Expanded Access Program (EAP) of Bezuclastinib in Patients with Systemic Mastocytosis (SM)

Lindsay Rein[1], Ali Malinowski[2], Jenni Nicoloro SantaBarbara[3], Ravi Jalluri[2], LouAnn Cable[2], Karyn Bouhana[2], Michelle Crow[2], Ben Exter[2], Dana Harkin[2], Jay Chatfield[2], Dana Martin[2], Rachael Easton[2], Cem Akin[4]

[1]Duke University, Durham, NC, USA; [2]Cogent Biosciences, Inc. Waltham, MA, USA; [3]Brigham and Women's Hospital, Boston, MA, USA; [4]University of Michigan, Ann Arbor, MI, USA

MPN-574

BACKGROUND

Systemic mastocytosis (SM) is a spectrum of diseases composed of 6 subtypes:

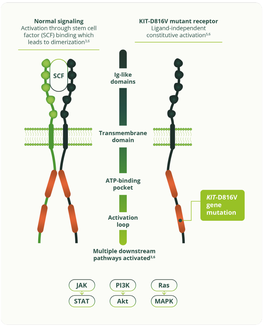
- NonAdvanced SM (NonAdvSM), which is characterized by debilitating symptomatology and reduced patient quality of life resulting from MC degranulation and mediator release, is the most common type of SM.
  - indolent SM (ISM)
  - bone marrow mastocytosis (BMM)
  - smoldering SM (SSM)
- Advanced SM (AdvSM), characterized by organ damage and dysfunction from MC infiltration, leading to decreased survival
  - aggressive SM (ASM)
  - SM with an associated hematologic neoplasm (SM-AHN)
  - mast cell leukemia (MCL)

The role of KIT in SM

- Up to 95% of SM cases are the result of gain-of-function somatic mutations in KIT tyrosine kinase[1,2]
- KIT is involved in cell proliferation, differentiation, survival, apoptosis, immune response, and inflammation[3-6]

The KIT–D816V mutation

- Found in >95% of patients with SM, located in exon 17 of the activation loop[2,5,7]
- Leads to constitutive SCF-independent mast cell proliferation, growth and activation causing the symptoms of SM[2,5,6]
- Patients with multilineage myeloid and/or lymphoid KIT D816V mutations show a higher risk of progression to more advanced forms of SM or acute leukaemia than patients with MC-restricted mutations[8]
- High-sensitivity PCR assay to detect *KIT*–D816V mutations are recommended to avoid false negative results[9]



Bezuclastinib, an investigational type I tyrosine kinase inhibitor (TKI)[10]

- Bezuclastinib is an oral, potent, and selective type 1 tyrosine kinase inhibitor (TKI) with activity against KIT D816V.
- Bezuclastinib binds the active conformation of KIT to inhibit D816V mutations[10]
  - Binds KIT-D816V in the ATP binding pocket[10-11]
  - Aims to inhibit uncontrolled mast cell proliferation and activation caused by KIT-D816V[5, 10-11]
- Bezuclastinib is being evaluated in Phase 2 studies:
  - Apex clinical trial in AdvSM (NCT04996875) is expecting top-line results by the end of 2025.
  - Summit clinical trial in NonAdvSM (NCT05186753) reported top-line results in July 2025.

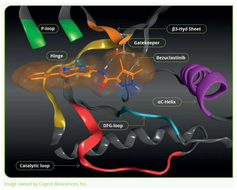


Image owned by Cogent Biosciences, Inc.

Bezuclastinib potently and selectively inhibits KIT-D816V[10]

- Oral, selective, and type I TKI with potent activity against KIT D816V, an activation loop mutation[10]
- In non-clinical models, spares closely related kinases, has minimal brain penetration, and favorable PK properties[10]
- Inhibition of closely related kinases have been linked to off-target toxicities, such as bleeding, edema, and pleural effusions[10]

Kinase inhibition profile of clinical stage and approved KIT–D816V agents; Cell IC_{50} (nm)

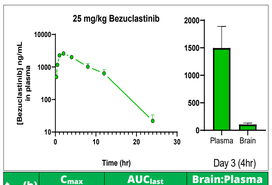
Compound	KIT V560G/D816V (HMC 1.2)	WT KIT	PDGFRα	PDGFRβ	CSF1R	FLT3	KDR
Bezuclastinib	**14**	**114**	**>10,000**	**>10,000**	**>10,000**	**>10,000**	**>10,000**
Avapritinib	13	76	53	11	447	400	>1,000
Elenestinib	5	231	20	17	161	453	>1,000

Adapted from Guarnieri *et al.* 2022.

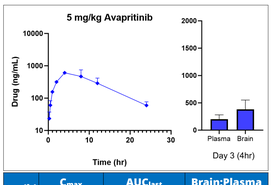
High IC50 numbers indicate low levels of activity against off-target kinases, limiting associated toxicities, e.g. bleeding, edema, hypertension, and pleural effusion

Bezuclastinib demonstrates minimal brain penetration in non-clinical models[10]

- In non-clinical models, bezuclastinib shows minimal brain penetration with a brain to plasma ratio of 0.07 compared to 2.0 for avapritinib[10]
- The absence of brain penetration is a preferred feature for a KIT A-Loop inhibitor given the CNS-related adverse events that have been observed in this targeted class[10]



$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	Brain:Plasma ratio
7	2592 ± 364	21509 ± 2558	**0.07**



$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	Brain:Plasma ratio
13	672 ± 102	6980 ± 1156	**2.0**

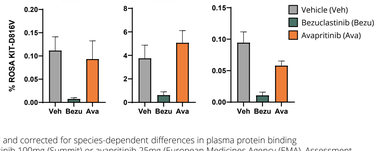
Nonclinical Data Suggests Optimal Activity Against Mastocytosis May Require Higher Exposures Than Clinically Tolerable With Available Therapy

- Mice engrafted with SCF-independent human ROSA$^{KIT\ D816V}$ cells[8] were treated daily for 8 weeks with a KIT inhibitor at doses matching clinical exposures observed in NonAdvSM patients.
- At exposures comparable to those achieved in NonAdvSM patients, only bezuclastinib led to statistically significant decreases ($p<0.05$) in mutant mast cell burden in the peripheral blood, bone marrow and spleen compared to vehicle control, while avapritinib had no significant effect.

Total Drug Exposure Ratio Measured in SM Mouse Model

	Mouse Plasma AUC_{0-24} (ng·hr/mL)[a]	NonAdvSM Clinical Plasma AUC_{0-24} (ng·hr/mL)[b]	Total Drug Exposure Ratio (mouse/clinic)
Bezuclastinib	11775	17100	**0.7X**
Avapritinib	1318	1548	**0.9X**

MC Burden in SM Mouse Model



[a]Plasma exposures were measured at study end and corrected for species-dependent differences in plasma protein binding
[b]Arithmetic mean steady state AUC for bezuclastinib 100mg (Summit) or avapritinib 25mg (European Medicines Agency (EMA). Assessment Report: Ayvakyt – European Public Assessment Report (EPAR). Published 9 Nov 2023.)

CLINICAL RESULTS FOR INVESTIGATIONAL BEZUCLASTINIB

Summit: A Phase 2 Double-Blind, Placebo-Controlled Randomized Clinical Study in Nonadvanced SM

- In Summit Part 2, bezuclastinib was superior to placebo in controlling the symptoms and reducing the markers of mast cell burden in patients with NonAdvSM, with a favorable safety profile
  - Clinically meaningful and statistically significant efficacy results across all primary and key secondary endpoints
    - The bezuclastinib arm had a mean reduction of 24.3 points in MS2D2 TSS at 24 weeks, versus the placebo arm which had a mean reduction of 15.4 points in TSS, (p=0.0002)
      - Placebo-adjusted MS2D2 TSS improvement was 8.91 points.
    - 87.4% of patients demonstrated a ≥50% reduction in serum tryptase
  - Favorable tolerability profile, positioning bezuclastinib for long-term use in chronic disease population
    - Significant majority of TEAEs reported as Grade 1 (70%) and reversible
    - 5.9% patients discontinued, all due to higher grade ALT/AST; all resolved rapidly after discontinuation
    - Other than lab abnormalities, no hepatic events reported

Apex: A Phase 2 Open-Label Clinical Study in Advanced SM

- In a Part 1 analysis of 7 patients receiving investigational bezuclastinib at a dose delivering exposure levels selected for Part 2: [14]
  - Safety and tolerability:
    - No discontinuations due to AEs with 100mg BID dose
  - Efficacy:
    - 83% overall response rate per mIWG-MRT-ECNM
    - All patients receiving 100mg BID achieved PR or better based on PPR criteria

SYSTEMIC MASTOCYTOSIS EXPANDED ACCESS PROGRAM (NCT05186753)

Aim

- The SM Expanded Access Program (EAP, NCT06915766) is designed to provide the investigational treatment bezuclastinib outside of a clinical trial to real-world patients with AdvSM or NonAdvSM who meet specific criteria including, but not limited to, having no comparable or satisfactory alternative therapy to treat the disease.

Methods

- Patients are receiving oral bezuclastinib 100mg QD (NonAdvSM) or 150mg QD (AdvSM).
- The treating physician is responsible for standard of care patient assessments and reporting of any serious adverse events.
- The duration of bezuclastinib treatment will be determined by the treating physician but may continue until regulatory approval and commercial availability per indication.
- The EAP is currently open to receive requests for access from treating physicians in the United States.

Inclusion and Exclusion Criteria

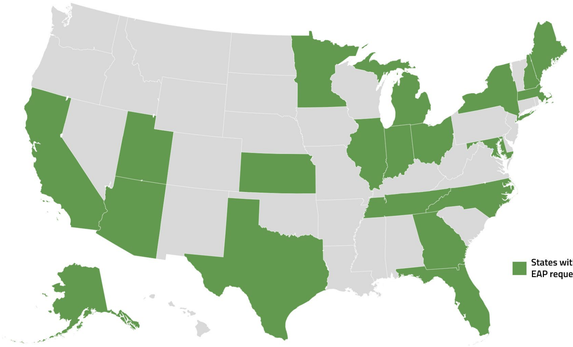
Key inclusion criteria	Key exclusion criteria
Diagnosis of any NonAdvSM or AdvSM subtypes according to WHO classification for SM	Eligibility for and/or enrolled in an ongoing bezuclastinib clinical trial
Lack of adequate disease control on current therapies	Discontinuation of investigational bezuclastinib due to toxicity or withdrawal of consent
Acceptable laboratory parameters	Pregnant or currently breastfeeding
≥18 years of age	Prior or ongoing clinically significant illness or medical or physical condition

*Other protocol-defined criteria apply.

RWE questions

- Limited patient and disease characteristics are being captured by HCPs for each patient request
- In collaboration with interested sites, additional real-world data and patient reported outcomes may be collected in the future to further understand management of SM.

Geographic Representation in United States



References: 1. Ungerstedt J *et al.* Cancers 2022; 14(16): 3942. doi: 10.3390/cancers14163942. 2. Scherber RM and Borate U. BJH 2018; 180: 11-23. 3. Gilreath JA *et al.* Clin Pharmacol 2019; 11:77-92. 4. Pardanani A. Am J Hematol 2021; 96(4): 508-25. 5. Piris-Villaespesa M and Alvarez-Twose I. Front Pharmacol 2020; 11(443): doi: 10.3389/fphar.2020.00443. eCollection 2020 (accessed September 2024). 6. Cruse G *et al.* Immunol Allergy Clin North Am 2014; 34(2): 219-37. 7. Shomali W and Gotlib J. Hematology 2018; 2018(1): 127-36. 8. Martelli M *et al.* Int J Mol Sci 2021; 21(11): 3987. 9. Gotlib J *et al.* NCCN 2024; 22(2)Dx240030. 10. Guarnieri A *et al.* Bezuclastinib is a Differentiated KIT Inhibitor that Exhibits Unique Selectivity to KIT A-loop Mutations, Minimal Brain and Favorable Pharmacokinetic Properties in Preclinical Models. Poster 147 presented at: AACR Annual Meeting 2022. Orleans, LA; 2022. 11. Wagner AJ *et al.* JAMA 2021; 7(9): 1-8. 12. Saleh et al. Blood, 2014; 124(1):111-120. 13. Rein et al. Blood, 2024. 144 (Suppl 1):4556. 14. DeAngelo et al. Blood 2024. 144 (Suppl 1) 659.

SUMMARY

〉 In up to 95% of patients, SM is driven by the somatic KIT c.2447 C>T (p.D816V) gain-of-function missense mutation.

〉 Bezuclastinib is an oral, potent, and selective type 1 tyrosine kinase inhibitor (TKI) with activity against KIT D816V.

〉 The SM Expanded Access Program (EAP, NCT06915766) is designed to provide access to the investigational treatment bezuclastinib outside of a clinical trial to real-world patients with AdvSM or NonAdvSM who meet specific criteria including, but not limited to, having no comparable or satisfactory alternative therapy to treat the disease.

〉 The EAP is currently open to receive requests for access from treating physicians in the United States. For questions or requests, please contact Medinfo@Cogentbio.com.

Presented by Lindsay Rein at the 2025 Society of Hematologic Oncology Annual Meeting

September 3-6, 2025 in Houston, TX

To obtain a digital copy of this poster, please scan the Quick Response (QR) code. Copies of this poster obtained through QR Code are for personal use only and may not be reproduced without permission from SOHO or the author of this poster

Acknowledgments/Disclosures This study was funded by Cogent Biosciences. The authors would like to acknowledge the patients who participated in the trial and those who support them, including family, caregivers, and patient advocates.