The Effect of Bezuclastinib on the Pathobiology of Advanced Systemic Mastocytosis: Results From the Pivotal Apex Trial

Tracy I. George[1], Daniel J. DeAngelo[2], Khalid Shoumariyeh[3], Tania Jain[4], Cristina Papayannidis[5], Jay L. Patel[1], Jonathan Lambert[6], Karin Hartmann[7], Jens Panse[8], Miguel Piris-Villaespesa[9], Cristina Bulai Livideanu[10], Anton Rets[1], Karen A. Moser[1], Madhu P. Menon[1], Amanda Pilla[11], Kim Dishman[11], Jenna Zhang[11], Catherine Wang[11], Rachael Easton[11], Deepti H. Radia[12]

[1]University of Utah, ARUP Laboratories, Salt Lake City, UT, USA, [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, [3]Department of Hematology, Oncology and Stem Cell Transplantation, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany, [4]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA, [5]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," Bologna, Italy, [6]Department of Haematology, University College Hospital, University College of London Hospitals NHS Foundation Trust, London, UK, [7]Division of Allergy, Department of Dermatology, Department of Clinical Research, Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland, [8]Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, Medical Faculty, RWTH Aachen University, Aachen, Germany, [9]Department of Hematology, Hospital Universitario Ramón y Cajal, Madrid, Spain, [10]CEREMAST Toulouse, Dermatology Department, Toulouse University Hospital, Toulouse, France, [11]Cogent Biosciences, Inc., Waltham, MA, USA, [12]Guy's and St. Thomas' NHS Foundation Trust, London, UK

MPN - 1161

INTRODUCTION

Bone Marrow Pathobiology Underpins the Clinical and Biological Complexity of AdvSM

- AdvSM is a life-threatening disease characterized by abnormal mast cell accumulation, driven by the gain-of-function KIT p.D816V mutation in most patients[1-4]
  - Subtypes: aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN), mast cell leukemia (MCL)
- Pathological and molecular markers of disease help determine AdvSM subtype and disease severity, monitor treatment response, and predict prognosis and survival[5-10]
  - Per 2022 WHO criteria, SM diagnosis requires 1 major plus 1 minor OR ≥3 minor criteria[5]

Major Criterion	Minor Criteria
Multifocal dense mast cell infiltrates (≥15 in aggregates) in BM or other extracutaneous organ(s)	1. **Aberrant CD25, CD30, and/or CD2 expression** on mast cells in BM, blood, or other extracutaneous organ(s) 2. **>25% atypical or spindle-shaped mast cells in infiltrates** in BM or other extracutaneous organ(s) 3. **Baseline serum tryptase >20 ng/mL** in the absence of AHN, levels should be adjusted in the case of HaT 4. **KIT p.D816V or other activating *KIT* mutation detected** In BM or other extracutaneous organ(s)

Bezuclastinib is an Investigational, Oral, Highly Selective Tyrosine Kinase Inhibitor with Potent Activity Against KIT D816V

- Results from the Apex study of bezuclastinib demonstrated favorable efficacy and safety in AdvSM[11]
- Herein we report the effect of bezuclastinib on pathological markers of SM from the pivotal portion of Apex

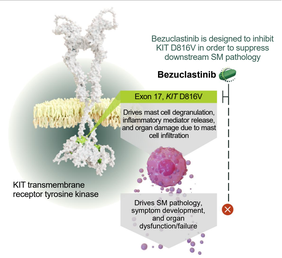


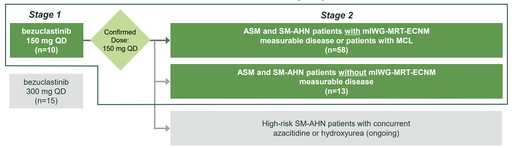
Figure developed by Cogent Biosciences, Inc.

METHODOLOGY

Apex (NCT04996875): Phase 2, Multipart, Multicenter, Open-Label Study Evaluating Efficacy and Safety of Bezuclastinib in Patients With AdvSM

Eligibility[a]

- ASM, SM-AHN, or MCL per WHO 2022 Classification
- No restrictions on prior therapy
- Serum tryptase ≥20 ng/mL
- Platelet count ≥50×10^9/L



Part 2 Endpoints

Primary: ORR (CR/CRh + PR + CI) per mIWG-MRT-ECNM criteria

Key Secondary: ORR (CR/CRh + PR) per Pure Pathologic Response (PPR) criteria

Other Secondary & Exploratory[a]: Changes in objective measures of disease (MC & BM characteristics)

- BM biopsy and aspirate, serum tryptase, and KIT p.D816V variant allele frequency (VAF) collections were tested centrally at baseline, every three 28-day cycles for the first 12 months, and then every six cycles
- Morphology, mast cell burden, aggregation, and immunophenotype (tryptase, CD25, CD30) were assessed
- Immunohistochemical (tryptase, CD25, CD30, CD34, CD117) and special (reticulin, trichrome) stains were performed on BM sections

[a]Additional criteria and endpoints are defined in the protocol.

RESULTS

Baseline Characteristics Reflected a Broad AdvSM Population

Characteristic		Bezuclastinib 150 mg QD (N=81)
Female, n (%)		23 (28)
Median age, years (range)		70 (43-87)
ECOG Performance Status, n (%)	0	22 (27)
	1	40 (49)
	≥2	19 (23)
AdvSM subtype per central eligibility review, n (%)	ASM	11 (14)
	SM-AHN[b]	57 (70)
	MCL[c]	13 (16)
***SRSF2/ASXL1/RUNX1* mutation detected in peripheral blood, n (%)**		48 (59)
Prior TKI therapy for AdvSM, n (%)		28[d] (35)
Prior midostaurin		24 (30)
Prior avapritinib		6 (7)
Prior imatinib		3 (4)

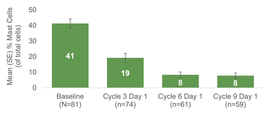
Characteristic		Bezuclastinib 150 mg QD (N=81)
Median *KIT* p.D816V in peripheral blood, % (range)		6.7 (0-91.4)
KIT p.D816V VAF detected[e], n (%)		71 (90[f])
Median BM mast cell burden, % (range)		35 (3-95)
Median serum tryptase, ng/mL (range)		191 (23-1987)
Myelofibrosis Grade, n (%)[g]	MF-0	7 (9)
	MF-1	38 (48)
	MF-2	26 (33)
	MF-3	9 (11)
ORR-Evaluable Populations, n (%)		
Patients evaluable per mIWG-MRT-ECNM criteria by Eligibility Committee		68 (84)
Patients evaluable per PPR criteria		81 (100)

- Median (range) duration of treatment at data cutoff: 63.0 (1.0-135.3) weeks

[b]AHN subtypes: CMML (n=37), MDS (n=6), MPN (n=4), MDS/MPN-U (n=10). [c]Includes 2 with MCL-AHN (MDS-MLD). [d]5 received 2 prior TKIs. [e]Droplet digital PCR limit of detection=0.03%. [f]Of 79 with baseline assessment. [g]Of 80 with baseline assessment.

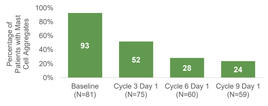
Bezuclastinib Reduced Mast Cell Burden and Cleared Pathologic Mast Cell Aggregates, the Major Criterion for SM Diagnosis, in Bone Marrow

Percentage of Mast Cells in BM Biopsies

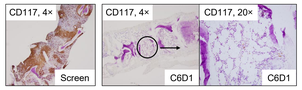


- **89%** (71/80) achieved ≥50% reduction in mast cells or clearance of aggregates postbaseline
  - Median (range) time to first ≥50% reduction: 8.3 (7.0–45.9) weeks
- **81%** (60/74) achieved clearance of mast cell aggregates postbaseline
  - Median (range) time to first clearance: 10.7 (7.0–68.1) weeks
- Mean (SE) best percent change from baseline in BM biopsy mast cells postbaseline was **–77%** (4)
  - Similarly, mean (SE) best percent change from baseline in BM aspirate mast cells postbaseline was **–61%** (11)

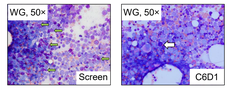
Percentage of Patients with Mast Cell Aggregates in BM[h]



[h]Percentage of patients with multifocal dense infiltrates of mast cells present (≥15 mast cells in aggregates) out of those with mast cell infiltrates present at the specified timepoint.



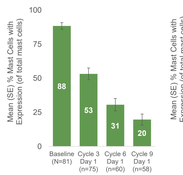
65-yo M with MCL-MDS-MLD, 1st response of PR at C3D1, best response of CR at C16D1 per PPR criteria; illustrative BM biopsy sections demonstrate clearance of MC aggregates and reduction in MC burden (brown) post-treatment



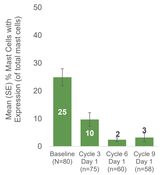
80-yo M with SM-CMML-0, 1st and best response of CR at C3D1 per PPR criteria; illustrative BM aspirate smears demonstrate reduction of promastocytes (green arrows indicate examples of these hypogranular cells) to <1%, with only a single well-differentiated MC found (white arrow) post-treatment

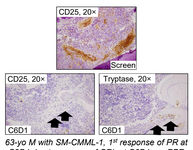
Bezuclastinib Reduced Aberrant CD25 and CD30 Expression on Mast Cells in Bone Marrow, Supporting Targeted Mast Cell Modulation

Percentage of BM Mast Cells with CD25 Expression



Percentage of BM Mast Cells with CD30 Expression

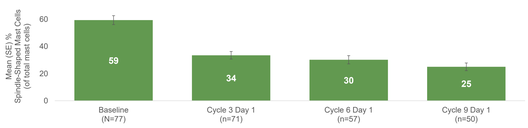


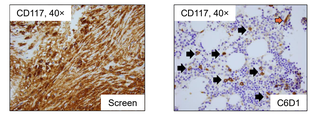


63-yo M with SM-CMML-1, 1st response of PR at C3D1, best response of CRh at C6D1 per PPR criteria; illustrative BM biopsy sections demonstrate clearance of multifocal, dense, CD25+ MC aggregates post-treatment (arrows on the left indicate examples of where MCs should be, corresponding to MCs stained brown by tryptase IHC on the right)

Bezuclastinib Reduced Atypical Mast Cell Morphology in Bone Marrow

Percentage of Spindle-Shaped Mast Cells in BM Biopsies

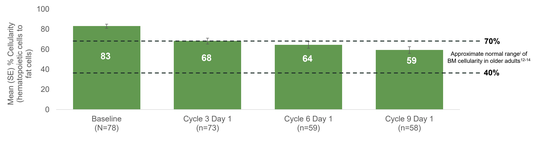




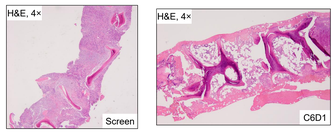
65-yo F with MCL, 1st response of PR at C3D1, best response of molecular CR at C9D1 per PPR criteria; illustrative BM biopsy sections demonstrate reduction in spindle-shaped MCs post-treatment (black arrows indicate examples of round MCs stained brown by CD117 IHC; orange arrow shows a spindle-shaped MC)

Bezuclastinib Reduced Bone Marrow Cellularity

BM Cellularity



- Hypercellularity at baseline reduced to normocellularity[12-14] as early as Cycle 3

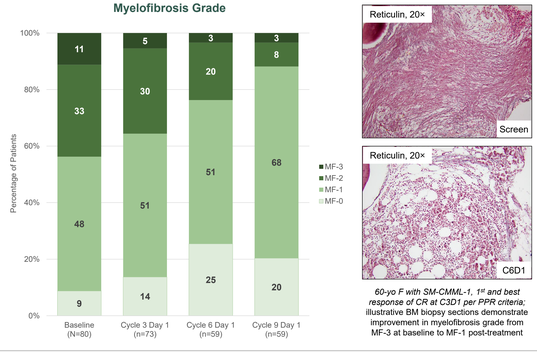


65-yo M with MCL-MDS-MLD, 1st response of PR at C3D1, best response of CR at C16D1 per PPR criteria; illustrative BM biopsy sections demonstrate hypercellularity at baseline (100%) to normocellularity (40%) post-treatment

[i]Normal BM cellularity range is age-dependent.

Bezuclastinib Treatment Led to Improvement in Myelofibrosis Grade

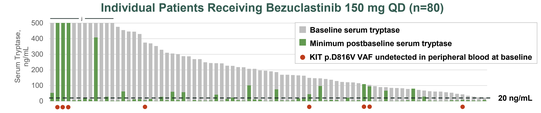
Myelofibrosis Grade



60-yo F with SM-CMML-1, 1st and best response of CR at C3D1 per PPR criteria; illustrative BM biopsy sections demonstrate improvement in myelofibrosis grade from MF-3 at baseline to MF-1 post-treatment

Bezuclastinib Reduced Serum Tryptase to Below Diagnostic Threshold Levels

Individual Patients Receiving Bezuclastinib 150 mg QD (n=80)

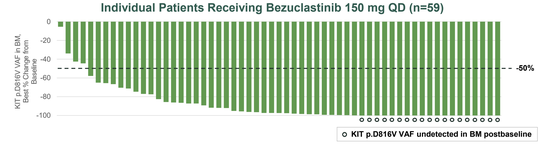


- **89%** of patients achieved >50% reduction of serum tryptase postbaseline
  - **71%** achieved serum tryptase reduction to <20 ng/mL (diagnostic threshold) postbaseline
  - **64%** achieved serum tryptase reduction to <11.4 ng/mL (normal level) postbaseline

[j]Patients with serum tryptase levels >500 ng/mL, axis is truncated for visual purposes.

Bezuclastinib Reduced KIT p.D816V Variant Allele Frequency (VAF) in Bone Marrow and Blood

Individual Patients Receiving Bezuclastinib 150 mg QD (n=59)



- **93%** of patients achieved ≥50% reduction of KIT p.D816V VAF in BM postbaseline
  - **32%** achieved undetectablek levels of KIT p.D816V VAF in BM postbaseline
- Peripheral blood results were consistent with reductions observed in BM

[k]Droplet digital PCR limit of detection=0.03%.

Bezuclastinib Demonstrated High Response Rates in AdvSM per Pure Pathologic Response (PPR) Criteria

Best Confirmed Response		All Evaluable Patients (N=81)
Overall Response Rate, n (%)	**CR+CRh+PR**	**66 (81)**
Best Overall Response, n (%)	Complete Remission (CR+CRh)	50 (62)
	Molecular CR/CRh	20 (25)
	Partial Remission (PR)	16 (20)
	Stable Disease	14 (17)
	Progressive Disease	0
	Not Evaluable	1 (1)

CONCLUSIONS

Pathobiology Results from the Apex Study Support the Potential of Bezuclastinib to Treat Underlying Disease Biology in AdvSM

- Bezuclastinib demonstrated robust changes in disease pathology, with effects observed as early as the first assessment at 8 weeks
  - High pure pathologic response (PPR) rates
  - Improvement (including normalization) in bone marrow mast cell distribution (aggregates and burden), atypical morphology, and aberrant immunophenotype
  - Improvements in broader bone marrow characteristics (cellularity, myelofibrosis)
  - Majority achieved normalization of serum tryptase
  - Approximately one-third achieved undetectable levels of *KIT* p.D816V VAF in bone marrow
- Marked reductions in objective measures of disease in most patients signifies impact on KIT-driven pathology and modification of underlying AdvSM disease with bezuclastinib treatment

Presented on behalf of the authors at the Society of Hematologic Oncology (SOHO) 2026 Annual Meeting
September 9-12, 2026
Houston, Texas

Abbreviations: AdvSM, advanced SM; AHN, associated hematologic neoplasm; ASM, aggressive SM; BM, bone marrow; CI, clinical improvement; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; CXDX, Cycle X Day X; ECOG, Eastern Cooperative Oncology Group; F, female; HaT, hereditary alpha-tryptasemia; H&E, hematoxylin and eosin stain; IHC, immunohistochemistry; M, male; MC, mast cell; MCL, mast cell leukemia; MCL-AHN, MCL with AHN; MDS, myelodysplastic syndrome; MDS/MPN-U, MDS/MPN unclassifiable; MF, myelofibrosis; mIWG-MRT-ECNM, modified International Working Group–Myeloproliferative Neoplasms Research and Treatment–European Competence Network on Mastocytosis; MLD, multilineage dysplasia; MPN, myeloproliferative neoplasm; ORR, overall response rate; PCR, polymerase chain reaction; PPR, Pure Pathologic Response; PR, partial remission; QD; once daily; SE, standard error; SM, systemic mastocytosis; SM-AHN, SM with AHN; TKI, tyrosine kinase inhibitor; VAF, variant allele frequency; WG, Wright-Giemsa stain; WHO, World Health Organization; yo, year-old.

References: **1.** Pardanani A. *Am J Hematol*. 2021;96(4):508-525. **2.** DeAngelo DJ, et al. *Nat Med*. 2021;27(12):2183-2191. **3.** Gotlib J, et al. *New Engl J Med*. 2016;374(26):2530-2541. **4.** Lübke J, et al. *J Clin Oncol*. 2022;40(16):1783-1794. **5.** Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719. **6.** Reiter A, et al. *Blood*. 2020;135(16):1365-1376. **7.** Hoermann G, et al. *J Allergy Clin Immunol Pract*. 2025;14(1):1-16. **8.** Greiner G, et al. *Haematologica*. 2020;105(2):366-374. **9.** Ustun C, et al. *Blood Adv*. 2025;9(9):2048-2062. **10.** Shomali W, Gotlib J. *Int J Mol Sci*. 2021;22(6):2983. **11.** DeAngelo DJ, et al. Oral presentation at the European Hematology Association (EHA) 2026 Congress. June 11-14 2026. Stockholm, Sweden. **12.** Wong J, et al. *Am J Clin Pathol*. 2024;161(2):170-176. **13.** Kvasnicka HM, Thiele J. *Atlas of Bone Marrow Pathology*. Springer; 2017. **14.** Classical Hematology. Bone Marrow Biopsy in Clinical Practice. Updated May 10, 2024.

Acknowledgements/Disclosures: The authors would like to thank the patients participating in the Apex study, as well as their families, the investigators, patient advocates, research and operations staff. The Apex study is sponsored by Cogent Biosciences, Inc. Originally presented at the European Hematology Association (EHA) 2026 Congress (June 11-14, 2026; Stockholm, Sweden).