Efficacy and Safety of Bezuclastinib in Patients With Advanced Systemic Mastocytosis: Results From the Apex Study

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INTRODUCTION & METHODS

Unmet Need Remains for Patients With Advanced Systemic Mastocytosis (AdvSM)

- AdvSM, a rare myeloid neoplasm, is an aggressive and life-threatening form of SM driven by the KIT p.D816V mutation in most patients[1-4]
  - Leads to increased production and accumulation of neoplastic mast cells (MC), organ damage and dysfunction from MC infiltration, and decreased overall survival[1,2]
  - Subtypes: aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN), mast cell leukemia (MCL)[4]
- Current approved therapies for AdvSM have limitations in efficacy, safety, and durability[3-8]

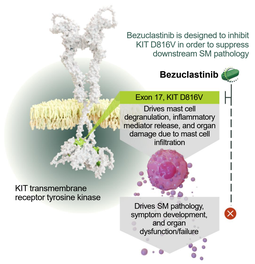


Figure developed by Cogent Biosciences, Inc.

- Bezuclastinib is an investigational, oral, highly selective tyrosine kinase inhibitor with potent activity against KIT D816V
- The Apex study (NCT04996875) evaluated the efficacy and safety of bezuclastinib in patients with AdvSM; **here, we present results from the pivotal portion of Apex**

Bezuclastinib Is an Investigational, Oral, Highly Selective Tyrosine Kinase Inhibitor With Potent Activity Against KIT D816V

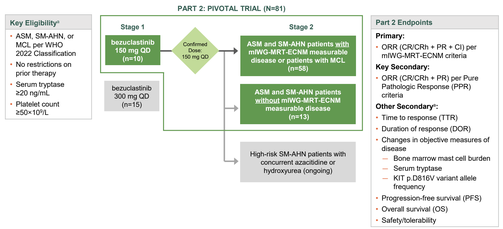
- From nonclinical studies, bezuclastinib[9,10]
  - Has high activity with specificity for mutations in KIT exons 11, 17, and 18
  - Spares closely related kinases, which may minimize off-target toxicities such as bleeding, edema, and pleural effusion
  - Demonstrates minimal brain penetration, which may reduce risk for CNS-related adverse events

Kinase Inhibition Profile of Investigational and Approved KIT Inhibitors for Systemic Mastocytosis; Cell IC_{50} (nM)

Compound	KIT V560G/D816V	WT KIT	PDGFRα	PDGFRβ	CSF1R	FLT3	KDR
Bezuclastinib	**14**	**114**	**>10,000**	**>10,000**	**>10,000**	**>1000**	**>1000**
Avapritinib	13	76	53	11	447	400	>1000
Elenestinib	5	231	20	17	161	453	>1000
Midostaurin	244	182	301	88	542	17	>1000
Imatinib	>1000	424	75	247	611	>1000	>1000

Within 10× potency of KIT D816V | Within 5× potency of KIT D816V | Potency > KIT D816V

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



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

RESULTS

Baseline Characteristics

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[a]	57 (70)
	MCL[b]	13 (16)
Median bone marrow mast cell burden, % (range)		35 (3–95)
Median serum tryptase, ng/mL (range)		191 (23–1987)
Median KIT p.D816V VAF in peripheral blood, % (range)		6.7 (0–91.4)
KIT p.D816V VAF detected[c], n (%)		71 (90[d])
***SRSF2/ASXL1/RUNX1* mutation detected in peripheral blood, n (%)**		48 (59)
Prior TKI therapy for AdvSM or AHN, n (%)		28[e] (35)
Prior midostaurin		24 (30)
Prior avapritinib		6 (7)
Prior imatinib		3 (4)

Data cutoff: March 31, 2026.
[a]AHN subtypes: CMML (n=37), MDS (n=6), MPN (n=4), MDS/MPN-U (n=10). [b]Includes 2 with MCL-AHN (MDS-MLD). [c]Droplet digital PCR limit of detection=0.03%. [d]Of 79 with baseline assessment. [e]5 received 2 prior TKIs.

Bezuclastinib Demonstrated High Response Rates Across AdvSM Subtypes, per mIWG-MRT-ECNM Criteria

Best Overall Response, n (%)	All Evaluable Patients (N=68)	ASM (n=8)	SM-AHN (n=47)	MCL (n=13)
Overall Response Rate (CR+CRh+PR+CI)	**44 (65)**	**5 (63)**	**34 (72)**	**5 (38)**
CR+CRh+PR	**39 (57)**	**3 (38)**	**31 (66)**	**5 (38)**
CR+CRh	**16 (24)**	**0**	**14 (30)**	**2 (15)**
Complete Remission (CR)	7 (10)	0	6 (13)	1 (8)
CR with Partial Hematologic Recovery (CRh)	9 (13)	0	8 (17)	1 (8)
Partial Remission (PR)	23 (34)	3 (38)	17 (36)	3 (23)
Clinical Improvement (CI)	5 (7)	2 (25)	3 (6)	0
Stable Disease	21 (31)	3 (38)	12 (26)	6 (46)
Progressive Disease	2 (3)	0	0	2 (15)
Not Evaluable	1 (1)	0	1 (2)	0

- Median (range) treatment duration: 62.1 (6.7–135.3) weeks
- Median (range) time to first response (CR, CRh, PR, CI): 8.4 (7.8–44.3) weeks
- Median duration of response was not estimable at time of data cutoff

Bezuclastinib Demonstrated High Response Rates Across AdvSM Subtypes, per Pure Pathologic Response (PPR) Criteria

Best Overall Response, n (%)	All Evaluable Patients (N=81)	ASM (n=11)	SM-AHN (n=57)	MCL (n=13)
Overall Response Rate (CR+CRh+PR)	**66 (81)**	**9 (82)**	**51 (89)**	**6 (46)**
CR+CRh	**50 (62)**	**6 (55)**	**39 (68)**	**5 (38)**
Complete Remission (CR)	33 (41)	2 (18)	26 (46)	5 (38)
CR with Partial Hematologic Recovery (CRh)	17 (21)	4 (36)	13 (23)	0
Molecular CR/CRh[a]	20 (25)	1 (9)	18 (32)	1 (8)
Partial Remission (PR)	16 (20)	3 (27)	12 (21)	1 (8)
Stable Disease	14 (17)	1 (9)	6 (11)	7 (54)
Progressive Disease	0	0	0	0
Not Evaluable	1 (1)	1 (9)	0	0

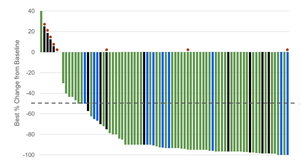
Data cutoff: March 31, 2026.
[a]Patients with molecular CR/CRh are a subset of those patients with overall CR/CRh who also achieved undetectable (<0.03%) levels of KIT p.D816V variant allele frequency.

- Median (range) treatment duration: 63.0 (1.0–135.3) weeks
- Median (range) time to first response (CR, CRh, PR): 8.3 (7.8–70.4) weeks
- Median duration of response was not estimable at time of data cutoff

Bezuclastinib Demonstrated Marked Reductions in Objective Measures of Disease in Patients With AdvSM

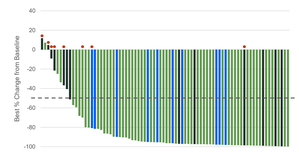
Individual Patients Receiving Bezuclastinib 150 mg QD

Bone Marrow MC Burden (n=80)



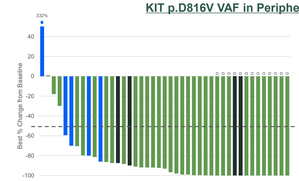
- **89%** achieved ≥50% reduction
  - Median time to 1st ≥50% reduction: 8.3 weeks
- **81%** (60/74) achieved clearance of MC aggregates
  - Median time to 1st clearance: 10.7 weeks

Serum Tryptase (n=80)



- **89%** achieved ≥50% reduction
  - Median time to 1st ≥50% reduction: 2.0 weeks
- **71%** achieved <20 ng/mL
  - Median time to 1st <20 ng/mL: 11.3 weeks
- **64%** achieved <11.4 ng/mL
  - Median time to 1st <11.4 ng/mL: 16.0 weeks

KIT p.D816V VAF in Peripheral Blood[a] (n=43)



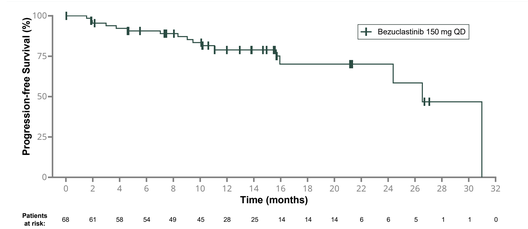
- **91%** achieved ≥50% reduction
  - Median time to 1st ≥50% reduction: 6.3 weeks
- **30%** achieved undetectable VAF
  - Median time to 1st undetectable VAF: 28.1 weeks

SM-AHN ■ ASM ■ MCL
KIT p.D816V VAF undetected in PB at baseline
KIT p.D816V VAF undetected in PB postbaseline

Data cutoff: March 31, 2026. Median (range) treatment duration: 63.0 (1.0–135.3) weeks.
[a]Droplet digital PCR limit of detection=0.03%.

Bezuclastinib Demonstrated Early Evidence of Durable Responses and Prolonged PFS in Patients With AdvSM

PFS[a] per mIWG-MRT-ECNM criteria (n=68)



PFS and OS
- 12-month PFS rate: **79%** (95% CI: 65.5, 87.6)
- 12-month OS rate: **87%** (95% CI: 77.8, 93.0)

Event rates for PFS and OS were low at time of data cutoff, indicating that these endpoints are immature at a median follow up of 62 weeks

Disease Progressions
- Progression of AHN (n=8)
- Progression to AML (n=3)
- Progression of SM (n=2)
- Progression to MCL (n=1)

Data cutoff: March 31, 2026.
[a]PFS progression includes death or Central Response Review Committee assessment of progressive disease.

Bezuclastinib Demonstrated a Favorable Safety Profile in AdvSM

	Bezuclastinib 150 mg QD (N=81)	
Treatment-related AEs (TRAEs), n (%)	**75 (93)**	
Treatment-related SAEs, n (%)	**6 (7)**	
Dose reductions due to TRAEs, n (%)	**13 (16)**	
Discontinuations due to TRAEs, n (%)	**1 (1)**	
TRAEs in ≥10% of patients, n (%)	**Any grade**	**Grade ≥3**
Hematological events		
Neutropenia[a]	**25 (31)**	**19 (24)**
Thrombocytopenia[a]	**20 (25)**	**11 (14)**
Anemia	**13 (16)**	**8 (10)**
Non-Hematological events		
Hair color changes	**25 (31)**	**0**
Altered taste[a]	**23 (28)**	**0**
ALT/AST increased[a]	**17 (21)**	**2 (3)**
ALP increased	**11 (14)**	**4 (5)**
Diarrhea	**13 (16)**	**1 (1)**
Nausea	**12 (15)**	**2 (3)**
Alopecia	**9 (11)**	**0**
Peripheral edema	**9 (11)**	**0**

Data cutoff: March 31, 2026.
[a]Pooled terms.

- Median (range) duration of exposure: 63.0 (1.0–135.3) weeks
  - Majority of patients remained on their starting dose of bezuclastinib
- Dose reductions were primarily due to hematological events
- Hematological events were reversible and manageable
- Treatment-related hepatic events were transient and manageable lab abnormalities
  - No treatment-related Grade 4 hepatic AEs
  - Of 2 patients who experienced treatment-related AEs of Grade 3 ALT/AST increase, 1 discontinued treatment and 1 remains on study following dose reduction
- No treatment-related deaths were reported

CONCLUSIONS

Results from Apex Support Bezuclastinib as a Highly Active Therapy, Validating the Paradigm of Selective KIT Inhibition in AdvSM

- Patients receiving bezuclastinib achieved high rates of response
  - **65%** ORR per mIWG-MRT-ECNM criteria
  - **81%** ORR per Pure Pathologic Response criteria
- Marked reductions in objective measures of disease underscore impact on KIT-driven pathology
  - Bone marrow mast cell burden: ↓ ≥50% in **89%** of patients
  - Serum tryptase: ↓ ≥50% in **89%**
  - KIT p.D816V variant allele frequency in peripheral blood: ↓ ≥50% in **91%**
- Bezuclastinib was well tolerated, with infrequent need for dose reduction or discontinuation for treatment-related adverse events; majority of patients remained on their starting dose
- NDA submission of bezuclastinib for the AdvSM population is planned imminently

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Abbreviations: AdvSM, advanced systemic mastocytosis; AE, adverse event; AHN, associated hematologic neoplasm; ALP, alkaline phosphatase; ALT, AML, acute myeloid leukemia; AST, aspartate aminotransferase; ASM, aggressive SM; CI, confidence interval; alanine aminotransferase; CMML, chronic myelomonocytic leukemia; CNS, central nervous system; CR, complete remission; CRh, CR with partial hematologic recovery; CSF1R, colony-stimulating factor 1 receptor; ECOG, Eastern Cooperative Oncology Group; FLT3, FMS-like tyrosine kinase 3; IC_{50}, half-maximal inhibitory concentration; KDR, kinase insert domain receptor; KIT, KIT proto-oncogene, receptor tyrosine kinase; LAdvSM, advanced systemic mastocytosis; MC, mast cell; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MDS/MPN-U, MDS/MPN unclassifiable; mIWG-MRT-ECNM, modified International Working Group–Myeloproliferative Neoplasms Research and Treatment–European Competence Network on Mastocytosis; MLD, multilineage dysplasia; MPN, myeloproliferative neoplasm; NDA, New Drug Application; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PDGFRα, platelet-derived growth factor receptor α; PDGFRβ, platelet-derived growth factor receptor β; PFS, progression-free survival; PPR, Pure Pathologic Response; PR, partial remission; QD, once daily; SAE, serious AE; SM, systemic mastocytosis; SM-AHN, SM with associated hematologic neoplasm; TKI, tyrosine kinase inhibitor; TRAE, treatment-related AE; VAF, variant allele frequency; WHO, World Health Organization; WT, wild type.

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