

Abbreviations: BID=twice daily, NA=not applicable, QD=once daily.

A dose interruption of up to 28 days is allowed for treatment-emergent adverse events (TEAEs) considered to be at least possibly related to study drug to return to ≤ Grade 1 or Baseline. TEAEs that are considered at least possibly related to study drug and require dose interruptions of more than 28 days will result in the permanent discontinuation of bezuclastinib.

Recommended dose modifications for TEAEs considered at least possibly related to study drug are provided in the following table.

Dose Modification Criteria for TEAEs At Least Possibly Related to Bezuclastinib

TEAE	Criteria or CTCAE v5.0 Grade	Dose Modification
Anemia, neutropenia, thrombocytopenia (a)	Grade 4 anemia for ≥7 days Grade 4 neutropenia for ≥7 days, or Grade 3 or worse neutropenia associated with bacterial or fungal infection requiring systemic therapy Febrile neutropenia (any grade) Grade 4 thrombocytopenia for ≥7 days, or Grade 3 or worse thrombocytopenia associated with bleeding	Hold bezuclastinib until resolved to ≤ Grade 1 or baseline. If recovered to ≤ Grade 1 or baseline in ≤28 days, reduce by 1 dose level. If not recovered to ≤ Grade 1 or baseline after 28 days, discontinue study drug.
ECG QT prolonged	Grade 3: >500 msec or >60 msec increase from baseline (b)	Hold bezuclastinib until QTc ≤500 msec (≤ Grade 2); then reduce by 1 dose level If not recovered to ≤ Grade 1 or baseline after 28 days, discontinue study drug.
	Grade 4: Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Permanently discontinue study drug.
Transaminase increases	ALT or AST >8 × ULN ALT or AST >5 × ULN for more than 2 weeks ALT or AST >3 × ULN and TBL >2 × ULN or INR >1.5 ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	Consider the possibility of drug-induced liver injury. If drug-induced liver injury is suspected, permanently discontinue study drug if it is in the best interest of the subject.
Other non-hematological toxicity (excluding Grade 3 nausea, vomiting, or diarrhea lasting ≤72 hours with adequate prophylactic and supportive care), including clinically significant non-hematologic	Grade 3	Hold bezuclastinib until resolved to ≤ Grade 1 or baseline. If recovered to ≤ Grade 1 or baseline in ≤28 days, reduce by 1 dose level. If not recovered to ≤ Grade 1 or baseline after 28 days, discontinue study drug.

laboratory parameters (excluding elevations in alkaline phosphatase)	Grade 4	Permanently discontinue study drug unless considered unrelated to treatment.

Abbreviations: AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CTCAE=Common Terminology for Adverse Events, ECG=electrocardiogram, INR=international normalized ratio, MCL=mast cell leukemia, QTc=corrected QT interval, TBL=total bilirubin, TEAE=treatment-emergent adverse event, ULN=upper limit of normal.

(a) For subjects with MCL or subjects for whom Grade 3 cytopenia was recorded at Screening, a Grade 3 or Grade 4 event of cytopenia may not require dose interruption/modification, following discussion with the Investigator and Medical Monitor.

(b) Triplicate readings are required.

Key Eligibility Criteria:

To be eligible for enrollment in the study, subjects must be at least 18 years of age and have 1 of the following diagnoses based on World Health Organization diagnostic criteria: aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL), or SM-AHN. For subjects with SM-AHN, the associated hematologic neoplasm must be myeloid, with the following diagnoses excluded from study entry: acute myeloid leukemia, myelodysplastic syndrome that is very high- or high-risk as defined by the Revised International Prognostic Scoring System for Myelodysplastic Syndromes, and Philadelphia Chromosome positive malignancies, and 10% blast cells in bone marrow. Subjects evaluable for the primary efficacy endpoint must have measurable disease according to modified IWG-MRT-ECNM consensus eligibility and response criteria for CI. The diagnosis and evidence of measurable disease must be evaluated and confirmed by the EC prior to randomization in Part 1 and Part 2 Stage 1 and the first dose of study drug in Part 2 Stage 2. Subjects must have clinically acceptable laboratory screening results (clinical chemistry, hematology) within certain limits, including absolute neutrophil count ≥500/μL (Part 1 only); platelet count ≥50,000/μL prior to the first dose of study drug; aspartate transaminase and alanine transaminase ≤2.5 × upper limit of normal (ULN) or ≤5×ULN if there is liver involvement by AdvSM; direct bilirubin ≤1.5×ULN (if related to AdvSM, may be ≤3×ULN); calculated creatinine clearance (Cockcroft-Gault) ≥40 mL/min; and serum tryptase ≥20 ng/mL. Subjects must not have any persistent toxicity from previous therapy for AdvSM that has not resolved to ≤ Grade 1; have an associated hematologic neoplasm that requires immediate antineoplastic therapy; have clinically significant cardiac disease; or received strong CYP3A4 inhibitors or inducers within 14 days (or 5 half-lives, whichever is longer) before the first dose of study drug.

Study Drug Product(s), Dosages, and Modes of Administration:

Oral bezuclastinib will be administered daily as a single agent. One cycle is 28 days. Bezuclastinib will be supplied as 50 mg tablets.

Part 1: Dose Optimization: 4 dose cohorts of bezuclastinib Formulation A (50 mg BID, 100 mg BID, 200 mg BID, and 400 mg QD) will be tested.

Part 2: Expansion: Stage 1: 2 dose cohorts of bezuclastinib Formulation B (150 mg QD, 300 mg QD); Stage 2: Subjects will receive the selected optimal dose (either 150 mg QD or 300 mg QD) based on the data from Part 1 and Part 2 Stage 1 of the study.

Reference Therapy, Dosage, and Mode of Administration:

None

Statistical Considerations:

Efficacy Evaluation

The primary efficacy endpoint for subjects with AdvSM is ORR, defined as the percentage of subjects classified as confirmed responders (CR, CRh, PR, or CI) according to the response assessment based on modified IWG-MRT-ECNM response criteria by CRRC assessment.

Other efficacy assessments include DOR, TTR, and PFS, based on modified IWG-MRT-ECNM, PPR, and OS. Changes in liver and spleen size will be assessed by MRI.

Quality of Life Evaluation

Changes in patient-reported outcomes and quality of life will be assessed using PGIS, PGIC, MC-QoL, and MAS (where appropriate translations are available).

Safety Evaluation

Safety will be assessed by vital signs, hematology and chemistry laboratory studies, ECGs, and AEs, including all TEAEs, treatment-related AEs, SAEs, and AEs leading to dose modification. The primary safety endpoint is the incidence of TEAEs. The secondary safety endpoints include changes in laboratory parameters and changes in ECGs.

Pharmacokinetic Assessments

Blood samples will be taken predose and at various timepoints throughout the study in order to characterize the PK of bezuclastinib in subjects with AdvSM.

Pharmacodynamic Assessments

Blood and bone marrow will be obtained at various timepoints throughout the study to determine the effects of bezuclastinib on serum tryptase levels and mutation burden including *KIT* D816V mutation allele burden as a measure of pharmacodynamic activity in subjects with AdvSM.

Sample Size Considerations

Approximately 28 subjects will be randomized 1:1:1:1 into 4 dose cohorts (Formulation A) in Part 1, including up to 4 subjects who are non-evaluable per modified IWG-MRT-ECNM response criteria based on lack of evaluable organ damage per modified IWG-MRT-ECNM criteria. It was determined that approximately 6 subjects who are evaluable per modified IWG-MRT-ECNM response criteria per group (24 total) would allow for ruling out an ORR of 60% or higher if a dose group had an ORR estimate of 16.7% or less (ie, if the ORR for a dose is 1/6, the upper bound of the 1-sided 90% confidence interval is 51.0% via a Clopper-Pearson exact confidence interval). Dose decisions will be based on an assessment of safety, biomarker and clinical efficacy, and PK endpoints at each dose, with summary statistics and figures being used to illustrate dose-response.

Part 2 of the study will enroll approximately 75 subjects who are evaluable per modified IWG-MRT-ECNM criteria. In Part 2 Stage 2, up to an additional 15 subjects with AdvSM who are non-evaluable per modified IWG-MRT-ECNM criteria at study entry may be enrolled.

For Part 2 Stage 1, approximately 20 subjects who are evaluable per modified IWG-MRT-ECNM response criteria will be randomized in a 1:1 ratio to receive bezuclastinib 150 mg QD or 300 mg QD (Formulation B). It was determined that approximately 10 subjects who are evaluable per modified IWG-MRT-ECNM response criteria per group would allow for ruling out an ORR of 60% or higher if a dose group had an ORR estimate of 30.0% or less (ie, if the ORR for a dose is 3/10, the upper bound of the 1-sided 90% confidence interval is 55.2% via a Clopper-Pearson exact confidence interval). The determination of the optimal dose will be based on totality of the data, including assessment of safety, biomarker, and clinical efficacy, and PK endpoints at each dose.
For Part 2 Stage 2, approximately 55 subjects who are evaluable per modified IWG-MRT-ECNM response criteria will be enrolled. The null hypothesis is that ORR for subjects who received

bezuclastinib treatment will be the same as the historical control (28%) (RYDAPT SmPC, 2021). Assuming the ORR for subjects who received bezuclastinib is 60%, 55 evaluable subjects will provide at least 90% power to reject the null hypothesis based on a Chi square test at one-sided alpha of 0.025.

The inclusion of up to approximately 15 additional subjects in Part 2 Stage 2 who are non-evaluable per modified IWG-MRT-ECNM is intended to provide a broader understanding of efficacy including subjects with AdvSM without evaluable organ damage at baseline.

Multiplicity adjustment

There is no multiplicity adjustment planned for this study.

Analysis of Efficacy Endpoints

All efficacy endpoints will be summarized by study part/stage (Part 1, Part 2 Stage 1, or Part 2 Stage 2) and dose cohort. Efficacy endpoints will be listed as well. When appropriate, subjects across study parts and by indication may also be grouped.

Response Category for Responder Definition by Subject Type

Responder	Modified IWG-MRT-ECNM Criteria
Yes	Complete Remission (CR)
	Complete Remission with Incomplete Hematologic Recovery (CRh)
	Partial Remission (PR)
	Clinical Improvement (CI)
No	Stable Disease (SD)
	Progressive Disease
	Loss of Response
	Not Evaluable

Source: Gotlib et al, 2013.

Other Efficacy Analysis: Evaluation of biomarkers of mutation burden and variant allele frequency in bone marrow or other samples as appropriate before and after treatment with bezuclastinib ex vivo. Potential biomarkers will be correlated with clinical outcomes.

Pharmacokinetic Analyses: PK samples will be taken at various timepoints pre- and postdosing with bezuclastinib. Standard PK parameters will be estimated using noncompartmental methods. Bezuclastinib plasma concentrations and PK parameters will be summarized by study part and/or stage, dose, and visit.

Pharmacodynamic Analyses: A number of pharmacodynamic parameters (described above) will be measured. At each timepoint, each of these parameters will be summarized by study part and dose cohort. In addition, the parameters over time will be plotted for each subject. An analysis of pre-study versus on-study samples will be performed. If data are sufficient, graphical exploratory analysis of PK/pharmacodynamic relationships may be performed.

Safety Analysis: AEs will be reported according to the NCI CTCAE version 5.0 and coded according to the latest MedDRA version available at the time of database creation. The number and percent of subjects with any AE will be presented by System Organ Class and Preferred Term for each cohort and will be summarized by cohort. Vital signs, laboratory parameters, and ECG intervals will be summarized and listed by timepoint by study part.

Table 1: Schedule of Assessments and Procedures

	Screening	Cycle 1							Cycle 2				Cycles 3-15 (a, b)		Even-Numbered Cycles (C16+ beyond) (a, b)		Odd-Numbered Cycles (C17+ beyond) (a, b)		EOT (c)	SFU	Long-Term Follow-Up
Study Day	**-42 to -1**	**1**	**2**	**4***	**8**	**11***	**15**	**22**	**1**	**8***	**15**	**22***	**1**	**22**	**1**	**22**	**1**	**22**		**30 d after last dose**	**Every 3 months after SFU**
Window (Days)				**±1**	**±2**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**	**±7**
Informed consent	X																				
Randomization	X (d)																				
Medical history	X																				
Demographics	X																				
Physical examination (e)	X	X			X		X	X	X		X		X				X		X	X	
Vital signs; weight; height (f)	X	X			X		X	X	X		X		X				X		X	X	
ECOG performance status	X	X			X		X	X	X		X		X				X		X	X	
ECG (g)	X	X (h)	X				X		X (h)		X		X				X		X		
Hematology (i)	X	X		X*	X	X*	X	X	X	X*	X	X*	X		X		X		X	X	
Clinical chemistry (i)	X	X		X*	X	X*	X	X	X	X*	X	X*	X		X		X		X	X	
Serum tryptase (j)	X	X	X		X		X	X	X		X		X		X				X		

Table 1: Schedule of Assessments and Procedures

	Screening	**Cycle 1**							**Cycle 2**				**Cycles 3-15 (a, b)**		**Even-Numbered Cycles (C16+ beyond) (a, b)**		**Odd-Numbered Cycles (C17+ beyond) (a, b)**		**EOT (c)**	**SFU**	**Long-Term Follow-Up**
Study Day	**-42 to -1**	**1**	**2**	**4***	**8**	**11***	**15**	**22**	**1**	**8***	**15**	**22***	**1**	**22**	**1**	**22**	**1**	**22**		**30 d after last dose**	**Every 3 months after SFU**
Window (Days)				**±1**	**±2**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**	**±7**
Blood samples for mutational analysis (*KIT* D816V burden)	X										X		X		X				X		
Coagulation tests	X	X																	X		
Virus serology	X (k)																				
Pregnancy test (l)	X	X							X				X		X		X		X	X	
Blood sample for PD	Refer to Table 2 Schedule of Pharmacokinetic, Pharmacodynamic, and Biomarker Assessments.																				
Blood sample for PK	Refer to Table 2 Schedule of Pharmacokinetic, Pharmacodynamic, and Biomarker Assessments.																				
Bone marrow aspirate, biopsy, and PBS	Refer to Table 3 Schedule of Response Assessments.																				
Photography	Refer to Table 3 Schedule of Response Assessments.																				

Table 1: Schedule of Assessments and Procedures

	Screening	Cycle 1							Cycle 2				Cycles 3-15 (a, b)		Even-Numbered Cycles (C16+ beyond) (a, b)		Odd-Numbered Cycles (C17+ beyond) (a, b)		EOT (c)	SFU	Long-Term Follow-Up
Study Day	**-42 to -1**	**1**	**2**	**4***	**8**	**11***	**15**	**22**	**1**	**8***	**15**	**22***	**1**	**22**	**1**	**22**	**1**	**22**		**30 d after last dose**	**Every 3 months after SFU**
Window (Days)				**±1**	**±2**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**	**±7**
Radiological Evaluations - MRI/CT abdomen/ pelvis - Skeletal imaging (as appropriate)	Refer to Table 3 Schedule of Response Assessments.																				
Spleen palpation	Refer to Table 3 Schedule of Response Assessments.																				
QOL assessments (m)		X							X				X				X		X		
MAS (n)	X							X				X		X				X	X		
Bezuclastinib administration (o)		Daily through Cycle (a)																			
Study drug diary (p)		X							X				X (a)		X (a)		X (a)				
Overall response assessment	Refer to Table 3 Schedule of Response Assessments																				
AE monitoring (q)	X	X																			

Table 1: Schedule of Assessments and Procedures

	Screening	Cycle 1							Cycle 2				Cycles 3-15 (a, b)		Even-Numbered Cycles (C16+ beyond) (a, b)		Odd-Numbered Cycles (C17+ beyond) (a, b)		EOT (c)	SFU	Long-Term Follow-Up
Study Day	**-42 to -1**	**1**	**2**	**4***	**8**	**11***	**15**	**22**	**1**	**8***	**15**	**22***	**1**	**22**	**1**	**22**	**1**	**22**		**30 d after last dose**	**Every 3 months after SFU**
Window (Days)				**±1**	**±2**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**	**±7**
Concomitant medications (q)	X	X																			
Survival status (r)																					X
Disease status (s)																					X

Abbreviations: AE=adverse event, C=Cycle, CT=computed tomography, D/d=day, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, eCRF=electronic case report form, EOT=end of treatment, HCV=hepatitis C virus, ICF=informed consent form, IWG-MRT-ECNM=International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, MAS=Mastocytosis Activity Score, MRI=magnetic resonance imaging, PBS=peripheral blood smear, PE=physical examination, PK=pharmacokinetic, QOL=quality of life, SAE=serious adverse event, SFU=Safety Follow-up, TEAE=treatment-emergent adverse event.

One cycle = 28 days.

Standard of care assessments or procedures that may confirm study eligibility requirements may be performed prior to a subject signing the ICF.

On-treatment assessments and sample collections will be performed prior to dosing with study drug and, as applicable, prior to ECG for scheduled visits involving study drug administration and/or ECGs, unless otherwise noted. Additional assessments to evaluate subject safety and efficacy may be performed at unscheduled visits and will be recorded in the eCRFs.

* Additional hematology and chemistry assessments to be performed for subjects in Part 1 and Part 2 Stage 1 only.

(a) After 15 cycles, dispensation of study drug for at-home administration and study drug diary will be adjusted accordingly.

(b) At C15 and beyond, and at most other study visits, clinical chemistry, hematology, pregnancy testing (women of childbearing potential only), AE monitoring, and collection of concomitant medications will be performed.

(c) EOT assessments should be performed within 7 days of decision to permanently discontinue study treatment.

(d) Subjects should be dosed as soon as possible after randomization and preferably within 7 days before receiving their first dose on C1D1.

(e) A complete PE will be performed at Screening only. At all other study visits, a targeted PE will be performed based on Investigator's judgment and careful evaluation of the subject's signs and symptoms.

(f) Height at Screening only.

(g) A single 12-lead ECG will be performed after the subject has been resting in supine or semi-supine position for at least 5 minutes. At all predose and postdose intervals, each ECG should occur just prior to each PK blood sample collection.

(h) On C1D1 and C2D1, a single ECG will be performed predose (within 30 min prior to dosing) and at 1 (± 5 minutes), 3 (± 15 minutes), 5 (± 15 minutes), and 8 (± 30 minutes) hours postdose.

(i) Safety laboratory tests (hematology, chemistry) may be completed 1 day prior to the visit on C1D1 (after randomization) or on C2D1.

(j) Serum tryptase will be collected as indicated and at all response time points. Serum tryptase will be tested locally. A blood sample will also be collected and tested at a central laboratory. Additional exploratory analyses may be performed on blood samples to further explore pharmacodynamic markers in subjects with AdvSM.

(k) Subjects with a positive HCV antibody may be eligible if HCV RNA is undetectable on a quantitative HCV RNA assay, following discussion with the Medical Monitor.

(l) Women of childbearing potential only. A serum pregnancy test (β-human chorionic gonadotropin) will be performed at Screening, and a urine pregnancy test will be performed at subsequent visits.

(m) QOL assessments to include Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), and the Mastocytosis Quality of Life Questionnaire (MC-QoL). PGIC will be performed starting on C2D1.

(n) The MAS will be completed where appropriate translations are available at Screening on D -42 (±5 days) through D -35 (±5 days). Thereafter, the MAS will be completed on Days 22-28 of each 28-day cycle through C15 and on Days 22-28 of odd-numbered cycles at C17 and beyond. The MAS must be completed at EOT and continuing for 7 days total unless an MAS was completed within the previous 14 days. The time window for starting the MAS is ±2 days.

(o) Study drug bezuclastinib will be dispensed to the subject on Day 1 of each cycle for daily at-home administration. Treatment will be continuous; there will be no gaps between cycles. On days of a scheduled clinic visit, study drug will be administered at the clinic after visit procedures and assessments are performed.

(p) A Study Drug Diary will be dispensed to the subject at the start of each cycle. Beginning at Cycle 15, subjects will be provided with diaries for use over 2 cycles. Subjects bring their diary with them to each study visit. Diary information will be reviewed and/or collected by the site during study visits.

(q) From the signing of the ICF until the start of study treatment (C1D1), only SAEs or AEs related to on-protocol procedures will be collected. TEAEs will be collected from the start of study treatment until 30 days after the last dose of study drug. All medications will be recorded at Screening and collected through 30 days after the last dose of bezuclastinib. Any SAEs considered to have at least a possible relationship to the study drug and discovered by the Investigator at any time period after EOT should be reported.

(r) Survival follow-up may be done via phone (with subject or referring physician).

(s) Includes the recording of new anticancer therapy (therapy type, start and stop dates, and response to treatment).

Table 2: Schedule of Pharmacokinetics, Pharmacodynamics, and Biomarker Assessments

		Screening	Cycle 1			Cycle 2			Cycles 3-15 (a)	Odd-Numbered Cycles (C17 + beyond) (a)	EOT
Study Day		**-42 to -1**	**1**	**2**	**15**	**1**	**2**	**15**	**1**	**1**	
Blood sample for PGx (b)		X (b)									
Buccal swab for *TPSAB1* gene (HAT) (c)		X (c)									
Blood sample for bezuclastinib PK	Predose: -30 min		X	X	X	X	X	X	X	X	
	Postdose: 1 h (± 5 min), 3 h (± 15 min), 5 h (± 15 min), 8 h (± 30 min)		X (d)			X (d)					
	Any time during Study Visit										X

Abbreviations: C=cycle, D=day, ECG=electrocardiogram, EOT=end of treatment, HAT=hereditary alpha tryptasemia, PGx=pharmacogenomics, PK=pharmacokinetics.

Sample collections will be performed prior to dosing with study drug and, as applicable, prior to ECG for scheduled visits involving study drug administration and/or ECGs, unless otherwise noted. All samples will be sent to the central laboratory. Refer to the Laboratory Manual for details.

(a) After 15 cycles, blood sample collections will be performed on Day 1 of every odd-numbered cycle (eg, C17D1, C19D1) and as clinically indicated.

(b) Should be collected prior to the first dose of study drug if possible (at Screening), but may be collected at any time during the study.

(c) The buccal swab for tryptase alpha/beta 1 (*TPSAB1*) genetic testing of HAT should be collected prior to the first dose of study drug if possible (at Screening), but may be collected at any time during the study. Subjects should be instructed to refrain from eating or drinking for 60 minutes prior to the buccal swab.

(d) Postdose blood samples for PK at C1D1 and C2D1 will be collected for subjects in Part 1 and Part 2 Stage 1 (but not for subjects in Part 2 Stage 2).

Table 3: Schedule of Response Assessments

	Screening	Cycle 3	Cycle 6	Cycle 9	Even-Numbered Cycles (C12 + beyond) (a)	EOT
Study Day	**-42 to -1**	**1**	**1**	**1**	**1**	
BM sample for mutational analysis including myeloid mutation panel (b)	X	X	X	X	X	X
BM biopsy (or extracutaneous biopsy) for eligibility and response assessments (c)	X	X	X	X	X	X
Radiological evaluations (d) - MRI/CT abdomen/pelvis - Skeletal imaging (as appropriate)	X	X	X	X	X	X
Spleen palpation (e)	X	X	X	X	X	X
Photography (f)	X	X	X	X	X	X
Overall response assessment (g)		X	X	X	X	X

Abbreviations: BM=bone marrow, C=cycle, CI=clinical improvement, CR=complete response, CRh=CR with incomplete hematologic recovery, CT=computed tomography, D=day, ECG=electrocardiogram, EOT=end of treatment, IWG-MRT-ECNM=International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, MRI=magnetic resonance imaging, PR=partial response.

Sample collections will be performed prior to dosing with study drug and, as applicable, prior to ECG for scheduled visits involving study drug administration and/or ECGs, unless otherwise noted. All samples will be sent to the central laboratory. Refer to the Laboratory Manual for details.

(a) After 12 cycles, assessments will be performed every 6 cycles (eg, C18D1, C24D1, etc) and as clinically indicated.

(b) Additional exploratory analyses may be performed on BM samples to further explore pharmacodynamic markers in subjects with AdvSM.

(c) BM samples will be obtained per local standard of care at Screening, C3D1, every 3 cycles from Cycle 6 until Cycle 12 (D1 of C6, C9, C12), every 6 cycles after Cycle 12 (D1 of C18, C24, etc), and at EOT if a sample has not been obtained within 7 days. Bone marrow samples will be sent for routine pathology, cytogenetics, flow cytometry, and molecular analysis including assessment of *KIT* mutation status (eg, D816V). If an initial response (CR, CRh, PR, or CI) is achieved on or after C12, a repeat BM assessment will be performed 12 weeks after the initial documented response to confirm response per modified IWG-MRT-ECNM response criteria. BM samples (including those from unscheduled visits) will be sent for analysis at a central laboratory. For subjects who meet WHO diagnostic criteria for SM based on the presence of mast cell aggregates in extracutaneous organs rather than BM, biopsy of the extracutaneous organ should follow the same response assessment schedule.

(d) Imaging will be performed every 3 cycles beginning at C3D1 (C6, C9, C12), and then every 6 cycles thereafter (C18, C24, etc) thereafter and as clinically indicated. If an initial response (CR, CRh, PR, or CI) is achieved on or after C12, a repeat scan will be performed 12 weeks after the initial documented response to confirm response per modified IWG-MRT-ECNM response criteria. Liver and spleen size and volume will be measured by MRI to assess hepatomegaly and splenomegaly, respectively. A CT scan may be used if MRI cannot be performed. The same method of evaluation should be followed

from baseline. Skeletal imaging is required at Screening for all subjects to assess for baseline lytic lesions and/or pathologic fractures. Changes in the size of bony lesions will be assessed with skeletal imaging.

(e) Assessment of the spleen by palpation is required at Screening and response timepoints to confirm response per modified IWG-MRT-ECNM response criteria.

(f) Photography assessments for skin or other clinically relevant lesions will be repeated every 3 cycles (as applicable) if skin lesions are present at Screening or develop during the treatment period, per Investigator discretion. After 12 cycles, photography assessments will be performed every 6 cycles and as clinically indicated.

(g) Overall response assessment will be performed at C3D1, and every 3 cycles thereafter beginning at C6D1 (C6, C9, C12), and then every 6 cycles (C18, C24, etc) thereafter and as clinically indicated and during the 12-week confirmation of response, as applicable. If an initial response (CR, CRh, PR, or CI) is achieved on or after C12, an overall response assessment will be performed 12 weeks after the initial documented response to confirm response per modified IWG-MRT-ECNM response criteria.

SPECIAL CONSIDERATION FOR THE USE OF REMOTE VISITS

When necessary and appropriate, investigative sites may use telemedicine visits, using adequate audio and video equipment, to interact with subjects to make health assessments in the home for the purpose of augmenting care, assessing emerging or existing adverse events, adjusting concomitant medications, or arranging for study-related local laboratory assessments.

If needed, due to subject/site circumstances such as COVID-19, study safety laboratory assessments may be obtained at a laboratory closer to the subject's home per the discretion of the treating physician and with approval from the Sponsor. The laboratory assessments should be reviewed, and appropriate follow-up should be completed per protocol and standard of care. The normal limits for laboratory findings for such laboratory assessments should be included in the subject's health records and recorded on the appropriate electronic case report form (eCRF). If alternative laboratories are used frequently, additional paperwork may be required for the study files and databases in accordance with regulations. Please discuss with the Medical Monitor and/or Sponsor.

The Investigator should contact the Medical Monitor and/or Sponsor to discuss the plan for the remote visit and the documentation requirements. Telemedicine visits may be used as nonscheduled or interim study visits where the Investigator feels it appropriate to assess the subject via a telemedicine visit in advance or instead of an onsite study visit. The use of a telemedicine visit must be documented in the subject's health record and eCRF. If any scheduled protocol-related assessments are not conducted, the missing assessment and reason must be documented in the subject's health record and in the study database.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation	Definition
AdvSM	advanced systemic mastocytosis
AE	adverse event
AHN	associated hematologic neoplasm
ALT	alanine aminotransferase
ASM	aggressive systemic mastocytosis
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice a day
C#D#	Cycle # Day #
CI	clinical improvement
C_{max}	maximum observed concentration
CR	complete response
CRh	complete response with incomplete hematologic recovery
CRRC	Central Response Review Committee
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
EC	Eligibility Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GIST	gastrointestinal stromal tumor
GLP	Good Laboratory Practice
HCV	hepatitis C virus
hERG	human ether-à-go-go related gene
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee

Abbreviation	Definition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent to treat
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis
MAS	Mastocytosis Activity Score
MCL	mast cell leukemia
MC-QoL	Mastocytosis Quality of Life Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NOAEL	no observed adverse effect level
ORR	overall response rate
OS	overall survival
PBS	peripheral blood smear
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Principal Investigator
PK	pharmacokinetic
PPR	pure pathologic response
PR	partial response
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SM	systemic mastocytosis
SM-AHN	systemic mastocytosis with an associated hematologic neoplasm
SSC	Study Steering Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TKI	tyrosine kinase inhibitor
TTR	time to response
ULN	upper limit of normal
VAF	variant allele frequency
WHO	World Health Organization
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1. MASTOCYTOSIS

Mastocytosis is a group of rare disorders characterized by an abnormal clonal proliferation of mast cells in the bone marrow, skin, gastrointestinal tract, and other organs (Gilreath et al, 2019; Gotlib et al, 2018; Pardanani, 2019). The disorder has been characterized by the 2016 World Health Organization (WHO) classification into 2 distinct categories, cutaneous mastocytosis and systemic mastocytosis (SM) (Arber et al, 2016). Systemic mastocytosis, characterized by mast cell infiltration of 1 or more extracutaneous organs (with or without skin involvement), encompasses a spectrum of diagnoses ranging from non-advanced to advanced disease. Advanced systemic mastocytosis (AdvSM), an aggressive and life-threatening form of the disease contains 3 subtypes: aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL) (NCCN Systemic Mastocytosis, Version 2.2019; Pardanani, 2019; Shomali et al, 2018). These conditions are described in detail in the 2016 WHO classification of myeloid neoplasms (Arber et al, 2016).

SM is considered an orphan disease in the United States and European Union. AdvSM comprises 10% of the general SM population. WHO diagnostic criteria for SM include 1 major diagnostic criterion (multifocal, dense infiltrates of mast cells [≥15 mast cells in aggregates] detected in the biopsy sections of bone marrow and/or other extracutaneous organs) and 4 minor diagnostic criteria (the presence of atypical mast cells in lesional tissues, the presence of *KIT* D816V mutation, the aberrant expression of CD25 with or without CD2 on neoplastic mast cells, and a persistently elevated serum tryptase level [>20 ng/mL; unless there is associated clonal myeloid disorder, in which case this criterion is not valid]). A diagnosis requires 1 major and 1 minor criterion or at least 3 minor criteria (Gotlib et al, 2018; Gotlib et al, 2013; Pardanani, 2019). The molecular pathogenesis of SM is driven by mutations in the *KIT* gene leading to constant proliferation of mast cells, with 95% of patients with systemic mastocytosis having a mutation on exon 17, D816V (Garcia-Montero et al, 2006; Jara-Acevedo et al, 2015; Vaes et al, 2017).

Clinically, patients with SM present with a variety of symptoms depending on the subtype of disease and presence of B- and C-findings. B-findings refer to organ involvement without organ dysfunction and C-findings refer to organ involvement with organ dysfunction (Magliacane et al, 2014). SM symptoms are related to mediator release and include skin rashes, diarrhea, vomiting, abdominal pain, fatigue, headache, cognitive impairment, anxiety and depression, and anaphylaxis (Gotlib et al, 2018; Jennings et al, 2014). Other clinical findings arise from (noncutaneous) organ filtration such as cytopenias, hepatomegaly with liver dysfunction, splenomegaly, malabsorption and weight loss, and skeletal involvement (Gotlib et al, 2018; Pardanani, 2019; Rossignol et al, 2019). The symptoms of SM can be severe and unpredictable and negatively affect quality of life (Chang et al, 2000; Emanuel et al, 2012; Gotlib et al, 2018; Jennings et al, 2014; Ustun et al, 2016).

AdvSM is a serious and life-threatening disease. Depending on the subtype of AdvSM, the median overall survival can range from 2 months in patients with MCL to 41 months in patients with ASM (Gotlib et al, 2018; NCCN Systemic Mastocytosis, Version 2.2019; Pardanani, 2019; Rossignol et al, 2019; Shomali et al, 2018).

1.2. BEZUCLASTINIB

Bezuclastinib (CGT9486) is a tyrosine kinase inhibitor (TKI) that targets mutated KIT. Nonclinical studies with this molecule indicate that bezuclastinib is highly active against primary exon 9 and 11 mutations, as well as secondary activation-loop mutations localized in exons 17 and 18 such as D816V. In vitro screens indicate that bezuclastinib selectively targets KIT mutations relative to other kinase receptors, unlike many other TKIs (Smyth et al, 2009).

1.2.1. Nonclinical Experience

The in vitro potency and selectivity of bezuclastinib has been demonstrated in purified enzyme systems and confirmed in cell-based assays. Bezuclastinib is a low nanomolar inhibitor (1-3 nM half-maximal inhibitory concentration [IC_{50}]) of KIT-D816 mutants in enzymatic assay systems. Selectivity screening identified only 8/373 kinases within 3-fold of the KIT-D816V IC_{50}, including Abl, Arg, cSRC, Fgr, Fyn, Lyn, Yes, and ZAK, and no targets were identified in a screen of 71 central or peripheral receptors, ion channels, transporters, and enzymes. In cell-based models, bezuclastinib potently inhibited KIT-D816V phosphorylation in HMC1.2 cells (IC_{50} of 14 nM) and was inactive against closely related kinases in cell-based assays, including platelet-derived growth factor (PDGFR) alpha and PDGFR beta.

In vivo activity of bezuclastinib was demonstrated in Ba/F3 cells engineered to stably express KIT-D816V that is used as a model for systemic mastocytosis (Mayerhofer et al, 2008). The in vivo proliferation of the cells and appearance of splenomegaly are directly dependent on KIT-D816V and can be blocked by oral administration of compounds that are effective inhibitors. Mice displayed an exposure-dependent reduction in splenomegaly in response to bezuclastinib treatment with half-maximal efficacy correlating to a plasma area under the concentration-time curve (AUC) of ~1650 ng·h/mL, which represents a minimally efficacious exposure in this model. Higher plasma exposures led to improved efficacy with near maximal efficacy (EC_{85} or EC_{90}) at plasma exposures of ~19,000 or 36,000 ng·h/mL, respectively. This correlated well with in vivo plasma concentrations required to inhibit KIT phosphorylation in HMC1.2 tumor-bearing nude mice, as well as downstream signaling proteins, KIT and AKT, in response to bezuclastinib treatment.

The safety pharmacology of bezuclastinib was evaluated in vitro and in vivo. Human ether-à-go-go (hERG) channel expressed in human embryonic kidney (HEK) cells was not inhibited by bezuclastinib up to the solubility limit. No notable effects have been observed in Good Laboratory Practice (GLP)-compliant central nervous system, respiratory, or cardiovascular in vivo safety pharmacology studies. The collection of pharmacology data suggests potential activity against KIT-driven diseases and supports the investigation of bezuclastinib in SM.

Nonclinical studies evaluating bezuclastinib reveal a metabolically stable drug that displays high protein binding and low aqueous solubility and permeability. In vitro studies suggest bezuclastinib is a substrate for the CYP3A4 enzyme and BCRP efflux transporter. Bezuclastinib did not inhibit or induce any human CYP drug-metabolizing enzymes or transporter genes in vitro. Low brain to plasma concentration ratios were observed in rats following intravenous administration and repeat-dose oral administration.

In a 28-day GLP toxicology study, Sprague Dawley rats were treated orally with bezuclastinib at daily doses of 10, 50, or 250 mg/kg/day. No bezuclastinib-related adverse effects were observed on clinical observations, body weights, food consumption, coagulation, urinalysis, ophthalmology, or organ weights. Mild to moderate hepatocellular necrosis was observed at all dose levels in males and in the 50 and 250 mg/kg/day groups of females, and was correlated with elevations in liver enzymes, which trended toward reversibility after cessation of dosing. Bezuclastinib-related alterations in hematology parameters (reduction in red and white cell parameters) were noted; however, the changes were reversible, did not correlate with histopathology observations, and were considered nonadverse. The no observed adverse effect level (NOAEL) for this rat study was 10 mg/kg/day in females and was not defined in males because findings in the liver were considered adverse at all dose levels.

A 13-week GLP study was conducted in Sprague Dawley rats with daily oral administration of bezuclastinib at dose levels of 5, 25, and 100 mg/kg/day. No bezuclastinib-related effects were observed across dose levels on clinical observations, body weights, food consumption, coagulation, urinalysis, ophthalmology, organ weights, or macroscopic findings. Mild increases in liver enzymes and microscopic hepatocellular necrosis were observed and were reversible following a 28-day recovery period. The NOAEL in this study was considered to be 100 mg/kg/day.

Similar findings (incidence and severity) in liver histopathology and transaminase levels were observed in both 28-day and 13-week studies at similar exposures; there was no apparent progression from 28 days to 13 weeks. The NOAEL of 100 mg/kg/day in the 13-week study is supported by a lack of correlation between liver enzymes and severity of histopathology findings in the high-dose group on an individual animal basis, liver histopathology findings that were largely graded minimal, and that the majority of individual animal transaminase values were minimal and/or within the normal range for historical control.

In a 28-day cynomolgus monkey toxicology study, monkeys were treated orally for 28 days with bezuclastinib at daily doses of 10, 30, or 150 mg/kg/day. Bezuclastinib-related nonadverse effects included small changes in hematology (lower hemoglobin) and serum chemistry parameters (higher liver enzymes). Microscopic findings of minimal to mild hepatocellular cytoplasmic clearing (vacuolation) were observed in the livers of males and females at 150 mg/kg/day; however, the finding was reversible and considered nonadverse. In this cynomolgus monkey toxicology study, the NOAEL was the top dose level of 150 mg/kg/day.

In a 13-week cynomolgus monkey toxicology study, monkeys were treated orally with bezuclastinib at daily doses of 50, 150, or 300 mg/kg/day. Bezuclastinib-related nonadverse

effects included small changes in hematology (lower hemoglobin) and serum chemistry parameters (higher liver enzymes). Reversible, adverse, hepatocellular degeneration was observed at 300 mg/kg/day, which correlated with higher liver enzymes, and the NOAEL was considered to be 150 mg/kg/day.

Dose range finding and definitive embryofetal toxicity studies were completed in rats and rabbits. In rabbits, the maternal and embryo-fetal NOAEL in the definitive study was 70 mg/kg/day, the highest dose tested. In rats, the maternal NOAEL was 250 mg/kg/day and the embryo-fetal NOAEL was 100 mg/kg/day. At 150 mg/kg/day in rabbits in a dose range finding study, abortion and higher mean litter proportion of post-implantation loss were observed. At 250 mg/kg/day in rats in the definitive study, higher mean post-implantation loss was observed as well as fetal visceral morphology (situs inversus). No test article–related visceral developmental variations, external or skeletal fetal malformations, or external developmental variations were noted in the definitive rat study.

In GLP genotoxicity studies, bezuclastinib was not mutagenic in vitro in the presence or absence of S9 and did not produce structural or numerical chromosomal aberrations in human peripheral blood lymphocytes in the presence or absence of S9. Moreover, bezuclastinib did not result in increases in micronuclei in Sprague Dawley rats in vivo at doses up to 100 mg/kg/day.

1.2.2. Clinical Experience

Bezuclastinib has been evaluated in a Phase 1 pharmacokinetic study in healthy volunteers (Study PLX121-02) and as a single agent and in combination with pexidartinib or sunitinib in a Phase 1/2 study in subjects with advanced solid tumors including gastrointestinal stromal tumor (GIST) (Study PLX121-01), summarized below. In addition, clinical studies of bezuclastinib are being conducted in healthy subjects (CGT9486-21-101), subjects with nonadvanced SM (CGT9486 21-202 [Summit]), and subjects with GIST (CGT9486-21-301 [Peak]); available data are detailed in the current edition of the Investigator's Brochure (IB).

Study PLX121-02 is a completed Phase 1 study of pharmacokinetics (PK), safety, and tolerability that evaluated 3 single-ascending doses of bezuclastinib Formulation A (250 mg once daily [QD], 500 mg QD, and 1000 mg QD) in 27 healthy volunteers. All subjects who enrolled completed the study. There were no deaths in this study, and there were no serious adverse events (SAEs), life-threatening treatment-emergent adverse events (TEAEs), or severe TEAEs in this study. In addition, no subjects discontinued due to TEAEs. The only TEAE reported in >1 subject across cohorts was headache.

Study PLX121-01 is a completed 2-part Phase 1b and 2a study of bezuclastinib Formulation A as a single agent and in combination with pexidartinib or sunitinib in subjects with advanced solid tumors or locally advanced, unresectable, or metastatic GIST who were previously treated with a KIT-directed TKI. The recommended Phase 2 dose of bezuclastinib Formulation A determined from Study PLX121-01 was 1000 mg QD (the highest dose level tested) as a single agent or in combination with sunitinib.

With single-agent bezuclastinib in Part 1 of Study PLX121-01, bezuclastinib was generally well tolerated across a broad range of dose levels (250 mg to 1000 mg daily dose); a maximum tolerated dose (MTD) was not reached. The most commonly reported TEAEs included fatigue, aspartate aminotransferase (AST) increased, diarrhea, and nausea. There were no treatment-related SAEs or TEAEs with a fatal outcome. Two subjects required dose reduction for adverse events (AEs), and 2 subjects discontinued study drug because of an AE (fatigue, facial edema, periorbital edema).

Preliminary clinical activity was observed in subjects treated with single-agent bezuclastinib. Best overall tumor response in 23 evaluable subjects included 1 partial response (PR) in a subject who received bezuclastinib 1000 mg QD and 8 subjects with stable disease. The mechanism of action of bezuclastinib is supported by circulating tumor DNA data. A reduction in *KIT* exon 17 mutational burden was observed in subjects treated with bezuclastinib and this reduction was temporally associated with a reduction in tumor burden. Evidence of a dose-response is supported by an increase in overall response rate (ORR) (complete response [CR]+PR) from 0% in subjects receiving bezuclastinib at doses ≤500 mg QD to 8% in subjects receiving bezuclastinib 1000 mg daily (either 1000 mg QD or 500 mg twice daily [BID]). Similarly, median progression-free survival (PFS) increased from approximately 2 months in subjects who received bezuclastinib at doses ≤500 mg QD to approximately 6 months in subjects who received a total daily dose of bezuclastinib 1000 mg (Wagner et al, 2018). Further details are provided in the current edition of the IB. These data support bezuclastinib as a potentially active therapy in this KIT-driven disease.

1.3. STUDY RATIONALE

Two targeted therapies against KIT have been approved in some regions for the treatment of patients with AdvSM: avapritinib and midostaurin. Severe safety and tolerability issues have limited the use of both products in AdvSM such that the National Comprehensive Cancer Network (NCCN) guidelines include clinical trial enrollment as an appropriate first-line therapy. (RYDAPT SmPC, 2021; AYVAKIT SmPC, 2021; NCCN Systemic Mastocytosis, Version 3.2021). Additionally, access to avapritinib and midostaurin is limited in some regions. As of the initiation of this trial, in the United Kingdom, the National Institute for Health and Care Excellence (NICE) did not recommend the routine use of midostaurin for the treatment of AdvSM in the National Health Service as the benefit was considered uncertain with the currently available data (NICE Rydapt Recommendation). Imatinib, another TKI, is approved in some regions, such as the United States, for a very small subset of patients with AdvSM (D816V c-*KIT* negative or c-*KIT* mutational status unknown ASM, or eosinophilia with a FIP1L1-PDGFRA fusion protein). (Gilreath et al, 2019; Pardanani, 2019; Verstovsek, 2013) Other unapproved therapies have also been used to treat AdvSM, including interferon-alpha and cladribine; however, these treatments are limited by severe toxicities (Gotlib et al, 2018; Pardanani, 2019; Vaes et al, 2017; Verstovsek, 2013).

The United States Food and Drug Administration and European Medicines Agency approval of midostaurin for the treatment of patients with AdvSM was based on a single-arm Phase 2 study

of 116 subjects (Kasamon et al, 2018; Pardanani, 2019). While the study was designed to evaluate efficacy using modified Valent criteria, efficacy was also assessed by International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis (IWG-MRT-ECNM) criteria. For response-evaluable subjects, per IWG-MRT-ECNM criteria, the best CR+PR rate was 17% and CR+PR+clinical improvement (CI) rate was 34%, including a CR rate of 2%. Treatment discontinuation due to AEs occurred in 21% of subjects; 56% of subjects required dose modifications (interruption or reduction) due to AEs. Common AEs across all grades occurring in ≥20% of subjects were nausea, vomiting, diarrhea, edema, musculoskeletal pain, abdominal pain, fatigue, upper respiratory infection, constipation, fever, headache, and dyspnea. Grade ≥3 AEs occurring in ≥5% of subjects were fatigue, sepsis, gastrointestinal hemorrhage, pneumonia, diarrhea, febrile neutropenia, edema, dyspnea, nausea, vomiting, abdominal pain, and renal insufficiency (RYDAPT US Prescribing Information, Revised 4/2017).

Targeted therapies against KIT are emerging as a potential treatment for AdvSM. Avapritinib (Ayvakit®; Ayvakyt®) is a type I small molecule TKI approved for the treatment of patients with AdvSM in the United States and for the treatment of patients with AdvSM after at least one line of therapy in the European Union. The approval of avapritinib in the United States was based on a Phase 1 and Phase 2 single-arm study with a total of 53 modified IWG-MRT-ECNM response-evaluable subjects who received at least one prior therapy and the recommended starting dose of 200 mg daily. The ORR was 57% (CR+CR with incomplete hematologic recovery [CRh]=28%, PR=28%). Higher starting doses of avapritinib were originally explored in AdvSM clinical studies; however, due to the observed risk of intracranial hemorrhage, the recommended starting dose was reduced to 200 mg daily and subjects with pre-treatment thrombocytopenia (platelet count of $<50\times10^9$/L) were excluded from studies. Despite the reduced starting dose and amended study entry criteria, intracranial hemorrhage was still reported in 2.7% of subjects and further dose reduction was required in 68% of response-evaluable subjects. Permanent discontinuation of avapritinib due to adverse reactions was required in 10% of subjects. In subjects who received the recommended starting dose of 200 mg (N=80), the most common adverse reactions of any grade occurring in ≥20% of subjects were edema, diarrhea, nausea, and fatigue. Grade ≥3 AEs occurring in ≥1% of subjects were edema, fatigue/asthenia, vomiting, diarrhea, nausea, abdominal pain, cognitive effects, and arthralgia. Avapritinib has special warnings and precautions for use that include intracranial hemorrhages and cognitive effects (AYVAKIT US Prescribing Information, 2021).

Bezuclastinib is an inhibitor of KIT with potent activity against *KIT* exon 17 and 18 activation-loop mutations. Preliminary clinical activity with bezuclastinib has been observed in clinical Study PLX121-01 in subjects with GIST. A reduction in *KIT* exon 17 mutational burden was observed in subjects treated with bezuclastinib in that study and this reduction was temporally associated with a reduction in tumor burden. The ORR and median PFS of subjects receiving bezuclastinib at a 1000 mg daily dose are similar to the ORR and PFS reported for other KIT-inhibitors in patients with advanced GIST (Nemunaitis et al, 2020; von Mehren et al, 2019), suggesting bezuclastinib has potential as an active therapy in this KIT-driven disease.

1.3.1. Selection of Study Population

This study will enroll subjects with a diagnosis of AdvSM per WHO diagnostic criteria (Appendix A) and have measurable disease according to modified IWG-MRT-ECNM consensus eligibility and response criteria (Appendix F). The diagnosis of AdvSM and evidence of measurable disease will be confirmed by an Eligibility Committee (EC) consisting of a pathologist and at least 1 clinician who is skilled in the diagnosis and treatment of mastocytosis. The requirement for measurable disease is intended to ensure that the majority of enrolled subjects are evaluable for the primary efficacy endpoint of response per modified IWG-MRT-ECNM.

The study allows for a subset of subjects in both Part 1 and Part 2 with AdvSM who are not evaluable per modified IWG-MRT-ECNM. The diagnosis of AdvSM and evidence of measurable disease will be confirmed by an EC prior to randomization in Part 1 and Part 2 Stage 1 and the first dose of study drug in Part 2 Stage 2. This subset of subjects would be excluded from the primary efficacy analysis in Part 1 and Part 2 but would be included in secondary and exploratory analyses as appropriate. Efficacy in these subjects will be evaluated by pure pathologic response (PPR) (Appendix G) (Shomali et al, 2021). The inclusion of these subjects is intended to provide a broader analysis of efficacy and safety in the intended patient population, including patients with AdvSM with lack of evaluable organ damage at baseline.

Subjects requiring antineoplastic therapy for the appropriate management of their associated hematologic neoplasms (AHN) are not appropriate candidates for this clinical trial. Therefore, the protocol excludes patients with the following specific AHNs that are expected to require antineoplastic therapy due to their aggressive nature: acute myeloid leukemia, myelodysplastic syndrome that is very high or high risk as defined by the Revised International Prognostic Scoring System for Myelodysplastic Syndromes, Philadelphia Chromosome positive malignancies, and patients with ≥10% blast cells in bone marrow (see Inclusion Criterion 1 in Section 4.1). In addition, the protocol excludes subjects presenting with any other AHN who require immediate antineoplastic therapy (see Exclusion Criterion 2 in Section 4.2).

1.3.2. Rationale for Dose and Regimen

Part 1 of the study will evaluate the dose-exposure-response relationship, followed by a dose confirmation and expansion period in Part 2. Because AdvSM is driven by a single *KIT* D816V mutation, and based on the previous clinical experience with bezuclastinib, it is not expected that dosing at an MTD is needed to achieve optimal efficacy. Rather than dose escalating to reach an MTD, the goal of the study is to identify a biologically optimal dose.

Four dose cohorts of bezuclastinib Formulation A will be explored in Part 1: Dose Optimization (50 mg BID, 100 mg BID, 200 mg BID, 400 mg QD), and all are below the recommended Phase 2 dose of 1000 mg QD identified in Study PLX121-01 in patients with GIST. In that study, the geometric mean maximum observed concentration (C_{max}) in the bezuclastinib 250 mg dose cohort (the lowest dose level tested) on Cycle 1 Day 15 was 869 ng/mL (CV% 38.4); estimated steady-state trough concentration exceeded 600 ng/mL (in units of nM, exceeded 50 nM). This

value of 50 nM is 10- and 170-fold the IC_{50} values for inhibition of KIT D816V (IC_{50}=5 nM) and KIT-V560G/D816V (IC_{50}=0.29 nM) kinases, respectively.

A modified formulation of bezuclastinib (Formulation B) has been developed to increase the bioavailability. To support bridging from Formulation A in Part 1 to Formulation B in Part 2, Part 2 will be conducted with a 2-stage design: Stage 1 will confirm the optimal dose of bezuclastinib Formulation B, and Stage 2 will consist of an expansion period. In Stage 1, approximately 20 subjects who are evaluable per modified IWG-MRT-ECNM response criteria will be randomized 1:1 to receive 150 mg QD or 300 mg QD of bezuclastinib Formulation B. Based on available data from Part 1, 150 mg QD of bezuclastinib Formulation B is predicted to result in exposure comparable to the exposure range associated with early clinical activity observed in Part 1. A higher dose level of bezuclastinib Formulation B, 300 mg QD, will also be explored to determine if an increased dose results in increased clinical activity with acceptable safety and tolerability. Exposure at 300 mg QD of bezuclastinib Formulation B is predicted to be below the exposure at the recommended Phase 2 dose in patients with GIST observed in Study PLX121-01. In addition, QD dosing of bezuclastinib Formulation B at 300 mg or higher has been tested in an ongoing clinical study in patients with GIST (CGT9486-21-301) and has been shown to be safe and well tolerated. The totality of clinical data from Part 1 and Part 2 Stage 1 will be used to confirm the optimal dose of bezuclastinib Formulation B for Part 2 Stage 2 in subjects with AdvSM.

In Stage 2, approximately 55 subjects who are evaluable per modified IWG-MRT-ECNM response criteria will be enrolled to receive bezuclastinib Formulation B at the selected optimal dose.

In Study PLX121-02 in healthy volunteers, a high-fat meal resulted in approximately a doubling of C_{max} and a 70% increase in AUC from 0 to 24 hours ($AUC_{0\text{-}24h}$) postdose for bezuclastinib Formulation A. To maximize exposure, bezuclastinib Formulation A should be taken with food and water in Part 1 of this study. PK data from Study CGT9486-21-101 indicated higher exposure with Formulation B compared with Formulation A, with up to 80% and 62% increases in C_{max} and $AUC_{0\text{-}24h}$, respectively, across the dose range of 50 mg to 600 mg under fasted conditions. Since exposure achieved in Part 1 with Formulation A under fed conditions can be achieved with Formulation B under fasted conditions at a similar or lower QD dose level, subjects participating in Part 2 will be instructed to take their assigned dose of study drug on an empty stomach (at least 1 hour before or 2 hours after a meal).

PK data are not available for the lowest dose level that may be tested in this study (50 mg QD). However, using a conservative assumption that PK is linear with dose and extrapolating from the available 250 mg Formulation A data, a 50 mg dose would be estimated to result in estimates of trough concentrations of >10 nM, or 2- and 34-fold the IC_{50} values for inhibition of *KIT* D816V and *KIT* V560G/D816V kinases, respectively. Based on these data, it is expected that all dose levels to be studied may generate trough concentrations greater than IC_{50} for *KIT* D816V, and therefore have the potential to be clinically active.

1.3.3. Rationale for Study Design

Using a parallel-group design, the safety, efficacy, and biomarker data will be analyzed in approximately 7 subjects per dose cohort in Part 1.

Part 2 Stage 1 will confirm the optimal dose of bezuclastinib Formulation B based on the totality of available data after approximately 20 subjects have completed at least 2 cycles in Part 2 Stage 1, in addition to data from Part 1. Once the optimal dose is confirmed, the expansion period will be conducted in Part 2 Stage 2.

1.4. BENEFIT/RISK ASSESSMENT

AdvSM is a serious and life-threatening disease that involves the rapid and abnormal proliferation of a clonal mast cell population. Depending on the subtype of AdvSM, the average life-expectancy of a patient can range from 2 to 41 months (NCCN Systemic Mastocytosis, Version 2.2019; Rossignol et al, 2019). The pathogenesis of AdvSM is driven by activation of the KIT receptor, specifically through a mutation in exon 17 (D816V). There are approved therapies targeting *KIT* mutations in some regions for the treatment of patients with AdvSM; however, significant safety and tolerability issues have limited their use.

Bezuclastinib is a TKI that selectively targets *KIT* mutations, including D816V, as reported in nonclinical studies. Preliminary clinical activity with bezuclastinib has been observed in clinical Study PLX121-01 in subjects with solid tumors including GIST. A reduction in KIT exon 17 mutational burden was observed in subjects treated with bezuclastinib in that study, and this reduction was temporally associated with a reduction in tumor burden. Based on available clinical PK and nonclinical pharmacology data, it is expected that all dose levels to be studied may generate trough concentrations greater than IC_{50} for *KIT* D816V, and therefore have the potential to be clinically active.

Upon initiation of this clinical study, a total of 78 healthy volunteers and subjects with solid tumors have received bezuclastinib as a single agent or in combination with pexidartinib or sunitinib across 2 clinical studies. Safety data indicate that bezuclastinib has acceptable safety and tolerability at total daily doses up to 1000 mg as a single agent or in combination with sunitinib. The important potential risks associated with bezuclastinib, which include hepatotoxicity (ie, asymptomatic elevations in liver enzymes), hematological toxicity (ie, anemia, thrombocytopenia, and neutropenia) and gastrointestinal toxicity (ie, nausea, vomiting, and diarrhea), were selected based on bezuclastinib nonclinical safety data, clinical experience, and the assessment of risks for products with similar mechanisms. AEs observed with bezuclastinib in the completed clinical studies were primarily low-grade, non-serious, reversible, and manageable via recommended dose modifications.

Procedures to be performed as part of the clinical study are consistent with procedures that patients with AdvSM would receive as part of standard of care, such as blood draws and bone marrow biopsies. Study procedures may be performed at higher frequencies than performed as part of standard of care. However, subjects are closely monitored, and all study-related procedures are performed by experienced healthcare professionals.

2. TRIAL OBJECTIVES AND ENDPOINTS

Objectives and Endpoints:		
	Objectives	**Endpoints**
Part 1: Dose Optimization		
Primary	To identify a clinically active and tolerable systemic exposure range of bezuclastinib in subjects with AdvSM	• Safety assessments (incidence of adverse events [AEs], serious adverse events [SAEs], changes from baseline in laboratory results) and dose modifications • Pharmacokinetics (PK) and pharmacodynamic assessments • Overall response rate (ORR) based on the modified IWG-MRT-ECNM response criteria per Central Response Review Committee (CRRC)
Part 2 Stage 1: Dose Confirmation		
Primary	To confirm the optimal dose of bezuclastinib in subjects with AdvSM	• Safety assessments (incidence of AEs, SAEs, changes from baseline in laboratory results) and dose modifications • PK and pharmacodynamic assessments • ORR based on the modified IWG-MRT-ECNM response criteria per Central Response Review Committee (CRRC)
Part 2 Stage 2: Expansion		
Primary	To determine the efficacy of bezuclastinib at the selected optimal dose in subjects with AdvSM who are evaluable based on the modified IWG-MRT-ECNM response criteria	ORR defined as the percentage of subjects classified as confirmed responders (complete response [CR], CR with incomplete hematologic recovery [CRh], partial response [PR], and clinical improvement [CI]) according to modified IWG-MRT-ECNM response criteria as assessed by CRRC
Part 1 and Part 2		
Secondary	To characterize the safety and tolerability of bezuclastinib in subjects with AdvSM	Incidence of AEs, SAEs, AEs leading to dose modifications, and changes from baseline in laboratory results
	To evaluate additional efficacy parameters with bezuclastinib in subjects with AdvSM	Duration of response (DOR), defined as the date of the first documented response (CR, CRh, PR, or CI) to date of first documented disease progression or loss of response, or death from any cause, whichever occurs first, based on modified IWG-MRT-ECNM response criteria
		Time to response (TTR), defined as the date of randomization/first dose of study drug to the date of the first documented response (CR, CRh, PR, or CI) based on modified IWG-MRT-ECNM response criteria
		Progression-free survival (PFS), defined as the date of randomization/first dose of study drug to the date

Objectives and Endpoints:		
	Objectives	**Endpoints**
		of first documented disease progression, or death from any cause, whichever occurs first
		Overall survival (OS), defined as the date of randomization/first dose of study drug to the date of death from any cause
		Pure Pathologic Response (PPR), including complete remission, complete remission with partial hematologic recovery, molecular complete remission, and partial remission (Gotlib et al, 2020)
		Changes in spleen and liver size assessed by magnetic resonance imaging (MRI)
	To determine the effects of bezuclastinib on serum tryptase	Changes in the levels of serum tryptase
	To determine the effects of bezuclastinib on *KIT* D816V mutation allele burden	Changes in the levels of *KIT* D816V mutation allele burden in blood and bone marrow
	To evaluate histopathologic response in the blood and bone marrow	Change in pathologic findings in the blood and bone marrow, including mast cell infiltration, monocytosis, and eosinophilia
	To assess the PK of bezuclastinib in subjects with AdvSM	Plasma concentrations and PK parameters (eg, area under the plasma concentration-time curve [AUC] and maximum observed plasma concentration [C_{max}]) of bezuclastinib
	To assess patient-reported outcomes in subjects with AdvSM	Patient Global Impression of Change (PGIC) scale and change and percent change from baseline in the following patient-reported outcome measures: Patient Global Impression of Severity (PGIS) scale, Mastocytosis Quality of Life Questionnaire (MC-QoL), and Mastocytosis Activity Score (MAS) where appropriate translations are available (Siebenhaar et al, 2018; Siebenhaar et al, 2016)
	To explore the effect of bezuclastinib in subjects with AdvSM who are non-evaluable based on the modified IWG-MRT-ECNM response criteria	• Incidence of AEs, SAEs, AEs leading to dose modifications, and changes from baseline in laboratory results • PPR, including complete remission, complete remission with partial hematologic recovery, molecular complete remission, and partial remission (Gotlib et al, 2020)

Objectives and Endpoints:		
	Objectives	**Endpoints**
Exploratory	To explore various pharmacodynamic markers and their relationship with clinical safety and efficacy	Blood and bone marrow obtained at various timepoints throughout the trial to determine the effects of bezuclastinib on pharmacodynamic markers, including *KIT* D816V mutation allele burden and myeloid mutation profile as a measure of pharmacodynamic activity
	To explore the PK/pharmacodynamic relationships	Assessing the relationships between bezuclastinib PK and pharmacodynamic markers including *KIT* D816V mutation allele burden
	To explore changes in cutaneous lesions in subjects with baseline mastocytosis in skin	Change in number or pigmentation of cutaneous lesions by standardized photographs
	To explore changes in C-findings	Proportion of subjects with resolution of C-findings, including resolution of hypoalbuminemia and changes in size of skeletal lesions

3. INVESTIGATIONAL PLAN

3.1. STUDY DESIGN

This is a Phase 2, open-label, 2-part clinical study to evaluate the safety, efficacy, PK, and pharmacodynamics of the KIT inhibitor bezuclastinib in patients with AdvSM. Part 1 will determine a clinically active and tolerable exposure range of bezuclastinib in subjects with AdvSM using Formulation A. Part 2 will be conducted with a 2-stage design to support the introduction of Formulation B: Stage 1 will confirm the optimal dose of bezuclastinib Formulation B, and Stage 2 will consist of an expansion period.

3.1.1. Study Governance

An EC will review subject eligibility and will approve subject enrollment during the Screening Period. The clinical history and pathology must be centrally reviewed before a subject is enrolled. The EC will consist of a pathologist and at least 1 clinician who is skilled in the diagnosis and treatment of mastocytosis.

A Study Steering Committee (SSC) will be responsible for advising the Sponsor throughout Part 1 and Part 2 of the study. The SSC will be composed of Lead Principal Investigators and the Study Medical Monitor and will be responsible for assisting the Sponsor with protocol development, amendments, study conduct, and interpretation of data. The selected dose for Part 2 Stage 2 based on available data from Part 1 and Part 2 Stage 1 will be reviewed and confirmed by the SSC before the selected dose is administered in Part 2 Stage 2.

A Central Response Review Committee (CRRC) will retrospectively review disease-specific eligibility criteria and the presence of 1 or more baseline modified IWG-MRT-ECNM findings. The CRRC will review all available data to assess response per the modified IWG-MRT-ECNM response criteria. The CRRC will consist of an independent pathologist, 1 independent clinician, and at least 2 clinicians who are skilled in the treatment of mastocytosis.

An Independent Data Monitoring Committee (IDMC) will aid in the monitoring of accumulating study data to ensure the ongoing safety of trial participants and will play a role in confirming the recommendations and decisions made by the Sponsor across bezuclastinib clinical trials. The IDMC membership will be composed of external medical experts with relevant clinical experience. The IDMC will review the available data and recommendation from the SSC regarding the optimal dose selected in Part 2 Stage 1 for Part 2 Stage 2. The IDMC will have the right to recommend stopping the study at any time due to concerns for the safety of the subjects.

Charters will govern each of these committees as appropriate.

3.1.2. Part 1: Dose Optimization

In Part 1 of the study, approximately 28 subjects will be randomized to 1 of 4 dose cohorts of bezuclastinib (Formulation A), including up to 4 subjects who are non-evaluable per modified IWG-MRT-ECNM response criteria based on lack of evaluable organ damage per modified IWG-MRT-ECNM criteria. Subjects will be randomized in a 1:1:1:1 (50 mg BID:100 mg

BID:200 mg BID:400 mg QD) manner. Randomization will be stratified by evaluability per modified IWG-MRT-ECNM response criteria (ie, evaluable vs non-evaluable).

Table 4: Single-Agent Dose Optimization Cohort

	Bezuclastinib Dose × 28-Day Cycles			
	Dose Cohort 1	Dose Cohort 2	Dose Cohort 3	Dose Cohort 4
Initial Dose	50 mg BID	100 mg BID	200 mg BID	400 mg QD
Total Daily Dose	100 mg	200 mg	400 mg	400 mg

Abbreviations: BID=twice a day; QD=once daily.

Bezuclastinib Formulation A will be administered orally as a single agent and should be taken with food and water. Each 28-day period is 1 cycle. Subjects will receive bezuclastinib at their assigned dose cohort until confirmed disease progression, intolerable toxicity, Investigator decision, withdrawal of consent, or other protocol-specified reason for discontinuation of study drug, whichever occurs first. Once the optimal dose level of bezuclastinib Formulation B is confirmed in Part 2 Stage 1, subjects receiving Formulation A may be transitioned to receive Formulation B. Additional blood samples for PK may be collected following the transition from Formulation A to Formulation B.

3.1.3. Part 2: Dose Confirmation and Expansion

Part 2 will be conducted with a 2-stage design: Stage 1 will confirm the optimal dose of bezuclastinib Formulation B, and Stage 2 will consist of an expansion period.

In Stage 1, approximately 20 subjects who are evaluable per modified IWG-MRT-ECNM response criteria will be randomized 1:1 to receive 150 mg QD or 300 mg QD of bezuclastinib Formulation B. Randomization will be stratified by prior treatment of TKI (ie, yes vs no). Based on available data from Part 1, 150 mg QD of bezuclastinib Formulation B is expected to provide clinical activity with acceptable safety and tolerability. A higher dose level of bezuclastinib, 300 mg QD, will also be explored to determine if an increased dose results in increased clinical activity with acceptable safety and tolerability. The totality of clinical data from Part 1 and Part 2 Stage 1 will be used to confirm the optimal Formulation B dose of bezuclastinib in subjects with AdvSM. Subjects in Part 2 Stage 1 may have their dose adjusted once the optimal dose of bezuclastinib Formulation B is confirmed.

Once approximately 20 subjects have been enrolled in Part 2 Stage 1, enrollment may continue until the dose for Part 2 Stage 2 is confirmed. Following enrollment of 20 subjects in Part 2 Stage 1 and prior to analysis of Part 2 Stage 2 data, enrolled subjects will receive either 150 mg and/or 300 mg based on ongoing review of available data and following IDMC approval. Of the additional subjects who may be enrolled, those who receive the dose selected for Part 2 Stage 2 will contribute to the Stage 2 analysis population.

In Stage 2, approximately 55 subjects who are evaluable per modified IWG-MRT-ECNM response criteria will be enrolled to receive bezuclastinib Formulation B at the selected optimal

dose. Up to approximately 15 additional subjects who are non-evaluable per modified IWG-MRT-ECNM response criteria based on lack of evaluable organ damage per modified IWG-MRT-ECNM criteria may be enrolled.

To ensure the study population reflects the general AdvSM patient population, enrollment of the SM-AHN subtype will be capped at approximately 80% (Jawhar et al, 2019).

Bezuclastinib will be administered orally as a single agent. Each 28-day period is 1 cycle. Subjects will receive bezuclastinib at the selected Part 2 dose until confirmed disease progression, intolerable toxicity, Investigator decision, withdrawal of consent, or other protocol-specified reason for discontinuation of study drug (Section 4.3.1).

3.1.4. Response Assessments

A bone marrow assessment will be performed on Cycle 3 Day 1 to document initial response. Bone marrow assessments will be performed every 3 cycles (approximately every 12 weeks) from Cycle 6 until Cycle 12 (Day 1 of C6, C9, C12), and then every 6 cycles (C18, C24, etc.) thereafter. If an initial response (CR, CRh, PR, or CI) is achieved on or after C12, a repeat bone marrow assessment will be performed 12 weeks after the initial documented response to confirm response per modified IWG-MRT-ECNM response criteria. Changes in liver and spleen size will be assessed by MRI and palpation. A computed tomography scan may be used if MRI cannot be performed. Skeletal imaging is required at Screening for all subjects to assess for baseline lytic lesions and/or pathologic fractures. Changes in the size of bony lesions will be assessed with skeletal imaging. Refer to Section 6.15 for further information regarding disease assessments.

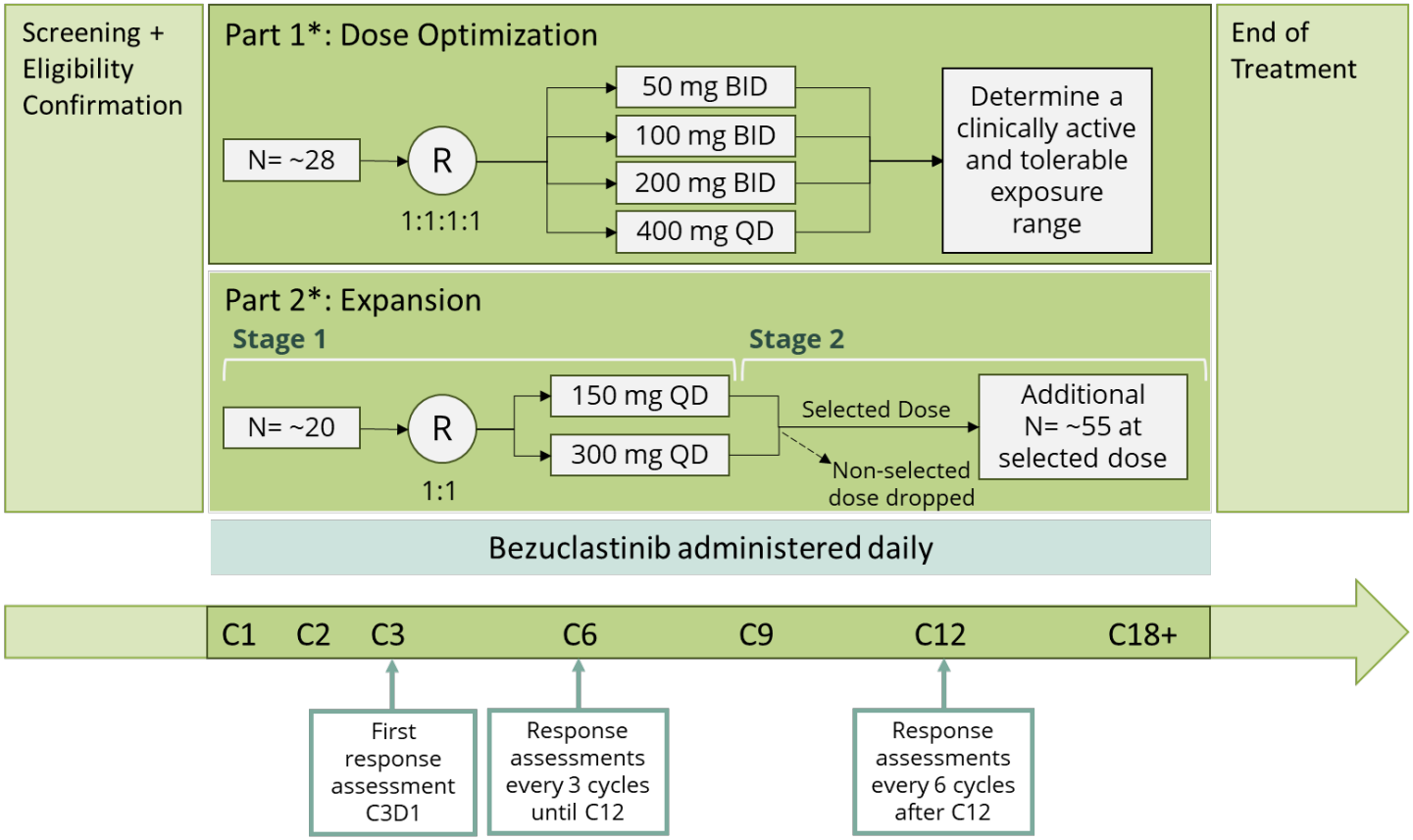
3.1.5. Safety Assessments

Safety will be assessed by AEs, physical examinations, vital signs, hematology and chemistry laboratories, and electrocardiograms (ECGs). AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the time of database creation and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 or higher.

3.1.6. Pharmacokinetic and Pharmacodynamic Assessments

Blood samples will be collected for determination of bezuclastinib PK. Predose PK blood samples will be collected within 30 minutes before initial daily dosing. Blood and bone marrow will be collected for analysis of the clinical and pharmacodynamic effects of bezuclastinib.

Figure 1: Study Schematic



*Of the 28 subjects randomized in Part 1, 4 subjects may be included who are non-evaluable per modified IWG-MRT-ECNM response criteria. In addition to the ~55 subjects who are evaluable per modified IWG-MRT-ECNM response criteria in Part 2 Stage 2, up to an additional ~15 subjects who are non-evaluable per modified IWG-MRT-ECNM response criteria may participate.

Abbreviations: C=cycle, D=day, IWG-MRT-ECNM=International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, QD=once daily.

Note: The study will continue until all subjects have completed at least 2 years of follow-up for overall survival, withdrawn from study participation, been lost to follow-up, or died, whichever occurs first.

4. STUDY POPULATION

4.1. INCLUSION CRITERIA

Consideration should be given to the suitability of available alternative therapies (eg, midostaurin, avapritinib) prior to study enrollment. Subjects must meet all of the following inclusion criteria:

1. Diagnosed with 1 of the following advanced mastocytosis diagnoses based on WHO diagnostic criteria (Appendix A):
    - ASM
    - SM-AHN (The associated hematologic neoplasm must be myeloid, with the following diagnoses excluded from study entry: acute myeloid leukemia, myelodysplastic syndrome that is very high- or high-risk as defined by the Revised International Prognostic Scoring System for Myelodysplastic Syndromes, Philadelphia Chromosome positive malignancies, and patients with ≥10% blast cells in bone marrow)
    - MCL
2. Measurable disease according to modified IWG-MRT-ECNM consensus eligibility and response criteria for CI (Appendix C)

    NOTE: Diagnosis and evidence of measurable disease (including at least 1 measurable C-finding per modified IWG-MRT-ECNM response criteria for patients with ASM and SM-AHN [patients with MCL do not require a C-finding]) must be confirmed by the EC prior to the first dose of study drug.

    NOTE: Up to 4 subjects in Part 1 and up to an additional 15 subjects in Part 2 Stage 2 who have AdvSM and are non-evaluable per modified IWG-MRT-ECNM response criteria based on lack of evaluable organ damage per modified IWG-MRT-ECNM may be enrolled.
3. Able to provide written informed consent
4. Able and willing to commit to study assessments and visit schedule
5. Age ≥18 years of age
6. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 3
7. Have clinically acceptable laboratory screening results (clinical chemistry, hematology) within certain limits specified below:
    a. Absolute neutrophil count >500/µL (subjects enrolled in Part 1 only)
    b. Platelet count ≥50,000/µL prior to the first dose of study drug
    c. AST and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN) or ≤5×ULN if there is liver involvement by AdvSM

d. Direct bilirubin ≤1.5×ULN; if related to AdvSM may be ≤3×ULN

e. Calculated creatinine clearance (Cockcroft-Gault) ≥40 mL/min

f. Serum tryptase ≥20 ng/mL

8. For women of childbearing potential (WOCBP; defined as physiologically and anatomically capable of becoming pregnant), confirmation of a negative serum pregnancy test and agreement to the use of a highly effective method of contraception with or without a barrier contraception method (in accordance with country-specific guidance) during the study treatment period and for 6 weeks after the last dose of bezuclastinib; for male subjects, agreement to use effective barrier contraception (ie, condoms) during the study treatment period and for 6 weeks after the last dose of bezuclastinib
9. Able to swallow pills

4.2. EXCLUSION CRITERIA

Subjects will not be eligible for inclusion in this study if any of the following criteria apply:

1. Persistent toxicity from previous therapy for AdvSM that has not resolved to ≤ Grade 1.
2. Patients presenting with an associated hematologic neoplasm who require immediate antineoplastic therapy.
3. Clinically significant cardiac disease, defined by any of the following:
    a. Uncontrolled or untreated cardiac arrhythmias
    b. Congenital long QT syndrome or concomitant medications known to prolong the QT interval except those required for infections that carry a low risk of QTc prolongation.
    c. A marked baseline prolongation of QT/QTc interval (eg, repeated demonstration of a QTcF [QT corrected using Fridericia's formula] interval >480 msec).
    d. History of clinically significant cardiac disease or congestive heart failure > New York Heart Association Class II. (Patients must not have unstable angina [anginal symptoms at rest] or new-onset angina within the last 3 months or myocardial infarction within the past 6 months.)
    e. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within the 6 months before study drug initiation (except for adequately treated catheter-related venous thrombosis occurring more than 1 month before the first dose of study drug).
4. Known positivity for the *FIP1L1-PDGFRA* fusion (except for patients who demonstrated relapse or disease progression on prior imatinib therapy). Patients with eosinophilia (eosinophil count >1.5×10^9/L) who do not have a detectable *KIT* D816V mutation must provide documentation of the lack of a PDGFRA fusion mutation by fluorescence in situ hybridization or polymerase chain reaction prior to enrollment.

5. Any other concurrent severe known disease or concurrent severe and/or uncontrolled medical condition (eg, uncontrolled diabetes or active uncontrolled infection), either of which could compromise participation in the study.
6. Seropositive for human immunodeficiency virus (HIV) 1 or 2, positive for hepatitis B surface antigen, or positive for hepatitis C virus (HCV) antibody. (Subjects with a positive HCV antibody may be eligible if HCV RNA is undetectable on a quantitative HCV RNA assay, following discussion with the Medical Monitor.)
7. Active, uncontrolled, systemic bacterial, fungal, or viral infections at Screening.

   NOTE: Oral antibiotics for a controlled infection are permitted with Medical Monitor approval. Patients on antimicrobial, antifungal, or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met.
8. History of clinically significant bleeding event within 30 days before the first dose of study drug or need for therapeutic anticoagulation on study.
9. Diagnosed with or treated for malignancy other than the disease under study within the prior 3 years before enrollment or expected to need treatment for an active malignancy. (The following are allowed within 3 years of study enrollment if the subject has received definitive local therapy [eg, surgical excision, external beam radiation, or other local therapy with curative intent]: non-melanoma skin cancers, localized prostate cancer, or carcinoma in situ.)
10. Any condition that could hamper compliance with the study protocol in the judgment of the Investigator.
11. Pregnant or currently breastfeeding.
12. Received any cytoreductive therapy (including midostaurin and other tyrosine kinase inhibitors, hydroxyurea, azacitidine) or any 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 bone marrow biopsy for this study.
13. Received hematopoietic growth factor (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor) support within 14 days before the first dose of study drug.
14. Received strong CYP3A4 inhibitors or inducers within 14 days or 5 drug half-lives, whichever is longer, before the first dose of study drug or the need to continue treatment with strong CYP3A4 inhibitors or inducers during the study (Refer to Appendix H).
15. Need for treatment with steroids (>10 mg prednisone or equivalent per day). Subjects on a stable dose of prednisone or equivalent that is ≤10 mg per day are eligible.
16. Known hypersensitivity to bezuclastinib or any of its components.

4.3. SUBJECT WITHDRAWAL CRITERIA

4.3.1. Treatment Discontinuation for Individual Subjects

Treatment discontinuation is defined as an instance in which a subject permanently stops receiving study drug and does not restart drug. Subjects who experience a TEAE that is assessed as at least possibly related to study drug and require a dose interruption of more than 28 days must permanently discontinue treatment with bezuclastinib. A subject should be discontinued from study treatment if, in the opinion of the Investigator or Sponsor, it is medically necessary to do so, or if it is the wish of the subject. A subject who becomes eligible for hematopoietic stem cell transplantation (HSCT) and for whom HSCT is the most appropriate therapeutic option should discontinue treatment and receive HSCT at the discretion of the Investigator.

A subject must discontinue study treatment for:

- Protocol-specified documented disease progression
- Investigator decision
- Subject withdrawal of consent
- Development of an AE, that in the opinion of the Investigator, would render continued participation harmful to the subject
- Subject pregnancy
- Lost to follow up (ie, inability by the Investigator to contact and/or effectively monitor the subject)
- Termination of study by Sponsor
- Enrollment in another therapeutic study
- Receiving a non-protocol-approved treatment plan for treatment of the subject's AdvSM

The Sponsor is to be immediately notified if a subject discontinues study treatment for any reason. The reason for treatment discontinuation must be documented on the appropriate electronic case report form (eCRF). Noncompliance with the protocol medication/treatments and/or required follow-up, as judged by the Investigator, may result in discontinuation of study drug.

4.3.2. Study Discontinuation for Individual Subjects

Subjects enrolled in this study may withdraw from the study at any time without penalty or loss of future medical care or any other benefits to which they are otherwise entitled. Subjects will be withdrawn from the study for any of the following reasons:

- Subject is lost to follow-up (ie, inability by the Investigator to contact and/or effectively monitor the subject)
- Subject withdrawal of consent

- Subject death
- Investigator decision
- Termination of study by Sponsor
- Adverse event
- Enrollment in another therapeutic study

The Sponsor is to be immediately notified if a subject is withdrawn from the study for any reason. The reason for study withdrawal must be documented on the appropriate eCRF.

The Sponsor must be notified if the Investigator identifies a subject who did not meet enrollment criteria but was inadvertently enrolled. Similarly, if the Sponsor identifies a subject who did not meet enrollment criteria but was inadvertently enrolled, the Investigator will be notified. A discussion must occur between the Medical Monitor and the Investigator to determine whether it is medically appropriate for a subject to continue in the study, with or without the study treatment regimen. The Investigator must then obtain documented approval from the Medical Monitor if the subject is to be allowed to continue in the study with or without the study treatment regimen.

4.4. STUDY STOPPING RULES

The IDMC will be convened to determine whether the study should be stopped or enrollment should be paused or discontinued for a particular dose cohort based on any of the following safety events:

- ≥2 subjects discontinuing treatment due to a treatment-related toxicity in a particular dose cohort (Part 1 or Part 2 Stage 1).
- Non-hematologic treatment-related Grade 4 toxicity that occurs within 30 days of initiating treatment.
- Treatment-related death that occurs within 30 days of initial dosing will result in enrollment pause across all dose cohorts until the IDMC has convened.

Additionally, the SSC will meet regularly to assess the totality of the data and assess response rate to determine whether the study should be stopped or enrollment should be paused or discontinued for a particular dose cohort based on lack of treatment effect under the following circumstance:

- ≤1 of 5 subjects in a given dose cohort with stable disease or better after 6 cycles of treatment (Part 1).

4.5. EARLY STUDY TERMINATION

The study may be terminated early at the discretion of the Sponsor. Circumstances that may warrant early termination include:

- Observation of an unexpected, significant risk to subjects
- Failure to enroll subjects at an acceptable rate
- Plans to modify, suspend, or discontinue the development of study drug

5. STUDY DRUG MATERIALS AND MANAGEMENT

5.1. DESCRIPTION OF BEZUCLASTINIB

There are 2 formulations of bezuclastinib described as Formulation A (original) and Formulation B (modified). Bezuclastinib Formulation A are wide, flat, oblong-shaped tablets, and available in a 50 mg strength for oral administration. Bezuclastinib Formulation B are capsule-shaped tablets, and available in a 50 mg strength for oral administration. Prior to the start of the study, the Sponsor will provide labeled supplies of bezuclastinib to the site investigational pharmacy.

Bezuclastinib will be supplied in bottles containing 50 mg tablets. The study drug is to be stored at controlled room temperature (not above 25°C/77°F).

Bezuclastinib will be labeled and packaged in an open-label fashion in accordance with Good Manufacturing Practices for clinical trials and country-specific guidelines.

Refer to the Pharmacy Manual and the current edition of the IB for further information on the study drug.

5.2. BEZUCLASTINIB ADMINISTRATION

Bezuclastinib will be administered as single agent 50 mg tablets. Since the bioavailability of Formulation A is limited by absorption and food has been shown to increase the oral bioavailability (PLX121-02), subjects participating in Part 1 will be instructed to take their assigned dose of study drug with food and water to maximize exposure. As higher exposure and faster absorption were observed with Formulation B relative to Formulation A (Study CGT9486-21-101), the exposure achieved in Part 1 with Formulation A under fed conditions can be achieved with Formulation B under fasted conditions at a similar or lower QD dose level. Therefore, subjects participating in Part 2 will be instructed to take their assigned dose of study drug on an empty stomach (at least 1 hour before or 2 hours after a meal). With either formulation, the entire dose should be taken within 30 minutes at approximately the same time each day. The dose taken should be recorded in the provided study drug diary. Bezuclastinib tablets should not be broken, crushed, or dissolved in solution.

For dose cohorts with a BID schedule (Part 1), the bezuclastinib doses should be taken approximately 12 hours apart (±3 hours). For dose cohorts with a QD schedule, the bezuclastinib doses should be taken approximately 24 hours apart (±6 hours). Missed or skipped doses should not be made up. One treatment cycle is 28 days. Treatment will be continuous; there will be no gaps between cycles.

On days of a scheduled clinic visit, subjects should be instructed to take study drug at the clinic after visit procedures and assessments are performed.

5.3. RANDOMIZATION

This is a randomized, open-label study. Subjects in Part 1 will be randomized to receive bezuclastinib Formulation A in a 1:1:1:1 (50 mg BID:100 mg BID:200 mg BID:400 mg QD)

manner. Randomization will be stratified by evaluability per modified IWG-MRT-ECNM response criteria (ie, evaluable vs non-evaluable).

Subjects in Part 2 Stage 1 will be randomized to receive bezuclastinib Formulation B in a 1:1 (150 mg QD:300 mg QD) manner. Randomization will be stratified by prior treatment of TKI (ie, yes vs no).

Subjects in Part 2 Stage 2 will receive bezuclastinib at the selected dose based on the totality of clinical data from Part 1 and Part 2 Stage 1.

5.4. TREATMENT COMPLIANCE

At each applicable visit, subjects will be given an adequate supply of study drug so that the subject will have enough doses until the next applicable visit. Study drug diaries will be provided to subjects at applicable study visits and used to track bezuclastinib administration.

Compliance for doses taken outside of the clinic will be assessed by a count of the tablets returned to the study trial site by the subject and reviewed with the subject.

5.5. STUDY DRUG ACCOUNTABILITY

The Investigator or designee is responsible for taking an inventory of each shipment of bezuclastinib investigational supplies received and comparing it with the accompanying drug accountability form.

Subjects will be instructed to bring all unused bezuclastinib tablets, empty bottles, and their study drug diary to each study visit. The study site will count all tablets that the subject returns, review the study drug diary, and account for taken doses, missed doses, doses reduced due to missing or lost tablets, etc. before dispensing new study drug to the subject. Any subject who does not take the prescribed dose will be requested to return the remaining drug to the clinical trial site for accountability.

All unused bezuclastinib will be retained at the site. After full drug accountability and reconciliation, the Investigator will dispose of the study drug at the clinical trial site according to site procedures, or at the Sponsor's request, will return all bezuclastinib to the Sponsor or its designee. If any study drug is lost or damaged, the disposition of the study drug should be documented.

5.6. CRITERIA FOR DOSE MODIFICATION

When treatment-related toxicities are observed, dosing with bezuclastinib may be interrupted until recovery from the observed treatment-related toxicities, and to consider if dose reductions are appropriate for continued therapy with bezuclastinib. Please refer to Table 5 for dose modification guidance for Formulation A and Formulation B. Repeated dose reductions are permitted; however, doses below 50 mg QD are not allowed. Subjects who are unable to tolerate bezuclastinib 50 mg QD will be discontinued from treatment. Subjects who require a dose reduction due to a treatment-related toxicity may have their bezuclastinib dose re-escalated if they are on the reduced dose for more than 28 days without recurrence of the observed toxicity

and with no new treatment-related events requiring dose modification. If another treatment-related event requiring a dose reduction occurs, the subject will not be allowed to re-escalate the dose again unless it is in the best interest of the subject per the Investigator and agreed to by the Sponsor. The Sponsor should be promptly informed prior to any decision to hold or change subject dosing.

Table 5: Bezuclastinib Dose Cohorts

	Bezuclastinib Dose Table					
	Formulation A (Part 1)				**Formulation B (Part 2)**	
	Dose Cohort 1	**Dose Cohort 2**	**Dose Cohort 3**	**Dose Cohort 4**		
Initial dose	50 mg BID	100 mg BID	200 mg BID	400 mg QD	150 mg QD	300 mg QD
First dose reduction	50 mg QD	50 mg BID	100 mg BID	200 mg QD	100 mg QD	150 mg QD
Second dose reduction	NA	50 mg QD	50 mg BID	100 mg QD	50 mg QD	100 mg QD
Third dose reduction	NA	NA	50 mg QD	50 mg QD	NA	50 mg QD

Abbreviations: BID=twice daily, NA=not applicable; QD=once daily.

A dose interruption of up to 28 days is allowed for TEAEs considered to be at least possibly related to study drug to return to ≤ Grade 1 or Baseline. TEAEs that are possibly related to study drug and require dose interruptions of more than 28 days will result in the permanent discontinuation of bezuclastinib.

Recommended dose modifications for TEAEs considered to be at least possibly related to study drug are provided in Table 6.

For risk management recommendations associated with the important potential risks of bezuclastinib, please refer to Section 6.2.4 of the current edition of the IB.

Table 6: Dose Modification Criteria for TEAEs At Least Possibly Related to Bezuclastinib

TEAE	**Criteria or CTCAE v5.0 Grade**	**Dose Modification**
Anemia, neutropenia, thrombocytopenia (a)	Grade 4 anemia for ≥7 days Grade 4 neutropenia for ≥7 days, or Grade 3 or worse neutropenia associated with bacterial or fungal infection requiring systemic therapy Febrile neutropenia (any grade) Grade 4 thrombocytopenia for ≥7 days, or Grade 3 or worse thrombocytopenia associated with bleeding	Hold bezuclastinib until resolved to ≤Grade 1 or baseline. If recovered to ≤Grade 1 or baseline in ≤28 days, reduce by 1 dose level. If not recovered to ≤Grade 1 or baseline after 28 days, discontinue study drug.

Table 6: Dose Modification Criteria for TEAEs At Least Possibly Related to Bezuclastinib

TEAE	Criteria or CTCAE v5.0 Grade	Dose Modification
ECG QT prolonged	Grade 3: >500 msec or >60 msec increase from baseline (b)	Hold bezuclastinib until QTc ≤500 msec (≤Grade 2); then reduce by 1 dose level If not recovered to ≤Grade 1 or baseline after 28 days, discontinue study drug.
	Grade 4: Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Permanently discontinue study drug.
Transaminase increases	ALT or AST >8×ULN ALT or AST >5×ULN for more than 2 weeks ALT or AST >3×ULN and TBL >2×ULN or INR >1.5 ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	Consider the possibility of drug-induced liver injury. If drug-induced liver injury is suspected, permanently discontinue study drug if it is in the best interest of the subject.
Other non-hematological toxicity (excluding Grade 3 nausea, vomiting, or diarrhea lasting ≤72 hours with adequate prophylactic and supportive care), including clinically significant non-hematologic laboratory parameters (excluding elevations in alkaline phosphatase)	Grade 3	Hold bezuclastinib until resolved to ≤Grade 1 or baseline. If recovered to ≤Grade 1 or baseline in ≤28 days, reduce by 1 dose level. If not recovered to ≤Grade 1 or baseline after 28 days, discontinue study drug.
	Grade 4	Permanently discontinue study drug unless considered unrelated to treatment.

Abbreviations: AE=adverse event, ALT=alanine transaminase, AST=aminotransferase, CTCAE=National Cancer Institute Common Terminology for Adverse Events, ECG=electrocardiogram, MCL=mast cell leukemia, QTc=corrected QT interval, TBL=total bilirubin, TEAE=treatment-emergent adverse event, ULN=upper limit of normal.

(a) For subjects with MCL or subjects for whom Grade 3 cytopenia was recorded at Screening due to disease progression, a Grade 3 or Grade 4 event of cytopenia may not require dose interruption/modification, following discussion with the Investigator and Medical Monitor.

(b) Triplicate readings are required.

5.7. CONCOMITANT MEDICATIONS

5.7.1. Prohibited Concomitant Medications

Therapies for the treatment of AdvSM (other than bezuclastinib) or any other investigational agents are prohibited during the treatment period. Subjects who receive a subsequent treatment for AdvSM or begin treatment with any investigational agent must discontinue treatment with bezuclastinib but may continue in the study follow-up period.

Strong inhibitors or inducers of CYP3A4 may affect the metabolism of bezuclastinib and should not be taken systemically by subjects within 14 days or 5 half-lives, whichever is longer, before the first dose of study drug or at any time during the study. These include anticonvulsants, aminoglycoside ("mycin") antimicrobials, and antiretrovirals. Some common examples of strong inhibitors/inducers include inhibitors such as clarithromycin, ketoconazole, nefazodone, and voriconazole and inducers such as carbamazepine, phenobarbital, phenytoin, glucocorticoids, and St. John's wort. In addition, foods or beverages containing grapefruit should be avoided throughout the study. A list of strong CYP3A4 inhibitors and CYP3A4 inducers is provided in Appendix H.

5.7.2. Permitted Concomitant Medications

Systemic corticosteroids at doses ≤10 mg per day of prednisone or equivalent and dose stable for at least 2 weeks before the first dose of bezuclastinib are permitted. Topical or inhaled corticosteroid medications are allowed. Emergency use of higher doses of corticosteroids for management of acute allergic events is allowed as clinically indicated.

Use of G-CSF is permitted in the setting of neutropenia.

Radiotherapy is permitted for localized treatment of symptomatic lytic lesions as clinically indicated.

Concomitant medication (eg, H1- and H2-antihistamines, leukotriene receptor antagonists, cromolyn sodium, omalizumab, ketotifen, epinephrine injection) is permitted if it is considered necessary for the subject's welfare and is not expected to interfere with the evaluation of safety or efficacy of the study drug, per the discretion of the Investigator and based on NCCN treatment criteria (NCCN Systemic Mastocytosis, Version 2.2019), or local guidelines for the treatment of AdvSM.

During the study, if the use of any concomitant treatment becomes necessary (eg, for treatment of an AE), the treatment must be recorded on the eCRF, including the reason for treatment, generic name of the drug, and start and stop dates of administration.

5.7.3. Gastric pH-Altering Agents

While it is unknown whether gastric pH-altering agents affect the absorption and plasma exposure of bezuclastinib, histamine receptor–blocking drugs may be essential in the management of symptoms of SM and should not be restricted in any way. However, proton-pump inhibitor drugs should be avoided where possible, and the treating clinician should try to

switch any subject receiving a proton-pump inhibitor to a histamine receptor–blocking drug, to be taken preferably 2 hours following the dose of bezuclastinib.

5.7.4. Contraception Requirements

The effects of bezuclastinib on conception, pregnancy, and lactation are unknown. WOCBP for the purposes of this protocol are defined as all women physiologically capable of becoming pregnant, unless they meet one of the following conditions:

- Postmenopausal: 12 months of natural (spontaneous) amenorrhea without an alternative medical cause
- Hysterectomy
- Bilateral oophorectomy
- Bilateral salpingectomy

WOCBP must agree to use a highly effective method of contraception with or without an effective barrier contraception method (please follow country-specific guidance) during the study treatment period and for 6 weeks after the last dose of study drug. Per the Clinical Trials Facilitation Group (CTFG) guidelines (2014), highly effective contraceptive methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly.

Methods of highly effective contraception include:

- Combined (estrogen and progesterone-containing) hormonal contraception associated with inhibition of ovulation, delivered orally, intravaginally, or transdermally
- Progestogen-only hormonal contraception associated with inhibition of ovulation, delivered orally, via injection, or implanted
- An intrauterine device
- An intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner, provided the partner is the sole sexual partner of the WOCBP subject and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence, when consistent with the preferred and usual lifestyle of the subject, can be considered acceptable based on the evaluation of the Investigator who should take into consideration the duration of the clinical trial. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

Egg/ovum donations are not permitted for women during the study treatment period and for 6 weeks after the last dose of bezuclastinib.

Female subjects who are using hormonal contraception must agree to remain on a stable regimen throughout the study unless a change is deemed medically necessary by the Investigator.

Post-pubertal men, unless having undergone permanent sterilization (includes bilateral orchidectomy), must agree to use effective barrier contraception (ie, condoms) during the study treatment period and for 6 weeks following the last dose of bezuclastinib. Male subjects must also not donate sperm during the study treatment period and for 6 weeks after the last dose of bezuclastinib.

6. STUDY PROCEDURES

6.1. INFORMED CONSENT

Subjects potentially eligible for study participation must sign an informed consent form (ICF) before initiating any study-specific assessments or procedures. Standard of care assessments or procedures that may confirm study eligibility requirements may be performed prior to a subject signing the ICF. Refer to Section 9.2 for additional details regarding the informed consent process.

6.2. INCLUSION AND EXCLUSION CRITERIA

Inclusion and exclusion criteria (Section 4.1 and Section 4.2) will be reviewed for each potential subject and the review will be documented in the subject's medical record. For subjects who are enrolled, the eligibility review will also be recorded in the eCRF.

Individuals who do not meet the criteria for participation in this study may be rescreened at the discretion of the Investigator.

6.3. ENROLLMENT

Enrollment will take place before the start of study drug administration. Once a subject has given written informed consent, the Investigator will commence all screening assessments. An Interactive Response Technology (IRT) system will be used for enrollment, randomization (in Part 1 and Part 2 Stage 1), and drug management. After all screening assessments have been completed and the EC has approved enrollment into the study, the IRT will assign each subject a Subject Identification Code.

The diagnosis and evidence of measurable disease must be evaluable according to response criteria and confirmed by the EC prior to randomization in Part 1 and Part 2 Stage 1 and prior to the first dose of study drug in Part 2 Stage 2. The EC will consist of a pathologist and at least 1 clinician who is skilled in the diagnosis and treatment of mastocytosis. The requirement for measurable disease is intended to ensure the eligibility of all subjects in Part 1 and Part 2 who are evaluable for response per modified IWG-MRT-ECNM criteria. The study allows for a subset of subjects in both Part 1 and Part 2 with AdvSM who are not evaluable per modified IWG-MRT-ECNM response criteria based on a lack of evaluable organ damage.

Subjects can be rescreened up to 2 times, at a maximum total of 3 screens, each screen consisting of all screening assessments and EC review.

6.4. MEDICAL HISTORY

Each subject's medical history will be recorded at Screening and will include documentation of all previous treatments and treatment results (eg, best response to previous disease-specific treatments and date of progression if applicable), prior procedures, current medications, and all medications used within 30 days prior to enrollment.

6.5. DEMOGRAPHICS

Demographic data will be collected during Screening. Demographic data will include sex, ethnicity, and race.

6.6. PHYSICAL EXAMINATION

A complete physical examination will be performed at baseline according to the clinical site's standard procedure and may include assessments of the following body systems: general appearance, head, eyes, ears, nose, and throat; cardiovascular; dermatologic; abdominal; genitourinary; lymph nodes; hepatic; musculoskeletal; respiratory; and neurological.

Symptom-directed physical examinations will be performed during the study according to the timepoints listed in the Schedule of Assessments (Table 1). Body systems included in targeted physical examinations will be based on Investigator judgment and evaluation of the subject's signs and symptoms to evaluate any treatment-emergent onset of AEs.

6.7. VITAL SIGNS

Vital signs to be measured include systolic/diastolic blood pressure, pulse, respiration rate, and temperature and will be performed in accordance with institutional standards at the timepoints listed in the Schedules of Assessments (Table 1). Any clinically significant vital sign abnormalities will be reported as AEs.

6.8. HEIGHT AND WEIGHT

Height will be recorded at Screening. Weight will be recorded at Screening and throughout the study at timepoints listed in the Schedule of Assessments (Table 1).

6.9. PERFORMANCE STATUS

The subject's ability to perform daily activities will be assessed at the timepoints specified in the Schedules of Assessments, according to the ECOG Performance Status grading system (Appendix J).

6.10. ELECTROCARDIOGRAM

For study conduct, ECGs will be classified as 12-lead safety ECGs. Single-read ECGs will be obtained after the subject has been resting in supine or semi-supine position for at least 5 minutes as specified in the Schedule of Assessments (Table 1). At all pre- and postdose intervals, each ECG should occur just prior to each PK blood sample collection.

The ECG results will be interpreted at the site by a medically qualified person and will also be submitted for central review. Assessed ECG parameters will include heart rate and PR, QRS, QT, and QTc intervals. QT will be corrected using Fridericia's (QTcF) formula.

6.11. STUDY DRUG DIARY

A Study Drug Diary will be dispensed to the subject at the start of each cycle. Diary information will be reviewed and/or collected from each subject during study visits. Beginning at Cycle 15, Study Drug Diaries will be provided at every other visit, per the visit scheduled outlined in the Schedule of Assessments (Table 1).

6.12. CLINICAL LABORATORY ASSESSMENTS

Clinical laboratory tests will be performed as specified in the Schedule of Assessments (Table 1). Additional tests may be performed as clinically indicated.

Clinical laboratory parameters to be obtained include:

- Hematology and clinical chemistry assessments
- Coagulation (partial thromboplastin time, prothrombin time, and international normalized ratio) assessments
- Serum tryptase levels

Local laboratories will be used for clinical laboratory safety assessments and eligibility and treatment decisions. Laboratory tests may be repeated if laboratory C-findings were assessed prior to the required time period from last therapy (see Exclusion 12). The local laboratory will provide collection supplies and perform analysis of clinical laboratory evaluations. Specimens will be appropriately processed, and laboratory reports will be provided to the Investigator. A central laboratory will also be used for the analysis of serum tryptase levels and bone marrow samples.

The clinical laboratory assessments listed in Table 7 are required study procedures. For collection timepoints, refer to the Schedules of Assessments (Table 1 and Table 2). Investigators must document their review of each laboratory safety report.

Table 7: Clinical Laboratory Assessments

Hematology:	CBC w/ differential			
Blood chemistry:	Sodium Potassium Chloride Bicarbonate Albumin	Total protein ALT AST Creatinine	Calcium Magnesium Phosphate Uric acid LDH	Bilirubin (total and direct) Glucose (non-fasting) Alkaline phosphatase Serum tryptase
Coagulation panel:	PT, PTT, INR			
Pregnancy test:	β-human chorionic gonadotropin			
Virus serology:	HIV 1, HIV 2 HBsAg, HBsAb, HBcAb Hepatitis C			

Abbreviations: Ab=antibody, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CBC=complete blood count, HBcAb=hepatitis B core antibody, HBsAb=hepatitis B surface antibody, HBsAg=hepatitis B surface antigen, HIV=human immunodeficiency virus, INR=international normalized ratio, LDH=lactic dehydrogenase, PT=prothrombin time, PTT=partial thromboplastin time.

6.13. PREGNANCY TESTING

For WOCBP, a serum pregnancy test (β-human chorionic gonadotropin) will be obtained at Screening, and a urine pregnancy test will be performed on study per the Schedule of Assessments (Table 1). The pregnancy tests will be performed by the local laboratory, following standard practice at the clinical site, and negative results must be confirmed before dosing with bezuclastinib.

6.14. PHARMACOKINETIC, PHARMACODYNAMIC, AND PHARMACOGENOMIC ASSESSMENTS

All samples will be labeled with a unique identification number that includes no subject identifying information. Samples will be stored for a duration allowed per local regulation.

Details regarding sample collection, preparation, handling, storage, and shipping instructions are provided in the Laboratory Manual.

6.14.1. Pharmacodynamic Assessments

Assessment of blood samples by droplet digital polymerase chain reaction for KIT mutational burden (D816) and variant allele frequency (VAF) will be performed by a central laboratory.

Assessment of bone marrow samples by next-generation sequencing of a myeloid gene panel to include *SRSF2*, *ASXL1*, *RUNX1*, and other relevant mutations associated with accompanying hematologic neoplasms will be performed by a central laboratory.

Assessment of buccal samples for the tryptase alpha/beta 1 (*TPSAB1*) gene to detect hereditary alpha tryptasemia will be performed by a central laboratory.

Additional exploratory analyses may be performed on blood and bone marrow samples collected to further explore pharmacodynamic markers in subjects with AdvSM.

6.14.2. Pharmacokinetic Assessments

Blood samples for PK assessments will be obtained according to the timepoints listed in the Schedule of Assessments (Table 1 and Table 2). Blood samples will be analyzed for bezuclastinib concentrations.

Blood samples for PK assessments should be taken after the ECG measurements if both are scheduled for the same study visit. The date and time of each sample collection and the date and time of the prior study drug dose must be recorded for all collected samples.

6.14.3. Pharmacogenomic Assessments

For subjects who participate in pharmacogenomic testing, a blood sample will be collected as indicated in the Schedule of Assessments (Table 2). This sample will be stored and may be analyzed to explore the relationship between genetic variability and parameters such as PK, pharmacodynamics, efficacy, tolerability, and/or safety analyses (eg, AEs).

6.14.4. Samples for Future Research

Any remaining or additional samples from protocol-specified tissue and blood collections may be used for biomarker analyses of proteins, DNA, RNA, and other molecules to understand AdvSM and/or the study medication pending subject consent (optional). Such samples may be stored until the samples are exhausted or until the repository is discontinued. The Sponsor will be the custodian of the samples and any unused samples will be destroyed at the Sponsor's discretion. The subject may request that samples be destroyed. Any samples that remain in storage may be destroyed by subject request, but data from samples already used will not be destroyed.

Collection and storage of the samples described above will be subject to discretionary approval from each center's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and the subject's informed consent.

6.15. DISEASE ASSESSMENTS

6.15.1. Bone Marrow Biopsy, Bone Marrow Aspirate, and Peripheral Blood Smears

A bone marrow assessment consisting of a bone marrow biopsy and aspiration, and peripheral blood smears will be performed according to the timepoints listed in the Schedule of Assessments (Table 1 and Table 3) and as described in Section 3.1.4. The specimen must be sent for central review of pathological response and pharmacodynamic endpoints. If a bone marrow aspirate cannot be performed, a bone marrow touch preparation should be performed. For subjects who meet WHO diagnostic criteria for SM based on the presence of mast cell aggregates in extracutaneous organs rather than bone marrow, biopsy of the extracutaneous

organ should follow the same response assessment schedule as for bone marrow biopsy (Table 1 and Table 3). Refer to the Laboratory Manual for details.

If a response (CR, CRh, PR, or CI) is achieved, a repeat bone marrow assessment will be performed 12 weeks after the initial documented response to confirm response per modified IWG-MRT-ECNM response criteria. A repeat bone marrow assessment will also be performed at least 4 weeks after disease progression to confirm progressive disease. For subjects progressing to acute myeloid leukemia or MCL, an optional repeat bone marrow at 4 weeks (±3 days) after progression may be performed. A repeat bone marrow assessment must be performed after at least 8 weeks of an initial assessment of loss of response. The specimen must be sent to the central laboratory for review and CRRC assessment.

Biopsies of other tissues may be collected at response timepoints per Investigator discretion.

6.15.2. Photography

At the discretion of the Investigator, photographs may be taken of representative area(s) of skin or other clinically relevant lesions at Screening and every 3 cycles (as applicable) if skin lesions are present at Screening or develop during the study. After 12 cycles, photography assessments will be performed every 6 cycles and as clinically indicated. Digital photographs should be obtained to record the change in the number or pigmentation of cutaneous lesions from baseline or the development of new lesions during the treatment period. Instructions for taking the photographs are provided in the Study Reference Manual.

6.15.3. Imaging

Liver and spleen size and volume will be measured by MRI and palpation to assess hepatomegaly and splenomegaly, respectively, at specified timepoints per the Schedule of Assessments (Table 1 and Table 3). A computed tomography scan may be used if MRI cannot be performed. The same method of evaluation should be followed from baseline. Radiological assessments must be sent to the central laboratory for review and will undergo central review by CRRC. Skeletal imaging is required at Screening for all subjects to assess for baseline lytic lesions and/or pathologic fractures. Changes in the size of bony lesions will be assessed with skeletal imaging. Refer to the Imaging Manual for details.

6.15.4. Quality of Life Assessments

Assessment of mastocytosis symptoms will be performed per the PGIS, PGIC, MC-QoL, and MAS (where appropriate translations are available). English language examples of these instruments are shown in Appendix I.

6.15.5. Overall Response Assessment

Response (CR, CRh, PR, and CI) will be evaluated according to modified IWG-MRT-ECNM response criteria at timepoints specified in the Schedule of Assessments (Table 1 and Table 3). Responses will be centrally adjudicated by the CRRC.

6.15.6. Survival and Disease Status

Subjects who discontinue study treatment but remain on study in long-term follow-up will be contacted as specified in the Schedule of Assessments (Table 1) for survival and disease status. Subjects will be followed for survival for at least 2 years after study drug discontinuation until death, withdrawal of consent, lost to follow-up, Investigator decision, enrollment in another therapeutic study, or the end of the study. New anticancer therapies must be recorded during this period including therapy type, start and stop dates, and response to treatment.

6.16. SAFETY ASSESSMENTS

6.16.1. Adverse Events

From the signing of the study informed consent form until the first dose of bezuclastinib, only SAEs and AEs considered related to on-protocol procedures will be collected. All AEs that are ongoing at the time of the first dose of bezuclastinib will be recorded as medical history. All new AEs will be collected from the first dose of bezuclastinib until 30 days after the last dose of study drug.

AEs will be reported as described in Section 7.2.

6.16.2. Prior and Concomitant Medications

All medications will be recorded at Screening and collected through 30 days after the last dose of bezuclastinib.

7. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

7.1. ADVERSE EVENTS

7.1.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE can arise from any use of the medicinal (investigational) product and from any route of administration, formulation, or dose, including overdose. The definition of an AE also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not AEs.

7.1.2. Definition of a Serious Adverse Event

An SAE is any AE that results in one of the following outcomes:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Note: The following are not considered SAEs in this study:

- Hospitalization for elective or preplanned treatment for a pre-existing condition unrelated to the condition under study and which has not worsened since the signing of informed consent.
- Hospital admission due to social or situational events (eg, conditions precluding the subject from traveling home safely during the treatment period).
- Progression of the subject's underlying disease and the signs and symptoms associated with disease progression are expected in this study population. As such, disease progression and its associated signs and symptoms (even if they lead to hospitalization,

are life-threatening, incapacitating, lead to permanent impairment or lead to death) will not be considered AEs/SAEs and will not be collected accordingly.

7.1.3. Adverse Events of Clinical Interest

AEs of clinical interest in this study are defined as the following AEs of Grade 3 or higher severity regardless of causality or seriousness: QTc prolongation, hepatic events, and bleeding events.

7.2. PROCEDURES FOR RECORDING AND REPORTING ADVERSE EVENTS

7.2.1. Adverse Event Recording

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

After the ICF is signed, site personnel will note any change in the condition(s) and the occurrence and nature of any AEs. From the signing of the study informed consent form until the first dose of bezuclastinib, only SAEs and AEs considered related to on-protocol procedures will be collected. TEAEs will be recorded from the start of study treatment until 30 days after the last dose of study drug.

All AEs (serious and non-serious) will be monitored until resolved, stabilized, or returned to baseline status during study participation.

After receipt of any study drug, all AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded via eCRF.

Laboratory abnormalities or other abnormal assessments (eg, physical examination findings, vital signs, ECGs) should only be recorded as AEs if clinically significant (ie, requiring medical or surgical intervention); abnormalities that lead to investigational therapy discontinuation, delay, or interruption; or abnormalities associated with clinical signs or symptoms.

Whenever possible, the clinical diagnosis, rather than the laboratory result or signs and symptoms, should be reported by the Investigator (eg, anemia vs decreased hematocrit) as 1 comprehensive event.

If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the eCRF. If a diagnosis is subsequently established, all previously reported AEs should be replaced based on the single diagnosis.

The AE term should be reported in standard medical terminology when possible.

7.2.2. Severity Assessment

AE severity will be graded using the NCI-CTCAE v5.0.

If the intensity (grade) changes within a day, the maximum intensity (grade) should be recorded. If the intensity (grade) changes over a longer period of time, the changes should be recorded as separate events (with separate onset and stop dates for each grade).

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met the criteria for an SAE.

7.2.3. Causality Assessment

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study treatment.

Investigators will be instructed to report their assessment of the potential relatedness of each AE to bezuclastinib via eCRF.

An Investigator causality assessment (Not Related, Unlikely Related, Possibly Related, or Related) must be provided for all AEs (both serious and non-serious). This assessment must be recorded in the eCRF and SAE forms as appropriate.

Not Related/Unrelated	Exposure to the study treatment did not occur, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to the study treatment
Unlikely Related	The study treatment and the AE were not closely related in time, and/or the AE could be explained more consistently by causes other than exposure to the study treatment product
Possibly Related	The study treatment and the AE were reasonably related in time, and the AE could be explained equally well by causes other than exposure to the study treatment product
Related	The study treatment and the AE were reasonably related in time, and the AE was more likely explained by exposure to the study product than by other causes, or the study treatment was the most likely cause of the AE

7.2.4. Serious Adverse Event Reporting

All SAEs that occur following the signing of informed consent are to be reported within 24 hours from the point in time when the Investigator becomes aware of the SAE. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. All SAEs must be reported whether or not they are considered causally related to the investigational product. SAE forms will be provided to each clinical site. The information collected will include subject number, a narrative description of the event and an assessment by

the Investigator as to the severity of the event and relatedness to bezuclastinib. Follow-up information on the SAE may be requested by the Sponsor or its designee.

Any SAE that is ongoing when the subject completes or discontinues the study (with the exception of subjects who withdraw consent) will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

Contact information for reporting SAEs is provided in the Operations Manual.

If an Investigator becomes aware of an SAE after the subject's participation in the study has ended that is considered related to study treatment, the Investigator should report the SAEs to the Sponsor.

7.2.5. Adverse Events of Clinical Interest Reporting

AEs of clinical interest are to be reported to the Sponsor per the same timelines and methods as SAEs.

7.2.6. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are considered at least possibly related to the investigational product or procedure by the Investigator and are not consistent in nature or severity with the reference safety information contained within the IB. Expectedness for bezuclastinib will be assessed per the reference safety information contained in the current bezuclastinib IB.

The United States 21 Code of Federal Regulations 312.32 and European Union Clinical Trials Regulation and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs; the Sponsor has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

7.2.6.1. Deaths

All on-treatment deaths, regardless of relationship to study treatment, will be reported within 24 hours per SAE reporting guidelines, with the exception of deaths due to disease progression (as noted above).

Death should be considered an outcome and not a distinct event. The underlying medical diagnosis or suspected diagnosis that caused or contributed to the fatal outcome should be reported when possible.

7.2.6.2. Pre-existing Medical Conditions

A pre-existing medical condition is one that is present during screening or before the first administration of study drug. Such conditions should be recorded on the Medical History eCRF. A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens after study treatment has been administered.

7.2.6.3. Overdose or Incorrect Administration

Any study treatment overdose or incorrect administration should be noted on the eCRF.

An overdose or incorrect administration is not an AE unless it results in untoward medical effects.

7.2.6.4. Exposure During Pregnancy

Pregnancy data will be collected during this study for all subjects. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure. All pregnancies occurring following exposure to bezuclastinib (in subjects or female partners of subjects) are to be reported in the same time frame as SAEs using the Pregnancy Report Form. The course of all pregnancies, including perinatal and neonatal outcome, regardless of whether the subject has discontinued participation in the study, will be followed until resolution, including follow-up of the health status of the newborn to 6 weeks of age.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that investigational product may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and many may meet criteria for an SAE (such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

A pregnancy or positive pregnancy test must be reported immediately using the Pregnancy Report Form to the contact information noted. The Investigator must follow-up and document the course and outcome of all pregnancies even if the subject was discontinued from the study. All outcomes of the pregnancy (from a female subject or the partner of a male subject) must be reported on the Pregnancy Report Form by the Investigator after he/she has gained knowledge of the delivery or elective abortion.

Any SAE that occurs during pregnancy must be reported on the SAE form (eg, maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) in accordance with SAE reporting procedures.

The effects of administration of the study drug regimen on the pregnant female or the developing fetus are unknown. Refer to Section 5.7.4 for detailed information regarding contraception requirements for female and male subjects and pregnancy testing requirements.

8. STATISTICAL METHODS AND DATA ANALYSIS

8.1. GENERAL STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan (SAP) will be finalized before database lock and will document the analysis methods, data handling procedures, the handling of missing data, and other statistical analysis issues. Statistical analyses will be performed using SAS® software version 9.4 or higher. Data for Part 1, Part 2 Stage 1, and Part 2 Stage 2 will be analyzed separately.

8.2. DETERMINATION OF SAMPLE SIZE

Approximately 28 subjects will be randomized 1:1:1:1 into 4 dose cohorts (Formulation A) in Part 1, including up to 4 subjects who are non-evaluable per modified IWG-MRT-ECNM response criteria based on lack of evaluable organ damage per modified IWG-MRT-ECNM criteria. It was determined that approximately 6 subjects evaluable per modified IWG-MRT-ECNM response criteria per group (24 total) would allow for ruling out an ORR of 60% or higher if a dose group had an ORR estimate of 16.7% or less (ie, if the ORR for a dose is 1/6, the upper bound of the 1-sided 90% confidence interval is 51.0% via a Clopper-Pearson exact confidence interval). Dose decisions will be based on an assessment of safety, biomarker, and clinical efficacy, and PK endpoints at each dose, with summary statistics and figures being used to illustrate dose-response.

Part 2 of the study will enroll approximately 75 subjects who are evaluable per modified IWG-MRT-ECNM criteria and up to an additional 15 subjects with AdvSM who are non-evaluable per modified IWG-MRT-ECNM response criteria at study entry.

For Part 2 Stage 1, approximately 20 subjects who are evaluable per modified IWG-MRT-ECNM will be randomized in a 1:1 ratio to receive bezuclastinib 150 mg QD or 300 mg QD (Formulation B). It was determined that approximately 10 subjects evaluable per modified IWG-MRT-ECNM response criteria per group would allow for ruling out an ORR of 60% or higher if a dose group had an ORR estimate of 30.0% or less (ie, if the ORR for a dose is 3/10, the upper bound of the 1-sided 90% confidence interval is 55.2% via a Clopper-Pearson exact confidence interval). The determination of the optimal dose will be based on totality of the data including assessment of safety, biomarker and clinical efficacy, and PK endpoints at each dose level.

For Part 2 Stage 2, approximately 55 subjects who are evaluable per modified IWG-MRT-ECNM response criteria will be enrolled. The null hypothesis is that ORR for subjects who received bezuclastinib treatment will be the same as the historical control (28%) (RYDAPT SmPC, 2021). Assuming the ORR for subjects who received bezuclastinib is 60%, 55 evaluable subjects will provide at least 90% power to reject the null hypothesis based on a Chi square test at one-sided alpha of 0.025.

Once approximately 20 subjects have been enrolled in Part 2 Stage 1, enrollment may continue until the dose for Part 2 Stage 2 is confirmed. Following enrollment of 20 subjects in Part 2 Stage 1 and prior to analysis of Part 2 Stage 2 data, enrolled subjects will receive either 150 mg

and/or 300 mg based on ongoing review of available data and following IDMC approval. Of the additional subjects who may be enrolled, those who receive the dose selected for Part 2 Stage 2 will contribute to the Stage 2 analysis population.

The inclusion of up to 4 subjects in Part 1 and up to approximately 15 additional subjects in Part 2 Stage 2 who are non-evaluable per modified IWG-MRT-ECNM is intended to provide a broader understanding of efficacy including subjects with AdvSM without evaluable organ damage at baseline.

8.3. MULTIPLICITY ADJUSTMENTS

There is no multiplicity adjustment planned for this study.

8.4. ANALYSIS SETS

Analysis sets will be defined for each part and stage and for evaluable and non-evaluable subjects separately.

8.4.1. Screened Population

The Screened Population will include all subjects who sign informed consent.

8.4.2. Intent-to-Treat Analysis Set

For Part 1 and Part 2 Stage 1, the Intent-to-Treat (ITT) Analysis Set will include all randomized subjects.

For Part 2 Stage 2, the ITT Analysis Set will include all subjects who received study drug.

The ITT Analysis Set will be the primary population for efficacy analysis.

8.4.3. Modified ITT Analysis Set

The Modified ITT Analysis Set will include all ITT subjects who received at least 1 dose of bezuclastinib and had at least 1 post-baseline response assessment.

8.4.4. Response-Evaluable Analysis Set

The Response-Evaluable Analysis Set includes subjects who are evaluable per modified IWG-MRT-ECNM criteria who enrolled in the study at least 20 weeks before the data cutoff, ie, all subjects enrolled within 20 weeks will be excluded from the analysis regardless of study discontinuation status. The minimum required follow up time to observe a confirmed response is 20 weeks. This analysis set will be used when not all subjects have been followed long enough to observe a confirmed response.

8.4.5. Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least 1 dose of bezuclastinib. This population will be used for all safety assessments.

8.4.6. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set will include all subjects who received at least 1 dose of bezuclastinib and have at least 1 measurable postdose concentration.

8.4.7. Pharmacodynamic Analysis Set

The Pharmacodynamic Analysis Set will include all subjects who received at least 1 dose of bezuclastinib and have at least 1 measurable postdose pharmacodynamic evaluation.

8.5. Treatment Assignment, Randomization, and Stratification

Subjects in Part 1 will be randomized to receive bezuclastinib (Formulation A) in a 1:1:1:1 (50 mg BID:100 mg BID:200 mg BID:400 mg QD) manner. Randomization will be stratified by evaluability per modified IWG-MRT-ECNM response criteria (ie, evaluable vs non-evaluable).

Subjects in Part 2 Stage 1 will be randomized to receive bezuclastinib (Formulation B) in a 1:1 (150 mg QD:300 mg QD) manner. Randomization will be stratified by prior treatment with TKI (ie, yes vs no).

Subjects in Part 2 Stage 2 will receive bezuclastinib at the selected optimal dose based on data from Part 1 and Part 2 Stage 1.

8.6. Background Characteristics

8.6.1. Subject Disposition

The number and percentage of subjects in each disposition category (eg, enrolled, included in each analysis set, completing a given number of treatment cycles, discontinuing treatment, and discontinuing study, with a breakdown of the reasons for discontinuation) will be summarized by dose cohort.

8.6.2. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by dose cohort for the Safety Analysis Set: sex at birth, race, age at Screening, disease type (ASM, SM-AHN, or MCL), and ECOG performance status. These parameters will be summarized by incidence (n, %). Additional parameters may be specified in the SAP.

8.7. Efficacy Analyses

The primary efficacy endpoint for subjects who are evaluable per modified IWG-MRT-ECNM response criteria is ORR, defined as the percentage of subjects classified as confirmed responders (CR, CRh, PR, or CI) according to the response assessment based on modified IWG-MRT-ECNM response criteria by CRRC assessment (see Table 8). Analysis of the primary efficacy endpoint will be performed on the ITT Analysis Set for Part 1, Part 2 Stage 1, and Part 2 Stage 2, separately. For the purposes of dose selection, subjects who had dose reductions will be treated as non-responders for their assigned dose arm as a sensitivity analysis. For each dose

group, summary statistics including the number and proportion of confirmed responders with 95% confidence intervals will be presented.

Other efficacy assessments include DOR, TTR, and PFS, based on modified IWG-MRT-ECNM, PPR, and OS. The endpoints based on modified IWG-MRT-ECNM response criteria will be summarized using the ITT Analysis Set. Sensitivity analysis for selected efficacy endpoint will be summarized using the mITT analysis set.

All efficacy endpoints will be summarized by study part/stage (Part 1, Part 2 Stage 1, and Part 2 Stage 2) and dose cohort. Efficacy endpoints will be listed as well. When appropriate, subjects across study parts and by disease subtype may also be grouped.

Table 8: Response Category for Responder Definition by Subject Type

Responder	Modified IWG-MRT-ECNM Criteria
Yes	Complete Remission (CR)
	Complete Remission with Incomplete Hematologic Recovery (CRh)
	Partial Remission (PR)
	Clinical Improvement (CI)
No	Stable Disease (SD)
	Progressive Disease
	Loss of Response
	Not Evaluable

Source: Gotlib et al, 2013.

The summaries for the following endpoints will be provided along with 95% confidence intervals. Individual subject responses will also be represented using waterfall plots.

- Number (%) of subjects in each tumor response category
- Number (%) of subjects who met the Overall Responder definition (CR+CRh+PR+CI)
- Number (%) of subjects who met the Complete Remission criteria (CR+CRh)
- Number (%) of subjects who met the criteria for PPR

For Part 2 Stage 2, ORR will be tested against null hypothesis of response rate 0.28 using Chi square test at one-sided alpha of 0.025.

For the following endpoints, PFS and OS will be summarized using Kaplan-Meier Product-Limit survival analysis, including the estimates of 25%, 50%, and 75% percentiles and 95% confidence intervals, and DOR and TTR will be summarized with mean and standard error (if data warrant):

- DOR, defined as the time from the date of first CR, CRh, PR, or CI to the date of disease progression or death from any cause, whichever occurs first. DOR can only be determined in subjects who have CR, CRh, PR, or CI.

- TTR, defined as the time from the date of randomization/first dose of study drug until the first documented response (CR, CRh, PR, or CI). Time to best response will also be calculated.
- PFS, defined as the date of randomization/first dose of study drug to the date of first documented confirmed disease progression or death from any cause, whichever occurs first.
- OS, defined as the date of randomization/first dose of study drug to the date of death from any cause.

The following censoring rules will apply to subjects who survive at the end of the study:

- All subjects will be censored at the last date of study participation.
- Subjects who are lost to follow-up and subjects who discontinued study for any reason will be censored at the last date of contact.

An assessment of OS and PFS will be performed with and without censoring for subsequent therapy.

Changes in spleen and liver sizes will be assessed by MRI and palpation.

Evaluation of biomarkers of mutation burden and VAF in bone marrow or other samples as appropriate before and after treatment with bezuclastinib ex vivo. Potential biomarkers will be correlated with clinical outcomes.

8.8. QUALITY OF LIFE ANALYSES

The PGIC and change and percent change from baseline in the patient-reported outcomes and quality of life scales PGIS, MC-QoL, and MAS (Appendix I) will be summarized by study part and stage (Part 1, Part 2 Stage 1, or Part 2 Stage 2) and dose cohort. These endpoints will be listed as well.

8.9. SAFETY ANALYSES

Safety will be assessed by vital signs, hematology and chemistry laboratory evaluations, ECGs, and AEs, including all TEAEs, treatment-related AEs, SAEs, and AEs leading to dose modification.

The primary safety endpoint is the incidence of TEAEs. The secondary safety endpoints include extent of exposure (PK), changes in laboratory parameters, and changes in ECGs.

AEs will be reported according to the NCI CTCAE version 5.0 or higher and coded according to the latest MedDRA version available at the time of database creation. The number and percent of subjects with any AE will be presented by System Organ Class and Preferred Term for each cohort and will be summarized by cohort. Vital signs, laboratory parameters, and ECG intervals will be summarized and listed by timepoint by study part.

AEs will be categorized according to MedDRA System Organ Class and Preferred Term. Additional subcategories will be based on event intensity (severity graded according to NCI CTCAE version 5.0) and relationship to study drug.

Deaths, SAEs, AEs of clinical interest, and AEs leading to study drug discontinuation will be tabulated on a per subject basis, as warranted by the data. These endpoints will be listed.

8.10. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

PK samples will be taken at various timepoints before and after dosing with bezuclastinib. Standard PK parameters will be estimated using noncompartmental methods. Bezuclastinib plasma concentrations and PK parameters will be summarized by study part and/or stage, dose and visit.

A number of pharmacodynamic parameters will be measured. Blood and bone marrow will be obtained at various timepoints throughout the study to determine the effects of bezuclastinib on PK/pharmacodynamic relationships, including *KIT* D816V mutation allele burden and serum tryptase levels as a measure of pharmacodynamic activity as a single agent. Histopathologic response will be evaluated based on the percent of mast cell infiltration in the bone marrow. At each timepoint, each of these parameters will be summarized by study part and dose cohort. In addition, the parameters over time will be plotted for each subject. An analysis of pre-study versus on-study samples will be performed. If data are sufficient, graphical exploratory analysis of PK/pharmacodynamic relationships may be performed.

8.11. EXPLORATORY ANALYSES

Exploratory analyses will include pharmacodynamic markers (including *KIT* D816V mutation allele burden) and their relationship with clinical safety, efficacy, and PK, and an exploration of the changes in C-findings. The proportion of subjects with resolution of C-findings (including resolution of hypoalbuminemia and changes in the size of lytic lesions) will be assessed. Change in the number or pigmentation of cutaneous lesions will be assessed by photographs taken per standard of care.

9. STUDY ADMINISTRATION

9.1. GOOD CLINICAL PRACTICE STATEMENT

This study is to be performed in accordance with the protocol, the Declaration of Helsinki, the International Council on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and all applicable local regulatory requirements.

9.2. INFORMED CONSENT

The Sponsor or its designee will provide a sample patient ICF for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH and GCP and must adhere to the IRB/IEC requirements and the ethical principles that have their origin in the Declaration of Helsinki.

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

The subject's signature (and date of signature) must be obtained on the ICF before any study-specific assessments or procedures are conducted.

The Investigator(s) must maintain the original, signed and dated ICF. A copy of the signed and dated ICF must be given to the subject.

The ICF and any other written information provided to the subjects will be revised whenever important new information becomes available that may be relevant to the patient's consent, or if there is an amendment to the protocol that necessitates a change to the content of the patient's informed consent. The Investigator will inform the subjects of changes in a timely manner and will ask the subjects to confirm continuation of their participation in the study by their signature on the revised ICF (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/IEC in advance of use. Any additional approvals from the initial ICF should be forwarded to the Sponsor.

9.3. PATIENT CONFIDENTIALITY

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by the Sponsor or its representative(s) will be identified by subject number and study code.

The written ICF will also explain that for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, and an IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include the patient's medical history.

The Investigator must ensure that the subjects' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by

their assigned subject number and study code. Documents not for submission to the Sponsor, such as signed ICF, should be maintained in strict confidence by the Investigator.

9.4. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE REQUIREMENTS

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC at each clinical trial site. The Principal Investigator (PI) must submit written approval to the Sponsor before he or she can enroll any patient into the study.

The PI is responsible for informing the IRB/IEC of any amendment to the protocol. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB/IEC annually or as applicable.

Progress reports and notifications of SAEs will be provided to the IRB/IEC according to regulations and guidelines.

9.5. STUDY MONITORING

Monitoring and auditing procedures approved by the Sponsor will be followed, to comply with GCP guidelines.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by a representative or designee of the Sponsor (site monitor) and will include review of the 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 subject confidentiality is maintained.

The site monitor will ensure that the investigation is conducted per protocol design and regulatory requirements by frequent communications (eg, letter, e-mail, telephone, and fax).

Regulatory authorities, the IRB/IEC, the Institutional Biosafety Committee, and other appropriate institutional regulatory bodies, and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for 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.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its designee may conduct a quality assurance audit.

9.6. ETHICS REVIEW

The final study protocol and corresponding ICF must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor or its designee before he or she can enroll any subject into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising

used to recruit subjects for the study and any written information to be provided to subjects (eg, drug diaries). The protocol (and corresponding ICF, if applicable) must be re-approved by the IRB or IEC upon receipt of amendments and annually, if local regulations require.

IRB/IEC approval and all materials approved by the IRB for this study must be maintained by the Investigator and made available for inspection.

The PI at each study site is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or its designee will provide this information to the PI.

Progress reports will be provided to the IRB or IEC per local regulations and guidelines.

9.7. DATA HANDLING AND RECORDKEEPING

9.7.1. Case Report Form Completion

The Sponsor or its designee will provide the clinical sites with access to an eCRF for each subject. The Investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data reported in a subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator or designated representative should complete the eCRF as soon as possible after information is collected. The Investigator must sign and date the eCRF to endorse the recorded data.

9.7.2. Inspection of Records

The Sponsor or its designee will be allowed to conduct site visits to the investigation facilities for monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks (if applicable), drug accountability records, subject medical records, other study source documents, and other records relative to study conduct.

9.7.3. Retention of Records

The study Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval or, if not approved, for 2 years after the discontinuation of the study drug investigational development, or per applicable regulatory requirements.

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.

9.7.4. Publication Policy

All information regarding the study drug is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required. Study results will be published in accordance with local and national regulations.

The information obtained from the clinical study may be presented at medical congresses or used for scientific exchanges or educational purposes. The information obtained from the clinical study may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the Investigator and/or the Investigator's institution.

The results of this study will be published in accordance with local regulations and guidance. Authorship eligibility will be determined in accordance with the International Committee of Medical Journal Editors authorship recommendation guidelines.

The Sponsor has full rights over any invention, discovery, or innovation, patentable or not, that may occur when performing the study.

10. LIST OF REFERENCES

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391-2405.

AYVAKIT US Prescribing Information. Blueprint Medicines Corporation, Cambridge, MA 2021.

AYVAKIT SmPC. (2021, 2021). Blueprint Medicines (Netherlands) B.V. , 2021, from https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf.

Chang VT, Hwang SS, Feuerman M, Kasimis BS, Thaler HT. The memorial symptom assessment scale short form (MSAS-SF). Cancer 2000;89(5):1162-1171.

El Hussein S, Chifotides HT, Khoury JD, Verstovsek S, Thakral B. Systemic Mastocytosis and Other Entities Involving Mast Cells: A Practical Review and Update. Cancers (Basel) 2022;14(14).

Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 2012;30(33):4098-4103.

Garcia-Montero AC, Jara-Acevedo M, Teodosio C, 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):2366-2372.

Gilreath JA, Tchertanov L, Deininger MW. Novel approaches to treating advanced systemic mastocytosis. Clin Pharmacol 2019;11:77-92.

Gotlib J, Gerds AT, Bose P, et al. Systemic mastocytosis, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2018;16(12):1500-1537.

Gotlib J, Pardanani A, Akin C, 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):2393-2401.

Gotlib J, Radia D, George T, et al. Avapritinib induces responses in patients with advanced systemic mastocytosis (AdvSM), regardless of prior midostaurin therapy. Proc EHA 2020:EP1079.

Jara-Acevedo M, Teodosio C, Sanchez-Munoz L, et al. Detection of the KIT D816V mutation in peripheral blood of systemic mastocytosis: diagnostic implications. Mod Pathol 2015;28(8):1138-1149.

Jawhar M, Schwaab J, Álvarez-Twose I, et al. MARS: Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis. J Clin Oncol 2019;37(31):2846-2856.

Jennings S, Russell N, Jennings B, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract 2014;2(1):70-76.

Kasamon YL, Ko CW, Subramaniam S, et al. FDA approval summary: midostaurin for the treatment of advanced systemic mastocytosis. Oncologist 2018;23(12):1511-1519.

Magliacane D, Parente R, Triggiani M. Current concepts on diagnosis and treatment of mastocytosis. Transl Med UniSa 2014;8:65-74.

Mayerhofer M, Gleixner KV, Hoelbl A, et al. Unique effects of KIT D816V in BaF3 cells: induction of cluster formation, histamine synthesis, and early mast cell differentiation antigens. J Immunol 2008;180(8):5466-5476.

NCCN Systemic Mastocytosis. NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw Version 2.2019:16, 12; 10.6004/jnccn.2018.0088.

NCCN Systemic Mastocytosis. National Comprehensive Cancer Network. Accessed November 23, 2021 Version 3.2021.

Nemunaitis J, Bauer S, Blay JY, et al. Intrigue: Phase III study of ripretinib versus sunitinib in advanced gastrointestinal stromal tumor after imatinib. Future Oncol 2020;16(1):4251-4264.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-655.

Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. Am J Hematol 2019;94(3):363-377.

Rossignol J, Polivka L, Maouche-Chretien L, et al. Recent advances in the understanding and therapeutic management of mastocytosis. F1000Res 2019;8.

RYDAPT SmPC. (2021, Updated 2021). Novartis Europharm Ltd. Retrieved 2021, from https://www.ema.europa.eu/en/documents/product-information/rydapt-epar-product-information_en.pdf.

RYDAPT US Prescribing Information (Revised 4/2017). RYDAPT US Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corp.

Shomali W, Gotlib J. The new tool "KIT" in advanced systemic mastocytosis. Hematology Am Soc Hematol Educ Program 2018;2018(1):127-136.

Shomali W, Gotlib J. Response Criteria in Advanced Systemic Mastocytosis: Evolution in the Era of KIT Inhibitors. Int J Mol Sci 2021;22(6).

Siebenhaar F, Sander B, Ho LHT, et al. Development and validation of the mastocytosis activity score. Allergy 2018;73(7):1489-1496.

Siebenhaar F, von Tschirnhaus E, Hartmann K, et al. Development and validation of the mastocytosis quality of life questionnaire: MC-QoL. Allergy 2016;71(6):869-877.

Smyth LA, Collins I. Measuring and interpreting the selectivity of protein kinase inhibitors. J Chem Biol 2009;2(3):131-151.

Trent J, Tap W, Chugh R, et al. The potent and selective KIT inhibitor PLX9486 dosed in combination with sunitinib demonstrates promising progression free survival (PFS) in patients with advanced gastrointestinal stromal tumor (GIST): Final results of a Phase 1/2 study. Annual meeting of the Connective Tissue Oncology Society (vitual oral presentation). 2020.

Ustun C, Arock M, Kluin-Nelemans HC, et al. Advanced systemic mastocytosis: from molecular and genetic progress to clinical practice. Haematologica 2016;101(10):1133-1143.

Vaes M, Benghiat FS, Hermine O. Targeted treatmentoptions in mastocytosis. Front Med (Lausanne) 2017;4:110.

Valent P, Akin C, Hartmann K, et al. Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal. Hemasphere 2021;5(11):e646.

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

von Mehren M, Serrano C, Bauer J, et al. INVICTUS: A phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as ≥ 4th-line therapy in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753). Ann Oncol 2019;30, S5:v925-v926.

Wagner A, Tap W, Shields A. A phase I pharmacokinetic and pharmacodynamic study of PLX9486 alone and in combination with the KIT inhibitors pexidartinib or sunitinib in patients with advanced solid tumors and gastrointestinal stromal tumor (GIST). ASCO Meeting Abstracts. 2018;36(15suppl):11509.

APPENDIX A. WHO 2022 DIAGNOSTIC CRITERIA OF SYSTEMIC MASTOCYTOSIS AND C-FINDINGS

Diagnosis of SM will be based WHO 2022 diagnostic criteria and requires the presence of at least 1 major criterion and at least 1 minor criterion or at least 3 minor criteria.

Major criterion:

Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s).

Minor criteria:

- >25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in dense and diffuse mast cell infiltrates in BM or other extracutaneous organ(s). [a]
- Activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT* [b] in the bone marrow or other extracutaneous organ(s).
- Mast cells in bone marrow, blood, or other extracutaneous organ(s) aberrantly express one or more of the following antigens: CD2, CD25, CD30. [c]
- Baseline serum tryptase concentration >20 ng/mL in the absence of a myeloid AHN. [d] In the case of a known HAT, the tryptase level should be adjusted. [e]

Abbreviations: AHN=associated hematologic neoplasm, HAT=hereditary alpha-tryptasemia, SM=systemic mastocytosis.

[a] In tissue sections, an abnormal mast cell morphology counts in both a dense infiltrate and a diffuse mast cell infiltrate. In the bone marrow smear, an atypical morphology of mast cells does not count as an SM criterion when mast cells are located in or adjacent to bone marrow particles. Morphologic criteria of atypical mast cells were referenced in the consensus proposal (Valent et al, 2021).

[b] Any type of *KIT* mutation is considered a minor SM criterion when published solid evidence regarding its transforming behavior is available (an overview of potentially activating *KIT* mutations was provided in the supplementary material of Valent et al, 2021).

[c] Expression has to be confirmed by either flow cytometry or immunohistochemistry or by both techniques.

[d] Myeloid neoplasms can lead to increased serum tryptase levels; thus, this criterion does not count in cases of SM-AHN.

[e] A possible method of adjustment has been proposed for known HαT (Valent et al, 2021); the basal tryptase level is divided by 1 plus the extra copy numbers of the alpha tryptase gene. For example, when the tryptase level is 30 and 1 extra copy of the alpha tryptase gene is found, the HαT-corrected tryptase level is 15 (30/2 = 15), and therefore, it is not a minor SM criterion in this case.

Adapted from El Hussein et al, 2022.

C-Findings:

C-Findings are indicative of organ damage produced by mast cell infiltration (should be confirmed by biopsy if possible).

1. Bone marrow dysfunction caused by neoplastic mast cell infiltration manifested by ≥1 cytopenia: absolute neutrophil count $<1.0 \times 10^9$/L, hemoglobin level <10 g/dL, and/or platelet count $<100 \times 10^9$/L
2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension

3. Skeletal involvement, with large osteolytic lesions (if the size of the lesion is ≥2 cm, it is considered large) with or without pathological fractures (pathological fractures caused by osteoporosis do not qualify as a C-finding). Small osteolytic and/or sclerotic lesions do not define advanced SM
4. Palpable splenomegaly with hypersplenism (defined as platelet count <100,000 due to sequestration from the large spleen)
5. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates (recommended to be in combination with 1 additional C-finding for eligibility)

APPENDIX B. 2016 WHO SYSTEMIC MASTOCYTOSIS VARIANTS

ISM
1. Meets the general criteria for SM 2. No C-findings 3. No evidence of an AHN 4. Low mast cell burden 5. Skin lesions are often present
Bone Marrow Mastocytosis
1. As above for ISM, but with BM involvement and no skin lesions
Smoldering SM
1. Meets the general criteria for SM 2. ≥2 B-findings; no C-findings 3. No evidence of an AHN 4. Does not meet criteria for MCL
SM-AHN‡
1. Meets the general criteria for SM 2. Meets the criteria for an AHN (ie, a myelodysplastic syndrome, myeloproliferative neoplasm, acute myeloid leukemia, lymphoma, or another hematologic neoplasm classified as a distinct entity in the WHO classification)
ASM§
1. Meets the general criteria for SM 2. ≥1 C-finding 3. Does not meet criteria for MCL 4. Skin lesions are usually absent
MCL¥
1. BM aspirate smears show ≥20% mast cells 2. In classic cases, mast cells account for ≥10% of the peripheral blood WBCs, but the aleukemic variant (in which mast cells account for <10%) is more common 3. Mast cell variants include: a. Acute MCL [≥1 C-finding(s)] vs. chronic MCL (no C-findings) b. MCL with an AHN vs MCL without and AHN c. Primary (de novo) vs secondary MCL (arising from another SM variant) 4. Skin lesions are usually absent

Abbreviations: AHN=associated hematologic neoplasm, ASM=aggressive systemic mastocytosis, BM=bone marrow, ISM=indolent systemic mastocytosis, MCL=mast cell leukemia, MDS=myelodysplastic syndromes, MPN=myeloproliferative neoplasms, SM=systemic mastocytosis, SM-AHN=SM with an associated hematologic neoplasm, WBC=white blood cell, WHO=World Health Organization.

‡ Usually, a myeloid neoplasm (ie, MDS, MPN, MDS/MPN, chronic eosinophilic leukemia, not otherwise specified, or acute myeloid leukemia). Lymphoid neoplasms (ie, multiple myeloma and chronic lymphocytic leukemia) constitute <10% of associated hematologic neoplasms.

§ ASM with 5% to 19% mast cells in BM aspirate smears is referred to as ASM in transformation and reflects evolution toward MCL.

¥ The aleukemic MCL variant (in which mast cells account for <10% of circulating white blood cells) is more common than cases with ≥10% circulating mast cells, which are more aggressive; MCL has also been divided into chronic (C-findings absent) and acute (C-findings present).

Adapted from Gotlib et al, 2013.

APPENDIX C. MEASURABLE C-FINDINGS PER MODIFIED IWG-ERT-ECNM

Measurable C-findings (ie, organ damage) allowed for eligibility (per modified IWG-MRT-ECNM consensus response criteria: eligibility and response criteria for CI):

	mIWG-MRT-ECNM Organ Damage Eligible for CI Response	**mIWG-MRT-ECNM CI Response Criteria**
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 (Grade 3) at least 28 days apart over 12 weeks before the start of treatment with one procedure performed 6 weeks before the start of treatment	1. Complete resolution of symptomatic ascites or pleural effusion (including trace or minimal on radiographic imaging)* AND 2. No longer in need of diuretic(s) for ≥12 weeks OR 3. No therapeutic paracenteses or thoracentesis for ≥12 weeks
Liver function abnormalities	≥ Grade 2 abnormalities in direct bilirubin (>1.5×ULN), AST (>3.0×ULN), ALT (>3.0×ULN), or ALP (>2.5×ULN) in the presence of: 1. Ascites *and/or* 2. Clinically relevant portal hypertension, *and/or* 3. Liver MC infiltration that is biopsy-proven *or* 4. Other causes for 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	Symptomatic or non-symptomatic spleen that is palpable >5 cm below the left costal margin and patient endorses symptoms of discomfort and/or early satiety	≥35% reduction in spleen volume based on 3D MRI or CT scan (when available), or else ≥50% reduction in palpable splenomegaly, for ≥12 weeks
Neutropenia	≥Grade 3 ANC (<1.0×10⁹/L)	≥100% increase in the ANC and an absolute increase ≥0.5×10^9/L for ≥12 weeks (with allowance for CRh)
Anemia (transfusion-independent)	≥Grade 2 Hgb (<10 g/dL)	An increase in Hgb of ≥2 g/dL that is maintained for ≥12 weeks (with allowance for CRh)
Anemia (transfusion-dependent)	Transfusion of ≥6 units PRBCs in the 12 weeks before the start of treatment with the most recent transfusion occurring within the 4 weeks before the start of	Transfusion independence for ≥12 weeks and maintenance of Hgb ≥8.5 g/dL at the end of the 12-week

	mIWG-MRT-ECNM Organ Damage Eligible for CI Response	**mIWG-MRT-ECNM CI Response Criteria**
	treatment *and* RBC transfusions are only considered as part of the baseline criteria if they are administered for Hgb ≤8.5 g/dL *and* are not associated with bleeding, hemolysis, or therapy	period of response duration (with allowance for CRh)
Thrombocytopenia (transfusion-independent)	≥Grade 2 thrombocytopenia (<75×10⁹/L)	≥100% increase in the platelet count and an absolute platelet count increase of ≥50×10^9/L and no need for platelet transfusion for ≥12 weeks (with allowance for CRh)
Thrombocytopenia (transfusion-dependent)	1. Transfusion of ≥6 units of apheresed platelets during the 12 weeks preceding treatment AND 2. ≥2 units transfused in the previous 4 weeks AND 3. Transfusions administered only for a platelet count <20×10⁹/L	Transfusion-independence for ≥12 weeks and maintenance of platelet count ≥20×10^9/L (with allowance for CRh)

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, BM=bone marrow, CI=clinical improvement, CRh=complete recovery with incomplete hematologic recovery, CT=computed tomography, Hgb=hemoglobin, IWG-MRT-ECNM=International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, LFT=liver function test, MC=mast cell, mIWG-MRT-ECNM=modified International Working Group- Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, MRI=magnetic resonance imaging, PRBC=packed red blood cell, RBC=red blood cell, ULN=upper limit of normal.

CRh (CR with partial hematologic recovery) requires the following minimum levels for peripheral blood counts: absolute neutrophil count ≥0.5×10^9/L with normal differential (absence of neoplastic mast cells and blasts <1%) and platelet count ≥50×10^9/L and hemoglobin ≥8.0 g/dL.

*Radiologic use of the term “trace” or “minimal” for ascites or pleural effusion indicates a substantial improvement of pretreatment pathologic fluid accumulation, which required medical intervention. These terms are acceptable in the absence of the radiologists’ use of the term(s) “complete disappearance” or “resolution” to describe the change in ascites or effusion.

APPENDIX D. MODIFIED (M)IWG-ERT-ECNM CRITERIA FOR OVERALL RESPONSES IN PATIENTS WITH ADVSM

Response Assessment	mIWG-MRT-ECNM Response Criteria
Complete remission (CR)*	Requires all 4 of the following criteria and response duration must be ≥12 weeks: No presence of compact neoplastic mast cell aggregates in the BM or other biopsied extracutaneous organ Serum tryptase level <20 ng/mL† Peripheral blood count remission defined as: ANC ≥1×10^9/L with normal differential (absence of neoplastic mast cells 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)‡
CR with partial recovery of peripheral blood counts (CR**h**)* *Requires all criteria for CR be met and response duration must be ≥12 weeks; however, patient may have residual cytopenias.*	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 mast cells and blasts <1%) and Platelet count >50×10^9/L and Hgb level >8.0 g/dL
Partial Remission (PR)*	Requires all 3 of the following criteria, and response duration must be ≥12 weeks, in the absence of both CR and PD: Reduction by ≥50% in neoplastic mast cells in the BM and/or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage Reduction of serum tryptase level by ≥50%† Resolution of ≥1 biopsy-proven or suspected SM-related organ damage (C-finding[s])‡
Clinical Improvement (CI)*	Response duration must be ≥12 weeks Requires ≥1 of the nonhematologic and/or hematologic response criteria to be fulfilled in the absence of CR, CRh, PR, or PD
Stable disease (SD)	Not meeting criteria for CR, CRh, PR, CI, or PD
Progressive Disease (PD)§	Requires at least 1 element from the criteria below; duration must be ≥4 weeks:

Response Assessment	mIWG-MRT-ECNM Response Criteria	
	Baseline	*Post-Baseline*
	Any grade 2 non-hematologic organ damage	Worsening by 1 grade *and* minimum 100% increase (doubling) of laboratory abnormality
	≥Grade 2 albumin	Worsening by 1 grade *and* decrease by ≥0.5 g/dL
	≥Grade 3 nonhematologic organ damage	Minimum 100% increase (doubling) of laboratory abnormality
	≥Grade 2 transfusion-independent anemia or thrombocytopenia	New transfusion dependence of ≥4 units of RBCs or platelets at 8 weeks
	Transfusion-dependent anemia or thrombocytopenia	≥100% increase in the average transfusion frequency for an 8-week period compared with the 12 weeks preceding treatment
	≥Grade 3 neutropenia	>50% decrease in neutrophil count *and* Absolute decrease of neutrophil count of ≥0.25×10^9/L *and* Grade 4 (<0.5×10^9/L)
	Baseline spleen size ≤5 cm or not palpable	Development of at least 10 cm palpable symptomatic splenomegaly *or* Increase in spleen volume ≥25%
	Baseline 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, CR_h, PR, or CI or downgrading of CR/CRh that must be for ≥8 weeks. Downgrading of CR to PR, or PR to CI is considered as such but is not considered a loss of response unless CI is also lost for ≥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 recovery, CRh=CR with incomplete hematologic recovery, Hgb=hemoglobin, IWG-MRT-ECNM=International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, LOR=loss of response, MC=mast cell, mIWG-MRT-ECNM=modified International Working Group- Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, PD=progressive disease, PR=partial response, RBC=red blood cell, SM=systemic mastocytosis.

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

† 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).

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

§ 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.

Adapted from NCCN Systemic Mastocytosis, Version 3.2021.

APPENDIX E. COMPARISON OF IWG-MRT-ECNM AND MODIFIED (M)IWG-MRT-ECNM RESPONSE CRITERIA FOR CLINICAL IMPROVEMENT (CI)

	IWG-MRT-ECNM Definition	IWG-MRT-ECNM Response Criteria	mIWG-MRT-ECNM Modifications
Non-hematologic C-Findings			
Ascites or pleural effusions	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 the start of treatment with one procedure performed 6 weeks before the start of treatment	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* No therapeutic paracenteses or thoracentesis for ≥12 weeks	As IWG-MRT-ECNM
Liver function abnormalities	≥Grade 2 abnormalities in direct bilirubin (>1.5 × ULN), AST (>3.0 × ULN), ALT (>3.0 × ULN), or ALP (>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 identified cause of abnormal liver function	Reversion of ≥1 LFTs to normal range for ≥12 weeks	As IWG-MRT-ECNM
Hypoalbuminemia	≥Grade 2 hypoalbuminemia (<3.0 g/dL)	Reversion of albumin to normal range for ≥12 weeks	As IWG-MRT-ECNM
Marked symptomatic splenomegaly	A spleen that is palpable **>5 cm** below the left costal margin and **patient endorses symptoms** of discomfort and/or early satiety	≥50% reduction in palpable splenomegaly (or ≥35% reduction in spleen volume based on 3D MRI or CT scan) and no endorsement of discomfort and/or early satiety for ≥12 weeks	Definition: Symptomatic or non-symptomatic splenomegaly palpable ≥5 cm below left costal margin. Response criteria: ≥35% reduction in spleen volume based

	IWG-MRT-ECNM Definition	IWG-MRT-ECNM Response Criteria	mIWG-MRT-ECNM Modifications
			on 3D MRI or CT scan for ≥12 weeks
Hematologic C-Findings			
Neutropenia	≥Grade 3 ANC (<1.0 × 10^9/L)	≥100% increase *and* an absolute increase ≥0.5 × 10^9/L for ≥12 weeks	As IWG-MRT-ECNM
Anemia (transfusion-independent)	≥Grade 2 Hgb (<10 g/dL)	An increase in Hgb ≥2 g/dL that is maintained for ≥12 weeks	As IWG-MRT-ECNM
Anemia (transfusion-dependent)	Transfusion of ≥6 units PRBCs in the 12 weeks before the start of treatment *and* Most recent transfusion occurring during the 4 weeks before the start of treatment *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	As IWG-MRT-ECNM
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	As IWG-MRT-ECNM
Thrombocytopenia (transfusion-dependent)	Transfusion of ≥6 units of apheresed platelets during 12 weeks preceding treatment *and* ≥2 units transfused during 4 weeks preceding treatment *and* Transfusions administered for platelet count <20 × 10^9/L	Transfusion independence for ≥12 weeks *and* maintenance of platelet count ≥20 × 10^9/L	As IWG-MRT-ECNM

Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, CT=computed tomography, Hgb=hemoglobin, IWG-MRT-ECNM=International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, LFT=liver function test, MC=mast cell, mIWG-MRT-ECNM=modified International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, MRI=magnetic resonance imaging, N/A=not applicable, PRBC=packed red blood cell, ULN=upper limit of normal.

CRh (CR with partial hematologic recovery) requires the following minimum levels for peripheral blood counts: absolute neutrophil count ≥0.5×10^9/L with normal differential (absence of neoplastic mast cells and blasts <1%) and platelet count ≥50×10^9/L and hemoglobin ≥8.0 g/dL.

Adapted from: Shomali et al, 2021.

APPENDIX F. COMPARISON OF IWG-MRT-ECNM AND MODIFIED (M)IWG-MRT-ECNM CRITERIA FOR RESPONSES IN PATIENTS WITH ADVSM

Response	IWG-MRT-ECNM Criteria for Response	mIWG-MRT-ECNM Modifications
Complete remission*	Requires all 4 of the following criteria, and response duration must be ≥12 weeks: • No presence of compact neoplastic mast cell aggregates in the BM or other biopsied extracutaneous organ • Serum tryptase level <20 ng/mL† • Peripheral blood count remission defined as: o ANC ≥1 × 10^9/L with normal differential (absence of neoplastic mast cells and blasts <1%) *and* o Platelet count ≥100 × 10^9/L *and* o Hgb level ≥11 g/dL • Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (C-findings)‡	As IWG-MRT-ECNM
CR with partial recovery of peripheral blood counts*	Not included	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 mast cells and blasts <1%) *and* • Platelet count >50 × 10^9/L *and* • Hgb level >8.0 g/dL
Partial remission*	Requires all 3 of the following criteria, and response duration must be ≥12 weeks, in the absence of both CR and PD: • Reduction by ≥50% in neoplastic mast cells in the BM and/or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage • Reduction of serum tryptase level by ≥50%† • Resolution of ≥1 biopsy-proven or suspected SM-related organ damage (C-finding[s])‡	As IWG-MRT-ECNM

<table>
<tr><th>Response</th><th colspan="2">IWG-MRT-ECNM Criteria for Response</th><th>mIWG-MRT-ECNM Modifications</th></tr>
<tr><td>Clinical improvement*</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 in the absence of CR, PR, or PD</td><td>As IWG-MRT-ECNM, plus absence of CR/CRh</td></tr>
<tr><td>Stable disease</td><td colspan="2">Not meeting criteria for CR, PR, CI, or PD</td><td>Not meeting criteria for CR/CRh, PR, CI, or PD</td></tr>
<tr><td rowspan="10">Progressive disease§</td><td colspan="2">Requires at least one element from the criteria below; duration must be ≥8 weeks:</td><td>As IWG-MRT-ECNM; duration must be ≥4 weeks</td></tr>
<tr><td>Baseline</td><td>Post baseline</td><td></td></tr>
<tr><td>Any grade 2 non-hematologic organ damage</td><td>Worsening by one grade and
Minimum 100% increase (doubling) of laboratory abnormality</td><td rowspan="7">Elements are per IWG-MRT-ECNM</td></tr>
<tr><td>≥Grade 2 albumin</td><td>Worsening by one grade and
Decrease by ≥0.5 g/dL</td></tr>
<tr><td>≥Grade 3 non-hematologic 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 at 8 weeks of ≥4 units of RBCs or platelets</td></tr>
<tr><td>Transfusion-dependent anemia or thrombocytopenia</td><td>≥100% increase in the average transfusion frequency for an 8-week period compared with the 12 weeks preceding treatment</td></tr>
<tr><td>≥Grade 3 neutropenia</td><td>>50% decrease in neutrophil count and
Absolute decrease of neutrophil count of ≥0.25 × 10^9/L and grade 4 (<0.5 × 10^9/L)</td></tr>
<tr><td>Baseline spleen size of not palpable or ≤5 cm</td><td>Development of at least 10 cm palpable symptomatic splenomegaly</td><td>Development of at least 10 cm palpable symptomatic splenomegaly or
Increase in spleen volume ≥25%</td></tr>
<tr><td>Splenomegaly >5 cm</td><td>>50% worsening and
Development of ≥10 cm of palpable symptomatic splenomegaly compared with the baseline value</td><td>>50% worsening and
Development of ≥10 cm of palpable symptomatic splenomegaly compared with the baseline value or
Increase in spleen volume ≥25%</td></tr>
</table>

Response	IWG-MRT-ECNM Criteria for Response	mIWG-MRT-ECNM Modifications
Loss of response	Loss of a documented CR, PR, or CI that must be for ≥8 weeks. Downgrading of CR to PR, or PR to CI is considered as such but is not considered a loss of response unless CI is also lost for ≥8 weeks. The baseline value for LOR is the pretreatment measurement(s) and not the nadir values during response.	As IWG-MRT-ECNM, plus loss or downgrading of CR/CRh

Abbreviations: ANC=absolute neutrophil count, BM=bone marrow, CI=clinical improvement, CR=complete recovery, CRh=CR with partial hematologic recovery, Hgb=hemoglobin, IWG-MRT-ECNM=International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, LOR=loss of response, MC=mast cell, mIWG-MRT-ECNM=modified International Working Group-Myeloproliferative Neoplasms Research and Treatment European Competence Network on Mastocytosis, PD=progressive disease, PR=partial response, RBC= red blood cell, SM=systemic mastocytosis.

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, PR, SD, PD, and loss of response 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 (e.g., gastrointestinal tract bleeding in the case of worsening anemia/transfusion-dependence) should be undertaken before assigning the designation PD or loss of response in a patient with worsening of baseline ≥grade 2 organ damage.

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

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

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

§ Preservation of at least one CI finding permits a patient to maintain the response of CI if one or more CI findings are lost but none meet criteria for PD. However, if one 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.

APPENDIX G. PURE PATHOLOGIC RESPONSE CRITERIA

The parameters of PPR criteria are described below. PPR criteria attempt to overcome potential challenges and obstacles posed by complex C-finding assessments. These criteria are restricted to changes in bone marrow mast cell burden and serum tryptase level, and additionally assess the degree of molecular response by assessing reduction in *KIT* D816V mutant allele burden using a sensitive assay with a limit of detection in the range of ~0.1%.

Response Category	Definition
Complete remission with full (CR) or partial (CRh) hematologic recovery (a)	Bone marrow mast cell aggregates eliminated and serum tryptase <20 ng/mL
Molecular complete remission (molecular CR/molecular CRh)	*KIT* D816V mutant allele fraction falls below limit of detection by sensitive assay (b)
Partial remission (PR)	≥50% reduction in bone marrow mast cells and serum tryptase level
Stable disease (SD)	Not in a CR, PR, or PD
Progressive disease (PD)	Transformation to acute myeloid leukemia (AML) or mast cell leukemia (MCL)

Abbreviations: AML=acute myeloid leukemia, ANC=absolute neutrophil count, CR=complete remission, CRh=complete remission with partial hematologic recovery, Hgb=hemoglobin, MC=mast cell, MCL=mast cell leukemia, PD=progressive disease; PR=partial remission, SD=stable disease.

(a) Partial hematologic recovery: 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.

(b) *KIT* D816V allele-specific polymerase chain reaction or digital droplet assay with sensitivity ~0.1%.

Source: Shomali et al, 2021.

APPENDIX H. EXAMPLES OF STRONG CYP3A4 INHIBITORS AND INDUCERS

Inhibitors	Inducers
ceritinib	barbiturates
clarithromycin	brigatinib
idelasib	carbamazepine
indinavir	efavirenz
itraconazole	enzalutamide
ketoconazole	glucocorticoids (a)
nefazodone	lorlatinib
nelfinavir	modafinil
ribociclib	nevirapine
ritonavir	oxcarbazepine
saquinavir	phenobarbital
telithromycin	phenytoin
voriconazole	pioglitazone
	rifabutin
	rifampin
	St. John's wort
	troglitazone

Abbreviations: AUC=area under the concentration-time curve, CYP=cytochrome P450.

Note: This list is not comprehensive and is intended for guidance only. Please refer to the associated website (https://drug-interactions.medicine.iu.edu/MainTable.aspx) for a current list of CYP3A4 inhibitors and inducers.

A strong inhibitor is one that causes a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

(a) Refer to Section 5.7.2 for allowed steroidal medication use during the study.

Source: Indiana University website: https://drug-interactions.medicine.iu.edu/MainTable.aspx (accessed 02 January 2021).

APPENDIX I. QUALITY OF LIFE ASSESSMENT TOOLS

AI-1. PATIENT GLOBAL IMPRESSION OF SEVERITY SCALE

Patient Global Impression of Severity in Symptoms Overall due to Advanced Systemic Mastocytosis (PGIS – Overall Symptoms)

Please choose the response below that best describes the severity of your symptoms overall due to your mastocytosis over the past week.

- □ None
- □ Mild
- □ Moderate
- □ Severe
- □ Very severe

Patient Global Impression of Severity of Gastrointestinal Symptoms due to Advanced Systemic Mastocytosis (PGIS – GI Symptoms)

Please choose the response below that best describes the severity of your gastrointestinal symptoms (e.g. abdominal pain, diarrhea, nausea, vomiting) due to your mastocytosis over the past week.

- □ None
- □ Mild
- □ Moderate
- □ Severe
- □ Very severe

Patient Global Impression of Severity of Skin Symptoms due to Advanced Systemic Mastocytosis (PGIS – Skin Symptoms)

Please choose the response below that best describes the severity of your skin symptoms (e.g. spots, itching, flushing) due to your mastocytosis over the past week.

- □ None
- □ Mild
- □ Moderate
- □ Severe
- □ Very severe

AI-2. PATIENT GLOBAL IMPRESSION OF CHANGE SCALE

Patient Global Impression of Change in Symptoms Overall due to Advanced Systemic Mastocytosis (PGIC – Overall Symptoms)

Please choose the response below that best describes the overall change in your symptoms overall due to your mastocytosis, since you started taking the study medication.

- □ Very much better
- □ Much better
- □ A little better
- □ No change
- □ A little worse
- □ Much worse
- □ Very much worse

Patient Global Impression of Change in Gastrointestinal Symptoms due to Advanced Systemic Mastocytosis (PGIC – GI Symptoms)

Please choose the response below that best describes the overall change in your gastrointestinal symptoms (e.g. abdominal pain, diarrhea, nausea, vomiting) due to your mastocytosis, since you started taking the study medication.

- □ Very much better
- □ Much better
- □ A little better
- □ No change
- □ A little worse
- □ Much worse
- □ Very much worse

Patient Global Impression of Change in Skin Symptoms due to Advanced Systemic Mastocytosis (PGIC – Skin Symptoms)

Please choose the response below that best describes the overall change in your skin symptoms (eg, spots, itching, flushing) due to your mastocytosis, since you started taking the study medication.

- □ Very much better
- □ Much better
- □ A little better
- □ No change
- □ A little worse
- □ Much worse
- □ Very much worse

AI-3. MASTOCYTOSIS QUALITY OF LIFE QUESTIONNAIRE

MC-QoL

(Mastocytosis Quality of Life Questionnaire)

Questionnaire Regarding Patient's Quality of Life with Mastocytosis

Instructions: Dear patients, in the following questionnaire you will find a variety of questions regarding your quality of life. Please read through each question carefully and select one of the following five answers that best describes your symptoms. Please do not think too much about your answers, but be careful to answer all the questions. Please provide one answer per question, i.e. please mark only one box per question.

	None	Somewhat	Moderately	Very	Very Much
How severely were you affected by the following symptoms in **the last 2 weeks**?					
1. Itching	❑	❑	❑	❑	❑
2. Skin redness/swelling (wheals)	❑	❑	❑	❑	❑
3. Sudden feeling of warmth and reddening of the face (flush episodes)	❑	❑	❑	❑	❑
4. Diarrhea/loose stools	❑	❑	❑	❑	❑
5. Fatigue/exhaustion	❑	❑	❑	❑	❑
6. Headache	❑	❑	❑	❑	❑
7. Muscle or joint pain	❑	❑	❑	❑	❑
8. Difficulty concentrating	❑	❑	❑	❑	❑
	Never	**Seldom**	**Occasionally**	**Often**	**Very often**
Please indicate how often you have been limited in your daily life in the areas listed below during the **past 2 weeks** because of your mastocytosis.					
9. School/university/work	❑	❑	❑	❑	❑
10. Sport/Physical activity	❑	❑	❑	❑	❑
11. Sleep	❑	❑	❑	❑	❑
12. Sexual activity	❑	❑	❑	❑	❑
13. Leisure time	❑	❑	❑	❑	❑
14. Relationships (friends, family, partner, coworkers)	❑	❑	❑	❑	❑
	Never	**Seldom**	**Occasionally**	**Often**	**Very often**
We would like to further study difficulties and problems that may be associated with your mastocytosis using the following questions. Please answer according to your experiences from the **past 2 weeks**.					
15. In the past 2 weeks, were you tired during the day because you did not sleep well at night?	❑	❑	❑	❑	❑

MC-QoL USA (English)

16. In the past 2 weeks, did you have to change your choices of foods and drinks due to your mastocytosis?	❑	❑	❑	❑	❑
17. Have you felt less capable in the past 2 weeks due to your mastocytosis?	❑	❑	❑	❑	❑
18. Have you been burdened by the symptoms of your mastocytosis in the past 2 weeks?	❑	❑	❑	❑	❑
19. Has your choice of what to wear been restricted in the past 2 weeks due to mastocytosis?	❑	❑	❑	❑	❑
20. In the past 2 weeks, were you ever afraid you might suffer an allergic reaction due to mastocytosis?	❑	❑	❑	❑	❑
21. In the past 2 weeks, were you ever afraid that you might receive the wrong treatment if you became unconscious or suffered an accident due to your mastocytosis?	❑	❑	❑	❑	❑
22. Have you felt uncomfortable in public during the past 2 weeks due to mastocytosis?	❑	❑	❑	❑	❑
23. In the past 2 weeks, have you ever been afraid of the further worsening of your mastocytosis?	❑	❑	❑	❑	❑

	Never	Seldom	Occasionally	Often	Very often
In the past 2 weeks did you feel					
24. ...a lack of motivation?	❑	❑	❑	❑	❑
25. ...alone with your illness?	❑	❑	❑	❑	❑
26. ...concerned?	❑	❑	❑	❑	❑
27. ...sad?	❑	❑	❑	❑	❑

MC-QoL USA (English)

AI-4. MASTOCYTOSIS ACTIVITY SCORE – MAS

Instructions: Please assess the severity of your symptoms associated with mastocytosis once daily in the evening over the last 24 hours on 7 consecutive days. Please select one of the five answers for each symptom per day.

		How do you assess the severity of your today's symptoms?							
	Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Itching	not at all	□	□	□	□	□	□	□	
	mild	□	□	□	□	□	□	□	
	moderate	□	□	□	□	□	□	□	
	severe	□	□	□	□	□	□	□	
	very severe	□	□	□	□	□	□	□	(0-28) ___ ___
Skin redness/swelling (wheals)	not at all	□	□	□	□	□	□	□	
	mild	□	□	□	□	□	□	□	
	moderate	□	□	□	□	□	□	□	
	severe	□	□	□	□	□	□	□	
	very severe	□	□	□	□	□	□	□	(0-28) ___ ___
Sudden feeling of warmth and reddening of the face (Flush episodes)	not at all	□	□	□	□	□	□	□	
	mild	□	□	□	□	□	□	□	
	moderate	□	□	□	□	□	□	□	
	severe	□	□	□	□	□	□	□	
	very severe	□	□	□	□	□	□	□	(0-28) ___ ___
Diarrhea/loose stools	not at all	□	□	□	□	□	□	□	
	mild	□	□	□	□	□	□	□	
	moderate	□	□	□	□	□	□	□	
	severe	□	□	□	□	□	□	□	
	very severe	□	□	□	□	□	□	□	(0-28) ___ ___
Abdominal cramps	not at all	□	□	□	□	□	□	□	
	mild	□	□	□	□	□	□	□	
	moderate	□	□	□	□	□	□	□	
	severe	□	□	□	□	□	□	□	
	very severe	□	□	□	□	□	□	□	(0-28) ___ ___
Muscle or joint pain	not at all	□	□	□	□	□	□	□	
	mild	□	□	□	□	□	□	□	
	moderate	□	□	□	□	□	□	□	
	severe	□	□	□	□	□	□	□	
	very severe	□	□	□	□	□	□	□	(0-28) ___ ___
Fatigue/exhaustion	not at all	□	□	□	□	□	□	□	
	mild	□	□	□	□	□	□	□	
	moderate	□	□	□	□	□	□	□	
	severe	□	□	□	□	□	□	□	
	very severe	□	□	□	□	□	□	□	(0-28) ___ ___
Headache	not at all	□	□	□	□	□	□	□	
	mild	□	□	□	□	□	□	□	
	moderate	□	□	□	□	□	□	□	
	severe	□	□	□	□	□	□	□	
	very severe	□	□	□	□	□	□	□	(0-28) ___ ___
Difficulty concentrating	not at all	□	□	□	□	□	□	□	
	mild	□	□	□	□	□	□	□	
	moderate	□	□	□	□	□	□	□	
	severe	□	□	□	□	□	□	□	
	very severe	□	□	□	□	□	□	□	(0-28) ___ ___
									Total MAS (0-252) ___ ___ ___

APPENDIX J. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

GRADE	ECOG PERFORMANCE STATUS
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 housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken et al, 1982

APPENDIX K. PROTOCOL CHANGES: AMENDMENT 05, VERSION 6

Rationale for Amendment 05, Version 6

The following table describes changes between Protocol CGT9486-20-201 version 5 (dated 20 December 2021) and Version 6 (dated 20 December 2022). These changes were made accordingly in the Synopsis, Schedule of Assessments, and Study Schematic. In addition to these changes, minor editorial, formatting, and organizational changes were made.

Text added is in bold and text removed is shown with a line through it.

Detailed Tabulation of Changes in Amendment 05, Version 6

Section	Changes	Rationale
Multiple Sections	Minor corrections of errors in consistency, punctuation, and grammar.	Corrected minor errors.
Header	Changed the date.	Reflects new date for Amendment 05, Version 6.
Title Page, Study Sponsor Similar edits in: Contact Information	Updated Sponsor Address: Cogent Biosciences, Inc. ~~200 Cambridge Park Drive, Suite 2500~~ ~~Cambridge, MA 02140~~ **275 Wyman Street, 3rd Floor** **Waltham, MA 02451** USA Telephone: 617-945-5576	Updated with new contact information.

Section	Changes	Rationale
Title Page Similar edits in: Sponsor Protocol Approval Investigator's Agreement	**EudraCT:** **2021-001010-10** **NCT:** **NCT04996875** **Protocol History:** 11 February 2021 Original (Version 1) **Date (Version)** 15 March 2021 Amendment 01 (Version 2) 16 April 2021 Amendment 02 (Version 3) 06 May 2021 Amendment 03 (Version 4) 20 December 2021 Amendment 04 (Version 5) **20 December 2022 Amendment 05 (Version 6)**	Added study registration numbers. Updated Protocol History to reflect new version and date for Amendment 05, Version 6.
Throughout	"Bezuclastinib" has been incorporated in place of "CGT9486".	Updated to incorporate CGT9486's international nonproprietary name.
Synopsis	The number of study centers has been updated from approximately 42 to approximately 55 centers.	Updated to incorporate new projections.
SOA	Updated the EOT window from 3 to 7 days.	Updated to reduce patient burden.
SOA, Table 1	Added a "Randomization" line and specified "Subjects should be dosed as soon as possible after randomization and preferably within 7 days before receiving their first dose on C1D1".	Updated to limit the time between randomization and administration of first dose of study drug on C1D1.
SOA, Table 1	Reduced the frequency of MAS assessments after Cycle 15 so that it is performed on odd-numbered cycles (instead of every cycle). This is in alignment with the schedule for QOL assessments.	Updated to align with other QOL assessments and reduce patient burden.

Section	Changes	Rationale
SOA, Table 1, Section 3.1.4 Response Assessments, Section 6.15.3 Imaging	Added "Spleen palpation" as an assessment.	Included to align with the modified IWG-MRT-ECNM eligibility and response criteria.
SOA, Table 1 and Table 2	The 7- and 9-hour post-dose blood samples collected for PK and associated ECG timepoints have been replaced with an 8-hour post-dose timepoint.	To reduce patient burden, the last two timepoints for post-dose PK blood collection have been replaced with one timepoint.
SOA, Table 2 Similar edits in Section 6.14.1 Pharmacodynamic Assessments	Clarified the assessment name (below) as well as the assessment timing and associated footnote: ~~HAT~~ **Buccal** swab **for TPSAB1 gene (HAT)**	Updated for accuracy and clarity.
SOA, Table 2	Added footnote (d) to clarify that postdose blood samples for PK will be collected for subjects in Part 1 and Part 2 Stage 1.	Updated for clarity.
Section 1.2.1 Nonclinical Experience	This section has been updated to include recent nonclinical data, including safety pharmacology, toxicology, and development and reproductive toxicology study results.	Updated to include recent, relevant nonclinical data.
Section 1.2.2 Clinical Experience	Updated to include: "**In addition, clinical studies of bezuclastinib are being conducted in healthy subjects (CGT9486-21-101), subjects with nonadvanced SM (CGT9486 21-202 [Summit]), and subjects with GIST (CGT9486-21-301 [Peak]); available data are detailed in the current edition of the Investigator's Brochure (IB).**"	Updated to include information on ongoing clinical studies with bezuclastinib.

<table>
<tr><th>Section</th><th>Changes</th><th>Rationale</th></tr>
<tr><td>Section 1.3 Study Rationale</td><td>Updated the information on avapritinib.</td><td>Updated to reflect recent regulatory approval.</td></tr>
<tr><td>Section 1.3.1 Selection of Study Population</td><td>Updated: “This study will enroll subjects ~~who meet~~ with a diagnosis of AdvSM per WHO diagnostic criteria ~~for AdvSM~~ (Appendix A) ….”</td><td>Updated for clarity.</td></tr>
<tr><td>Section 1.4 Benefit/Risk Assessment</td><td>This section has been updated to provide a more detailed risk/benefit analysis.</td><td>Updated for completeness.</td></tr>
<tr><td>Section 2 Trial Objectives and Endpoints</td><td>Updated:<table><tr><th colspan="2">Part 1 and Part 2 (Secondary)</th></tr><tr><td>To evaluate additional efficacy parameters with ~~CGT9486~~ bezuclastinib in ~~patients~~ subjects with AdvSM</td><td>Duration of response (DOR), defined as the date of the first documented response (CR, CRh, PR, or CI) to date of first documented ~~and confirmed~~ disease progression or loss of response, or death from any cause, whichever occurs first, based on modified IWG-MRT-ECNM response criteria</td></tr></table></td><td>Incorporated loss of response to comprehensively define DOR outcomes.</td></tr>
<tr><td>Section 2 Trial Objectives and Endpoints</td><td>Clarified that TTR, PFS, OS are measured from the date of randomization/first dose of study drug.</td><td>Updated for consistency with the protocol.</td></tr>
</table>

<table>
<tr><th>Section</th><th>Changes</th><th>Rationale</th></tr>
<tr><td>Section 2 Trial Objectives and Endpoints</td><td>Updated:<table><tr><th colspan="2">Part 1 and Part 2 (Secondary)</th></tr><tr><td>To evaluate additional efficacy parameters with ~~CGT9486~~ bezuclastinib in ~~patients~~ subjects with AdvSM</td><td>Pure Pathologic Response (PPR), including complete remission, complete remission with partial hematologic recovery ~~of peripheral blood~~, molecular complete remission, and partial remission (Gotlib et al, 2020)</td></tr></table></td><td>Updated to reflect appropriate nomenclature.</td></tr>
<tr><td>Section 2 Trial Objectives and Endpoints</td><td>Updated:<table><tr><th colspan="2">Part 1 and Part 2 (Secondary)</th></tr><tr><td>To assess the PK of ~~CGT9486~~ bezuclastinib in ~~patients~~ subjects with AdvSM</td><td>Plasma concentrations and PK parameters (eg, area under the plasma concentration-time curve [AUC] and maximum observed plasma concentration [C_{max}]) of ~~CGT9486~~ bezuclastinib</td></tr></table></td><td>Updated for clarity.</td></tr>
</table>

<table>
<tr><th>Section</th><th>Changes</th><th>Rationale</th></tr>
<tr><td>Section 2 Trial Objectives and Endpoints</td><td>Added:<table><tr><td colspan="2">Part 1 and Part 2 (Secondary)</td></tr><tr><td>To explore the effect of bezuclastinib in subjects with AdvSM who are non-evaluable based on the modified IWG-MRT-ECNM response criteria</td><td>Incidence of AEs, SAEs, AEs leading to dose modifications, and changes from baseline in laboratory results
Pure Pathologic Response (PPR), including complete remission, complete remission with partial hematologic recovery, molecular complete remission, and partial remission (Gotlib et al, 2020)</td></tr></table></td><td>Added to clarify analyses for subjects who are non-evaluable based on the modified IWG-MRT-ECNM response criteria.</td></tr>
<tr><td>Section 2 Trial Objectives and Endpoints</td><td>Updated:<table><tr><td colspan="2">Part 1 and Part 2 (Exploratory)</td></tr><tr><td>To explore the PK/pharmacodynamic relationships</td><td><s>Blood and bone marrow to determine</s> Assessing the <s>effects of CGT9486 on PK/pharmacodynamic</s> relationships between bezuclastinib PK and pharmacodynamic markers including KIT D816V mutation allele burden <s>as a measure of pharmacodynamic activity as a single agent</s></td></tr></table></td><td>Updated for clarity.</td></tr>
</table>

Section	Changes	Rationale
Section 3 Investigational Plan	This section has been updated to incorporate a modified formulation of bezuclastinib (Formulation B) into the study. Part 2 will be conducted in 2 stages: Stage 1 will confirm the optimal dose of bezuclastinib with Formulation B and Stage 2 will consist of an expansion period. Overall, the number of planned subjects to be included in the study has decreased from approximately 140 to approximately 120. Since the totality of data from Part 1 and Part 2 Stage 1 will be used to select the optimal dose of bezuclastinib to be used in Part 2 Stage 2, the number of subjects planned for Part 1 has decreased from approximately 60 to approximately 28. Part 2 will include approximately 20 subjects in Stage 1 and approximately 55 subjects in Stage 2 who are evaluable per modified IWG-MRT-ECNM criteria; an increase from the previous number of subjects anticipated to participate in Part 2 (~60). An additional 15 subject who are non-evaluable may participate in Part 2, decreased from the previous number of 20 subjects. Based on the updated study design to conduct Part 2 in 2 stages, related edits were made throughout the protocol:	A modified formulation of bezuclastinib (Formulation B) has been developed with higher bioavailability than the original formulation (Formulation A). Part 2 has been updated to include a dose confirmation portion (Stage 1) in addition to the expansion period (Stage 2). Stage 1 will evaluate two dose levels of Formulation B: 150 mg QD, which is expected to provide clinical activity with acceptable safety and tolerability based on available data from Part 1. A higher dose level of 300 mg QD, which is still expected to provide exposures below those achieved at the recommended Phase 2 dose identified in subjects with GIST, will also be evaluated to determine if

Section	Changes		Rationale
	Section 1.3.2 Rationale for Dose and Regimen, Section 1.3.3 Rationale for Study Design	These sections have been updated to include rationale for the updated Part 2 design, and rationale for the dose and regimen for Formulation B. Given the updated study design to select a dose level based on data from Part 1 and Part 2 Stage 1, an interim analysis in Part 1 is not needed and has been removed.	an increased dose results in increased clinical activity with acceptable safety and tolerability. The confirmed optimal dose level of Formulation B will then be used in the expansion period in Stage 2.
	Section 2 Trial Objectives and Endpoints	Updated the wording of Part 1 Primary objective: To ~~determine the optimal dose of oral CGT9486 in patients~~ **identify a clinically active and tolerable systemic exposure range of bezuclastinib in subjects** with AdvSM	
	Section 2 Trial Objectives and Endpoints	Updated to include primary objectives and endpoints for Part 2 Stage 1 and Part 2 Stage 2.	
	Section 4.1 Inclusion Criteria, Criterion 2 Note	Updated to reflect the number of subjects who may be enrolled who are non-evaluable per modified IWG-MRT-ECNM response criteria	
	Section 4.4 Study Stopping Rules	Added “or Part 2 Stage 1” in the first bullet.	
	Section 5.1 Description of Bezuclastinib, Section 5.2 Bezuclastinib Administration	These sections have been updated to include descriptions of and administration guidance for Formulation A and Formulation B.	

<table>
<tr><th>Section</th><th colspan="2">Changes</th><th>Rationale</th></tr>
<tr><td></td><td colspan="2"><table>
<tr><td>Section 5.3 Randomization, Section 8.5 Treatment Assignment, Randomization, and Stratification</td><td>Specified that subjects in Part 2 Stage 1 will be randomized 1:1 to receive either 150 mg QD or 300 mg QD and will be stratified based on prior treatment of TKI.</td></tr>
<tr><td>Section 5.6 Criteria for Dose Modification</td><td>Specified formulation-specific dose reduction guidance.
Table 5 was updated accordingly.</td></tr>
<tr><td>Section 6.3 Enrollment</td><td>Updated to include Part 2 Stage 1 and Stage 2.</td></tr>
<tr><td>Section 8</td><td>Updated to include Part 2 Stage 1 and Stage 2 and related information for sample size, analysis sets, and planned analyses.</td></tr>
</table></td><td></td></tr>
<tr><td>Section 3.1.3 Part 2: Dose Confirmation and Expansion</td><td colspan="2">Updated:
<s>The study will enroll a minimum of 5 subjects with each disease subtype to ensure adequate representation across subtype.</s>
To ensure the study population reflects the general AdvSM patient population, enrollment of the SM-AHN subtype will be capped at approximately 80% (Jawhar et al., 2019).</td><td>Updated to align enrollment thresholds with prevalence of disease subtype.</td></tr>
</table>

Section	Changes	Rationale
Section 3.1.4 Response Assessments, Section 6.15 Disease Assessments	Procedures associated with response assessments (eg, bone marrow biopsy) have been updated from every 4 cycles to every 3 cycles from Cycle 6 until Cycle 12; thereafter, these assessments will be performed every 6 cycles. Confirmatory response assessments will still take place 12 weeks after an initial response. Clarified that "If ~~a~~ **an initial** response (CR, CRh, PR, or CI) is achieved **on or after C12**, a repeat bone marrow assessment will be performed 12 weeks after the initial documented response to confirm response per modified IWG-MRT-ECNM response criteria ~~by CRRC assessment~~. For clarity, a new SOA table (Table 3) has been added for response assessments. After Cycle 16, serum tryptase and blood samples for mutational analysis (*KIT* D816V burden) will be collected on even-numbered cycles (instead of odd-numbered cycles) to overlap with response assessments (updated in Table 1).	Updated to harmonize response assessments with most common clinical practice. This change streamlines response assessments and avoids back-to-back biopsies for subjects requiring 12-week confirmatory response assessments.
Section 3.1.6 Pharmacokinetic and Pharmacodynamic Assessments	Clarified that predose PK blood samples will be collected within 30 minutes before initial daily dosing.	Updated for clarity.
Section 4.1 Inclusion Criteria	Updated: "Consideration should be given to the suitability of available alternative therapies **(eg, midostaurin, avapritinib)** prior to study enrollment."	Updated to harmonize to a global protocol.

Section	Changes	Rationale
Section 4.1 Inclusion Criteria	Criterion 7 updated: "Have clinically acceptable ~~local~~ laboratory screening results (clinical chemistry, hematology) within certain limits specified below: a. Absolute neutrophil count >500/µL (subjects enrolled in Part 1 only) b. Platelet count ≥50,000/µL ~~for 2 weeks~~ prior to the first dose of study drug c. AST and ALT ≤2.5× upper limit of normal (ULN) or ≤5×ULN if there is liver involvement by AdvSM d. Direct bilirubin ≤1.5×ULN; if related to AdvSM may be ≤3×ULN e. Calculated creatinine clearance (Cockcroft-Gault) >≥40 mL/min f. Serum tryptase ≥20 ng/mL	Removed "local" for consistency within the protocol. Removed "for 2 weeks" to alleviate patient burden of requiring multiple repeat CBCs. Updated calculated creatinine clearance from ">" to "≥40 mL/min" for consistency within the protocol.
Section 5.2 Bezuclastinib Administration	Updated: "Treatment will be continuous**; there will be no gaps between cycles**."	Updated for clarity.
Section 5.6 Criteria for Dose Modification	Added: "**If another treatment-related event requiring a dose reduction occurs, the subject will not be allowed to re-escalate the dose again unless it is in the best interest of the subject per the Investigator and agreed to by the Sponsor. The Sponsor should be promptly informed prior to any decision to hold or change subject dosing.**"	Updated to harmonize to a global protocol.
Section 5.6 Criteria for Dose Modification	The dose interruption window has been extended to 28 days from 14 days.	The dose modification interruption window has been extended to 28 days to ensure adequate recovery time so that subjects benefitting from therapy can remain on study.
Section 5.6 Criteria for Dose Modification	Added: "**For risk management recommendations associated with the important potential risks of bezuclastinib, please refer to Section 6.2.4 of the current edition of the IB.**"	Updated to harmonize to a global protocol.

Section	Changes	Rationale
Section 5.7.1 Prohibited Concomitant Medications	Clarified: "Strong inhibitors or inducers of CYP3A4 may affect the metabolism of ~~CGT9486~~ **bezuclastinib** and should not be taken **systemically** by subjects within 14 days or 5 half-lives, whichever is longer, before the first dose of study drug or at any time during the study."	Updated for clarify that topical therapies (eg, antifungal creams) are allowed.
Section 5.7.3 Gasteric pH-Altering Agents	Section 5.7.2 Permitted Concomitant Medications included a paragraph with guidance on gastric pH-altering agents. This paragraph has been separated into its own section (Section 5.7.3) for clarity. The text was also updated as follows: "~~Gastric~~ **While it is unknown whether gastric** pH-altering agents ~~should be avoided where possible, as these may be expected to impact~~ **affect** the absorption and plasma exposure of ~~CGT9486. If they cannot be avoided,~~ **bezuclastinib, histamine receptor–blocking drugs may be essential in the management of symptoms of SM and should not be restricted in any way. However, proton-pump inhibitor drugs should be avoided where possible, and** the treating clinician should try to switch any **subject** ~~patient~~ receiving a proton-pump inhibitor to a histamine receptor–blocking drug, to be taken preferably 2 hours following the dose of ~~CGT9486~~ **bezuclastinib**."	Updated to align with current understanding of the impact of gastric pH-altering agents on drug absorption and for clarity.
Section 5.7.4 Contraception Requirements	This section has been updated to reflect standard contraception recommendations in accordance with country-specific guidance. Inclusion criterion 8 was updated accordingly.	Updated to harmonize to a global protocol.

Section	Changes	Rationale
Section 5.7.4 Contraception Requirements	The duration during which subjects must agree to the use of a highly effective method of contraception after the last dose of study drug has been updated from “6 months” to “6 weeks”. Similarly, egg/ovum and sperm donations are not permitted for 6 weeks after the last dose of bezuclastinib. Inclusion criterion 8 was updated accordingly.	The elimination half-life for bezuclastinib (Formulation A and B) in humans is ~2-3 days. After approximately 4 weeks (approximately 10 half-lives), >99.9% of bezuclastinib should be eliminated from systemic circulation and the systemic exposure should have decreased to a concentration that is no longer considered relevant for human teratogenicity/fetotoxicity.
Section 6.10 Electrocardiogram	This section was updated to indicate that ECGs will be single-read, rather than triplicate.	Reduced requirement to alleviate patient burden as triplicate ECGs are not currently necessary.
Section 6.12 Clinical Laboratory Assessments, Table 7 Clinical Laboratory Assessments	Removed: - From Hematology: Platelet count - From Virus serology: HSV1, HSV2, CMV (IgG and IgM Ab), and VZV	This update was made for clarity (as platelet count is included in CBC) and consistency with the protocol (as HSV1, HSV2, CMV, and VZV are not needed for inclusion).

Section	Changes	Rationale
Section 6.15.1 Bone Marrow ~~Aspirate,~~ Biopsy, **Bone Marrow** Aspirate, and Peripheral Blood Smear**s**	Updated: "The specimen must be sent for central review **of pathological** ~~for~~ response ~~per CRRC assessment~~ and pharmacodynamic endpoints." "A repeat bone marrow assessment will also be performed ~~8~~ **at least 4** weeks after disease progression to confirm progressive disease. For subjects progressing to acute myeloid leukemia or MCL, an optional repeat bone marrow at 4 weeks **(±3 days)** after progression may be performed. **A repeat bone marrow assessment must be performed after at least 8 weeks of an initial assessment of loss of response**."	Updated for consistency within the protocol as the sample will be sent for central review. Updates were made to reduce patient burden (eg, addition of the ±3-day window), and consistency (repeat bone marrow assessment to be performed after 4 weeks instead of 8 weeks to confirm progressive disease, and addition of the repeat bone marrow assessment after at least 8 weeks of loss of response).
Section 6.15.1 Bone Marrow ~~Aspirate,~~ Biopsy, **Bone Marrow** Aspirate, and Peripheral Blood Smear**s**	Added: "**For subjects who meet WHO diagnostic criteria for SM based on the presence of mast cell aggregates in extracutaneous organs rather than bone marrow, biopsy of the extracutaneous organ should follow the same response assessment schedule as for bone marrow biopsy (Table 1 and Table 3).**"	Added for consistency with WHO diagnostic criteria.

Section	Changes	Rationale
Section 6.15.6 Survival **and Disease** Status	Updated to include "disease status": "Subjects who discontinue study treatment but remain on study in long-term follow-up will be contacted as specified in the Schedule of Assessments (Table 1) for survival **and disease status**. Subjects will be followed for survival for at least 2 years after study drug discontinuation until death, withdrawal of consent, lost to follow-up, ~~AE,~~ Investigator decision, enrollment in another therapeutic study, or the end of the study. **New anticancer therapies must be recorded during this period including therapy type, start and stop dates, and response to treatment.**"	Updated for consistency within the protocol.
Section 7.2.6 Suspected Unexpected Serious Adverse Reactions	Updated the definition of SUSARs as follows: "Suspected unexpected serious adverse reactions (SUSARs) are ~~serious events~~ **SAEs** that are ~~not listed in the Investigator's Brochure (IB) and that the Investigator identifies as~~ **considered at least possibly** related to the investigational product or procedure~~.~~ **by the Investigator and are not consistent in nature or severity with the reference safety information contained within the IB. Expectedness for bezuclastinib will be assessed per the reference safety information contained in the current bezuclastinib IB.** The United States 21 Code of Federal Regulations 312.32 and European Union Clinical ~~Trial Directive 2001/20/EC~~ **Trials Regulation** and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs; the Sponsor has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances. ~~Expectedness for CGT9486 will be assessed per the IB.~~"	Updated for clarity.
Section 8.3 Multiplicity Adjustments	Added a new section.	Added for clarity.

Section	Changes	Rationale
Section 8.4 Analysis Sets	Clarified that "analysis sets will be defined for each part and stage and for evaluable and non-evaluable subjects separately." Section 8.3.3 was removed accordingly since it is redundant with the updated clarifications to analysis sets.	Updated for clarity and consistency with the updated study design.
Section 8.4.4 Response-Evaluable Analysis Set	New section added to define the Response-Evaluable Analysis Set, which will be used when not all subjects have been followed long enough to observe a confirmed response.	Added for clarity
Section 8.11 Interim Analysis	This section has been deleted since an interim analysis in Part 1 is no longer needed.	Based on the updated study design, data from Part 1 and Part 2 Stage 1 will be used to confirm the optimal dose of Formulation B to be used in Part 2 Stage 2. Therefore, an interim analysis in Part 1 is not needed.
Section 9.7.4 Publication Policy	Added: "**Study results will be published in accordance with local and national regulations.** **The information obtained from the clinical study may be presented at medical congresses or used for scientific exchanges or educational purposes. The information obtained from the clinical study may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.**" And: "**The results of this study will be published in accordance with local regulations and guidance. Authorship eligibility will be determined in accordance with the International Committee of Medical Journal Editors authorship recommendation guidelines.**"	Updated for clarity.
Appendix A	Updated to the WHO 2022 diagnostic criteria of systemic mastocytosis and C-findings.	Updated to reflect new WHO diagnostic guidelines.

Section	Changes	Rationale
Appendix C	Updated to include "≥35% reduction in spleen volume based on 3D MRI or CT scan **(when available), or else ≥50% reduction in palpable splenomegaly**, for ≥12 weeks"	Updated for accuracy.
Appendix H	Removed "Moderate Inhibitors" of CYP3A4 column.	Updated for clarity since only strong CYP3A4 inhibitors and inducers are described in Section 5.7.1. Prohibited Concomitant Medications.
AI-3	Updated to the current version of the MC-QOL.	Updated to include the current version.