A Phase 2 Study of Bezuclastinib (CGT9486), A Novel, Highly Selective, Potent *KIT* D816V Inhibitor, in Adults with Advanced Systemic Mastocytosis (Apex): Methods, Baseline Data, and Early Insights

Daniel J. DeAngelo[1], Vinod Pullarkat[2], Miguel Piris-Villaespesa[3], Tracy I. George[4, 5], Jay L. Patel[4, 5], Celalettin Ustun[6], Prithviraj Bose[7], Mark L. Heaney[8], Amanda Pilla[9], Ben Exter[9], Zamaneh Mikhak[9], Hina A. Jolin[9], Tsewang Tashi[5]

[1]Dana-Farber Cancer Institute, Boston, [2]City of Hope, Duarte, [3]Hospital Universitario Ramón y Cajal, Madrid, Spain, [4]ARUP Laboratories, [5]Huntsman Cancer Institute, University of Utah, Salt Lake City, [6]Rush University Cancer Center, Chicago, [7]The University of Texas MD Anderson Cancer Center, Houston, [8]Columbia University Medical Center, New York, [9]Cogent Biosciences, Cambridge, United States of America

Advanced Systemic Mastocytosis (AdvSM)

Disease Overview: Aggressive and life-threatening form of systemic mastocytosis (SM) that is primarily driven by mutations in *KIT* D816V and leads to uncontrolled proliferation of mast cells (MC)[1-5]

- Subtypes: aggressive SM (ASM); SM with associated hematologic neoplasm (SM-AHN); mast cell leukemia (MCL)[6]
- Based on subtype, the median overall survival ranges from <6 months to 3-4 years[4-7]

Clinicopathologic Criteria: Defined by presence of clinical and pathological findings known as C-findings

- C-findings: organ damage from MC infiltration e.g., cytopenias, hepatomegaly with liver dysfunction, ascites, splenomegaly with cytopenias, malabsorption with hypoalbuminemia, large osteolytic lesions and/or pathologic fractures[5,8,9]

Unmet Need: Significant unmet need remains given dose-limiting toxicity profiles of the limited available therapies

- Reported toxicities for marketed therapies: nausea, vomiting, diarrhea, edema, intracranial bleeding, cognitive effects[10-12]

Bezuclastinib: Preclinical Data

- Oral, selective, and potent type I tyrosine kinase inhibitor (TKI) with potent activity against *KIT* D816V, an activation loop mutation
- Preclinically, highly active with specificity for mutations in *KIT* exons 9, 11, 17, and 18, including D816V
- Spares closely related kinases (***Table 1***), has minimal brain penetration, and favorable PK properties[13]
  - Inhibition of closely related kinases have been linked to off-target toxicities, such as bleeding, edema and pleural effusions[14,15]

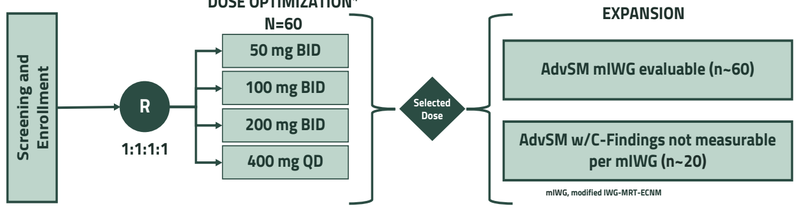
Table 1: Kinase Inhibition Profile of Clinical Stage and Approved *KIT* D816V Agents; Cell IC_{50} (nM)

Compound	*KIT* V560G/ D816V (HMC 1.2)	PDGFRα	PDGFRβ	CSF1R	FLT3	KDR
Bezuclastinib	**14**	**>10,000**	**>10,000**	**>10,000**	**>1000**	**>1000**
Avapritinib	13	53	10	249	305	>1000
BLU-263	6	21	6	161	345	>1000

Apex: Phase 2 Bezuclastinib Study Overview

- Phase 2, multi-center, open-label, 2-part clinical study to evaluate the safety, efficacy, PK, and PD of bezuclastinib in patients with AdvSM (NCT04996875; ***Fig. 1; Table 2***)

Fig. 1: Study Design



*Interim analysis (IA) will be performed after ~28 patients have completed at least 2 cycles of bezuclastinib

- Oral bezuclastinib administered once (QD) or twice (BID) daily
- Clinical activity assessed per mIWG response criteria by the Central Review Response Committee (CRRC)
- Optimal dose for Part 2 selected from Part 1 data

Table 2: Key Eligibility Criteria and Study Endpoints

Key Eligibility Criteria
• ASM, SM-AHN or MCL diagnosis per World Health Organization (WHO) 2016 criteria[14] • Measurable disease according to mIWG eligibility and response criteria for clinical improvement (CI) per central eligibility committee   • Subset of inevaluable patients per mIWG response criteria based on lack of evaluable organ damage per mIWG may be included • Clinically acceptable local lab results, including platelet count ≥50,000/μL for 2 weeks prior to first dose • Prior treatment with other TKIs (e.g., avapritinib, midostaurin) is permitted • Eastern Cooperative Oncology Group (ECOG) Performance Status 0-3 is permitted • Systemic corticosteroids (>10 mg prednisone or equivalent/day) are not permitted

	Primary Objectives	Primary Endpoints
Part 1	Determine the optimal dose of bezuclastinib	• Safety, PK, and PD assessments • Changes from baseline in laboratory results and dose modifications • Overall response rate (ORR) based on the mIWG response criteria
Part 2	Determine the efficacy of bezuclastinib at the selected optimal dose	ORR (CR, CR with incomplete hematologic recovery [CRh], PR, and CI) per mIWG as assessed by a CRRC

Apex, Phase 2 Bezuclastinib: Baseline Data + Early Insights

Baseline Characteristics: 11 mIWG-evaluable patients enrolled as of 24-May-2022; median age: 70 years; range: 48-87 (***Table 3***)

Table 3: Baseline Characteristics

Baseline Characteristics	50mg BID (N=3)	100mg BID (N=3)	200mg BID (N=3)	400mg QD (N=2)
Male, n (%)	2 (67)	3 (100)	2 (67)	2 (100)
ECOG PS 0-1	2 (67)	3 (100)	3 (100)	1 (50)
AdvSM Subtype per Central Eligibility Review, n (%)				
ASM	1 (33)	0 (0)	0 (0)	1 (50)
SM-AHN	2 (67)	2 (67)	3 (100)	1 (50)
MCL	0 (0)	1 (33)	0 (0)	0 (0)
***KIT* D816V in Whole Blood, Positive, n (%)**	3 (100)	3 (100)	2 (67)	2 (100)
Treatment Naive, n (%)	3 (100)	2 (67)	2 (67)	2 (100)
Prior Avapritinib, n (%)	0 (0)	1 (33)	1 (33)	0 (0)
Prior Midostaurin, n (%)	0 (0)	1 (33)	1 (33)	0 (0)
Median Bone Marrow MC Burden, % (range)	60 (30-70)	70 (30-80)	10 (7-30)	55 (30-80)
Median Serum Tryptase, ng/mL (range)	187 (169-605)	253 (144-1578)	83 (67.9-111)	301 (232-370)

Pharmacokinetics:

- Dose dependent increase in systemic exposure observed after the first dose
  - Steady state exposure to bezuclastinib remained above IC_{50} for inhibition of *KIT* D816V across all doses, consistent with reduction in serum tryptase

Safety and Tolerability:

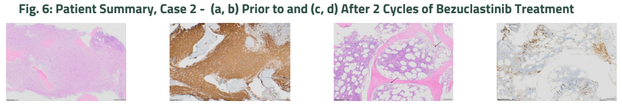
- Majority of treatment emergent adverse events (TEAE) were of low-grade with one serious adverse event (SAE) and no Grade 4 events (***Table 4***)
  - No periorbital/peripheral edema, cognitive effects or intracranial bleeding reported
- No treatment discontinuations; all patients remain on study
- Two patients dose reduced due to AEs; one re-escalated to randomized dose

Table 4: TEAE Occurring in >1 Patient and All Grade 3 Events

Preferred Term, n (%) (N=11)	TEAE		
	Grade 1/2	Grade 3	Grade 4
Anemia	2 (18)	1 (9)	0 (0)
Neutropenia	1 (9)	1 (9)	0 (0)
Thrombocytopenia	2 (18)	0 (0)	0 (0)
Diarrhea‡	0 (0)	1 (9)	0 (0)
Hypersensitivity†	0 (0)	1 (9)	0 (0)

‡ Investigator assessed as not related to treatment
† SAE of hypersensitivity (mediator flare); patient continued treatment and remains on study (See: Patient Summary; Case 2)

Fig. 6: Patient Summary, Case 2 - (a, b) Prior to and (c, d) After 2 Cycles of Bezuclastinib Treatment



(a) Diffuse marrow infiltration by MC with minimal residual trilineage hematopoiesis

(b) IHC staining: CD117 (cKIT)

(c) MC infiltration decreased, arranged in paratrabecular aggregates (arrows)

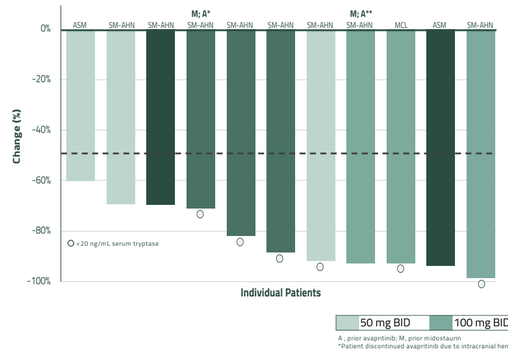
(d) IHC staining: CD117 (cKIT)

Courtesy of Guys' and St. Thomas' NHS Foundation Trust.
Investigator: Dr. Deepti Radia, BSC, MBBS, MRCPI, FRC Path, MSc Med Ed; Pathologist: Dr Yurina Miki, MBBS BSc FRCPath.

Summary of Clinical Activity:

- 11/11 patients experienced a >50% reduction in serum tryptase (***Fig. 2, 3***)
  - 6/11 patients achieved a serum tryptase level <20 ng/mL
- 8/8 patients with ≥2 cycles of treatment and available Cycle 3, Day 1 (C3D1) data achieved ≥50% reduction in bone marrow MC (***Fig. 4***)
  - 6/8 patients achieved complete clearance of MC aggregates by central review
- 8/8 patients with ≥2 cycles of treatment and available C3D1 data demonstrated decreases in *KIT* D816V variant allele fraction (VAF) by ddPCR (***Fig. 5***)

Fig. 2: Maximum Percent Change in Serum Tryptase from Baseline



A , prior avapritinib; M, prior midostaurin
*Patient discontinued avapritinib due to intracranial hemorrhage, **Patient discontinued avapritinib due to thrombocytopenia

Fig. 3: Time to Serum Tryptase Reduction and Duration on Treatment

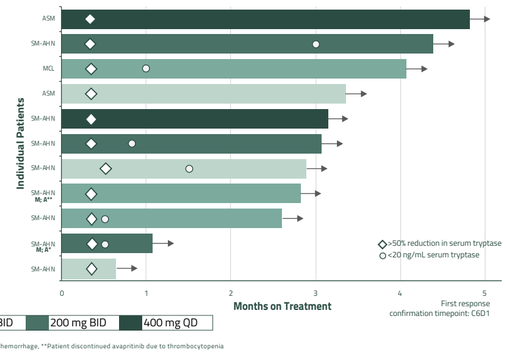


Fig. 4: Percent Change in Bone Marrow Mast Cell at C3D1

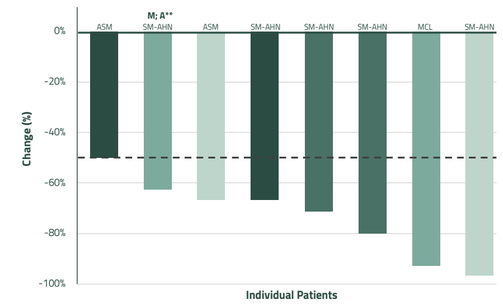
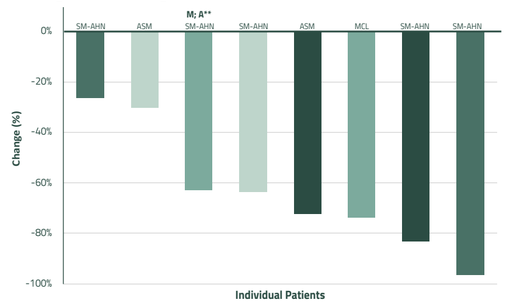


Fig. 5: Percent Change in *KIT* D816V VAF at C3D1



Patient Summaries (Treatment Ongoing)

Case 1

Background: Patient with SM-AHN, prior treatment with midostaurin (progression) and avapritinib (toxicity: Grade 3 thrombocytopenia and anemia); baseline labs: serum tryptase 1578 ng/mL, MC burden 80%, C-finding: platelets <75K/μL; randomized to bezuclastinib 100 mg BID

Safety: Grade 2 anemia; patient remains on study treatment >2 months without treatment interruption or dose reduction

Clinical Activity: 93% reduction in serum tryptase (>50% by C1D8), 63% reduction in bone marrow MC, and a 63% reduction in *KIT* D816V VAF

Case 2

Background: Patient with ASM, no prior TKI exposure. Baseline tryptase 370 ng/mL, baseline MC burden 80%, C-finding: spleen >5 cm below left coastal margin; randomized to 400 mg QD (***Fig. 6***)

Safety: Hypersensitivity (mediator flare) on C1D2, dose reduced from 400 mg QD to 200 mg QD without interruption; symptoms resolved within 24 hours; patient remains on study treatment >4 months

Clinical Activity: 94% reduction in serum tryptase (>50% by C1D8), 50% reduction in bone marrow MC, and 72% reduction in *KIT* D816V VAF

Summary

- Bezuclastinib is a highly potent and selective tyrosine kinase inhibitor that targets the *KIT* D816V mutation, the primary driver of AdvSM
- Bezuclastinib was generally well-tolerated across all dose levels
  - No reported periorbital/peripheral edema, cognitive effects or intracranial bleeding events, which have been associated with other TKIs
  - Hematological events are expected in this patient population with advanced hematologic disease, frequently presenting with baseline cytopenias related to underlying disease and/or prior therapy
- Encouraging early signs of clinical activity demonstrated by meaningful reduction in serum tryptase levels as well as reductions in MC burden, and *KIT* D816V VAF in all evaluable patients
  - Patients treated with prior KIT inhibitors, including avapritinib, demonstrated similar magnitude reductions across serum tryptase, MC burden, and *KIT* D816V VAF

Apex ADVANCED SM

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