



Apex Part 1: Updated Assessment of Bezuclastinib (CGT9486), a Selective KIT D816V Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis (AdvSM)

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Advanced Systemic Mastocytosis is Driven by the *KIT* D816V Mutation

- Advanced Systemic Mastocytosis (AdvSM) is an aggressive and life-threatening subtype of systemic mastocytosis (SM) that is primarily driven by *KIT* D816V mutation and leads to increased production and accumulation of neoplastic mast cells (MC)^{1,2}
 - Subtypes: aggressive SM (ASM); SM with associated hematologic neoplasm (SM-AHN); mast cell leukemia (MCL)¹
- Unmet need remains for approved therapies that provide long-term durability of responses and fewer associated clinically significant toxicities:
 - Reported lack of durability and poor tolerability with midostaurin³⁻⁶
 - Reported toxicities for approved D816V-targeted tyrosine kinase inhibitor (TKI) therapies also include nausea, vomiting, diarrhea, edema, intracranial bleeding, and cognitive effects⁷⁻⁸

Bezuclastinib: Highly Selective and Potent *KIT* D816V Inhibitor

- Oral, selective type I TKI with potent activity against *KIT* D816V, the driving mutation in 95% of patients with SM
- Preclinically, highly active with specificity for mutations in *KIT* exons 9, 11, 17, and 18
- Spares closely related kinases, has minimal brain penetration, and favorable PK properties¹
 - Inhibition of closely related kinases have been linked to off-target toxicities, such as bleeding, edema, and pleural effusions^{2,3}

Kinase Inhibition Profile of Clinical Stage and Approved *KIT* D816V Agents; Cell IC₅₀ (nM)

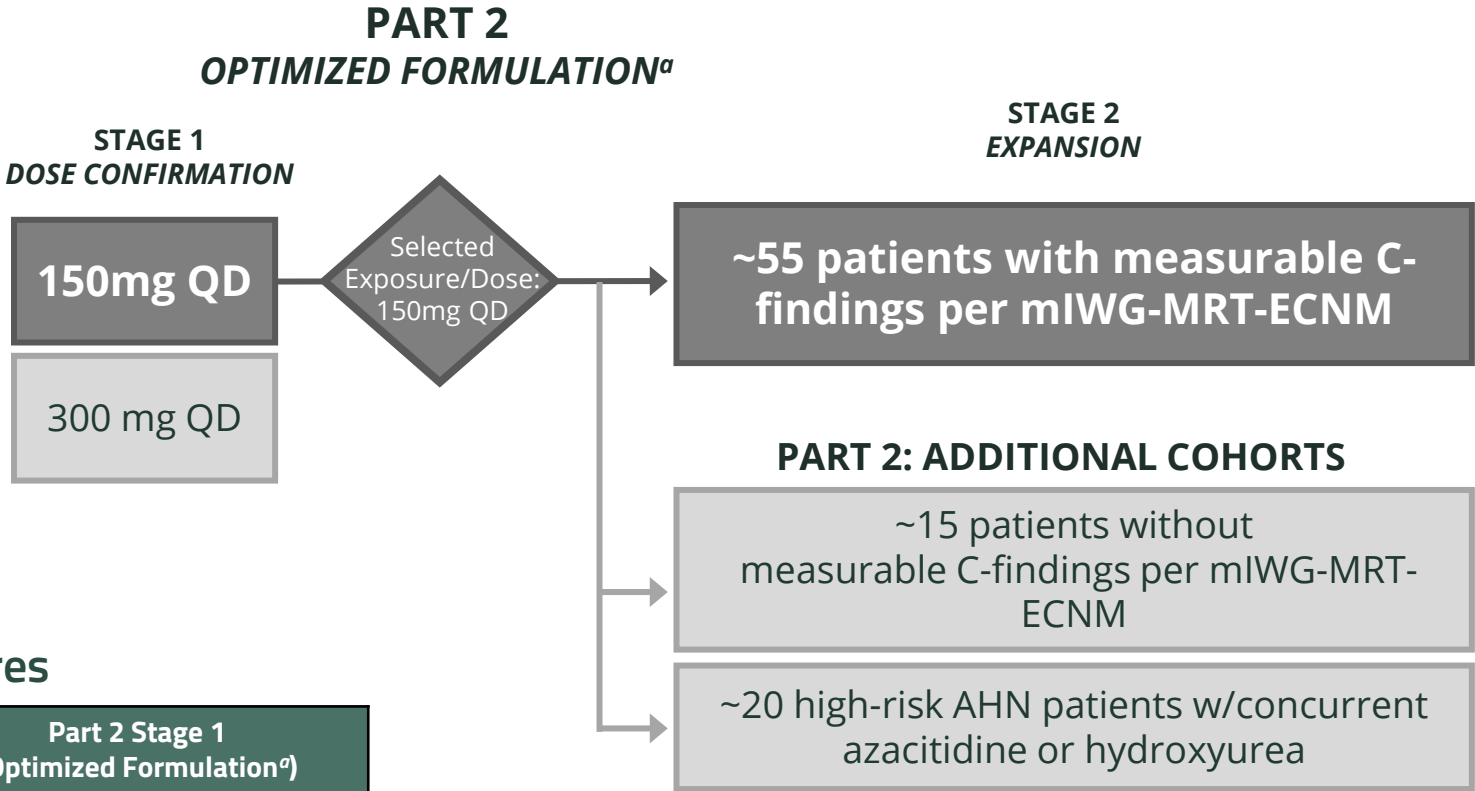
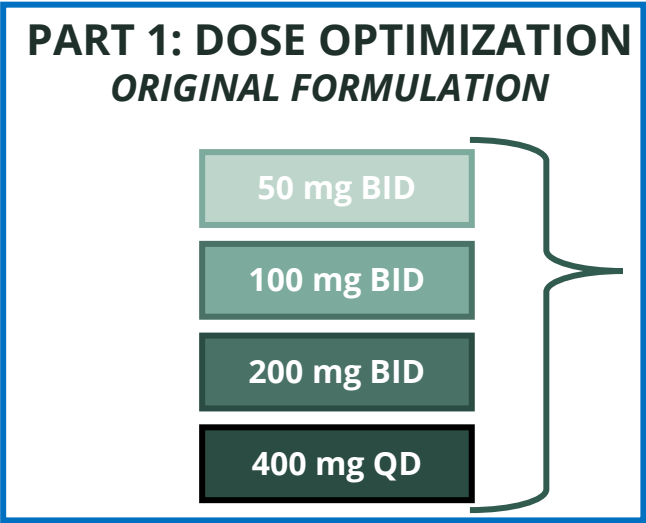
Compound	KIT V560G/D816V (HMC 1.2)	PDGFR α	PDGFR β	CSF1R	FLT3	KDR
Bezuclastinib	14	>10,000	>10,000	>10,000	>1000	>1000
Avapritinib	13	53	10	249	305	>1000
Elenestinib	6	21	6	161	345	>1000

Adapted from Guarnieri *et al.* 2022.

References: 1. Guarnieri A. et al. Abstract P257 Molecular Cancer Therapeutics, 2021. 20(12_Supplement), P257-P257. 2. Giles FJ et al, Leukemia. 2009;23(10):1698-1707. 3. Liu S, Kurzrock R. Seminars in Oncology. 2015;42(6):863-875

Apex (NCT04996875): A Phase 2 Open-Label, Multicenter Clinical Study of Bezuclastinib in Patients with Advanced Systemic Mastocytosis

FOCUS OF PRESENTATION



Mean (CV%) Steady-State (Cycle 2 Day 1) Exposures

Study Part (Formulation)	Part 1 (Original Formulation)	Part 2 Stage 1 (Optimized Formulation ^a)
Bezuclastinib Dose	100 mg BID (N=7)	150 mg QD (N=10)
C _{max, ss} (ng/mL)	861 (26.8)	850 (29.9)
AUC _{0-24hr,ss} (ng*hr/mL)	18,900 (30.8)	17,600 (31.3)

150 mg QD of the optimized formulation delivers similar exposures to 100 mg BID of original formulation

^aThe original formulation was modified to improve bioavailability.
DeAngelo DJ, et al. American Society of Hematology (ASH) 2024; San Diego, CA, 8 Dec 2024: Publication Number: 659

Apex (NCT04996875): A Phase 2 Open-Label, Multicenter Clinical Study of Bezuclastinib in Patients with Advanced Systemic Mastocytosis

Key Eligibility Criteria

- ASM, SM-AHN, or MCL per WHO Classification
- Confirmed measurable disease per mIWG-MRT-ECNM
- No restrictions on prior therapy
- Platelet count $\geq 50 \times 10^9/L$

Key Primary Endpoints

- **Part 1:** AEs/SAEs, laboratory changes, PK, biomarkers, ORR (confirmed CR, CRh, PR and CI) per mIWG-MRT-ECNM and assessed by Central Response Review Committee (CRRC)
- **Part 2:** ORR per mIWG-MRT-ECNM and assessed by CRRC

Key Secondary and Exploratory Endpoints

- Safety/Tolerability: Incidence of AEs leading to dose modification, changes in Patient Reported Outcomes (PROs)
- Efficacy: DOR, TTR, PFS, OS, pure pathologic response (PPR)
- PK/PD: plasma concentration of bezuclastinib, serum tryptase, *KIT* D816V burden, BM mast cells

Patient Demographics and Characteristics

33 patients enrolled^a; median age: 68 years; range: 33-87

	Total (N=32)	50mg BID (N=8)	100mg BID (N=7)	200mg BID (N=8)	400mg QD (N=9)
Male, n (%)	21 (65.6)	6 (75.0)	4 (57.1)	5 (62.5)	6 (66.7)
ECOG PS, n (%)					
0-1	27 (84.4)	8 (100)	5 (71.4)	7 (87.5)	7 (77.8)
2-3	5 (15.6)	0	2 (28.6)	1 (12.5)	2 (22.2)
AdvSM Subtype per Central Eligibility Review, n (%)					
ASM	7 (21.9)	2 (25)	0	0	5 (55.6)
SM-AHN ^b	23 (71.9)	5 (62.5)	6 (85.7)	8 (100)	4 (44.4)
MCL	2 (6.3)	1 (12.5)	1 (14.3)	0	0
Prior TKI therapy for AdvSM, n (%) ^c					
TKI Naïve ^d	22 (69)	7 (88)	4 (57)	6 (75)	5 (56)
Avapritinib	5 (16)	0	2 (29)	2 (25)	1 (11)
Midostaurin	10 (31)	1 (13)	3 (43)	2 (25)	4 (44)
SRSF2/ASXL1/RUNX1 Mutation in Peripheral Blood	19 (59.4)	5 (62.5)	5 (71.4)	5 (62.5)	4 (44.4)
KITD816V in Whole Blood, Positive, n (%)	29 (90.6)	8 (100)	6 (85.7)	7 (87.5)	8 (88.9)
Median KITD816V VAF, % (range)	6.1 (0-47.2)	3.4 (0-39.0)	29.2 (0-38.9)	2.9 (0-47.2)	1.9 (0-42.2)
Median Bone Marrow MC Burden, % (range)	30 (5-90)	50 (20-70)	70 (5-90)	10 (5-30)	40 (10-80)
Median Serum Tryptase, ng/mL (range)	153.5 (35-1578)	178 (130-605)	233 (54-1578)	97 (35-131)	182 (50-370)
Patients evaluable with mIWG-MRT-ECNM C-findings	27 (84.4)	7 (87.5)	6 (85.7)	7 (87.5)	7 (77.8)
Median (range) time on treatment, months	16.2 (0.1-32.2)	18.0 (4.7-30.9)	23.0 (10.2-31.3)	7.0 (0.1-16.6)	17.4 (1.2-32.2)

Data as of: 11Oct2024
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^aOne patient never dosed was excluded
^bCMML [n=18]; MDS and/or MPN [n=5]
^cAdditional therapies included cytoreductives and biologics
^dPatients who have received no prior SM-directed therapy with midostaurin and/or avapritinib

Apex Part 1: Responses by mIWG-MRT-ECNM Criteria Were Observed In Both TKI Exposed and Naïve Patients

	Confirmed mIWG-MRT-ECNM Responses per CRRC		
Best Response, n (%) ^a	All	TKI [‡] Therapy Naïve	Prior TKI ^b Exposure
	N=27	N=18	N=9
Overall response rate			
CR + CRh + PR + CI ^c	14 (52)	11 (61)	3 (33)
CR + CRh + PR	13 (48)	10 (56)	3 (33)
Complete Response (CR + CRh)	7 (26)	7 (39)	0
Partial Response (PR)	6 (22)	3 (17)	3 (33)
Clinical Improvement (CI)	1 (4)	1 (6)	0
Stable Disease (SD)	10 (37)	6 (33)	4 (44)
Not evaluable	3 (11)	1 (6)	2 (22)

^a 5 patients without measurable C-finding at baseline were excluded for being non-evaluable per mIWG-MRT-ECNM criteria; one additional patient was excluded due to discontinuation prior to first dose (not dosed [ND]).

^b SM-directed therapy with midostaurin only (n=4) or midostaurin and avapritinib (n=5)

^c Primary endpoint of Apex study

Data as of: 11Oct2024

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Bezuclastinib Treatment Results in a High Response Rate Based on PPR Criteria

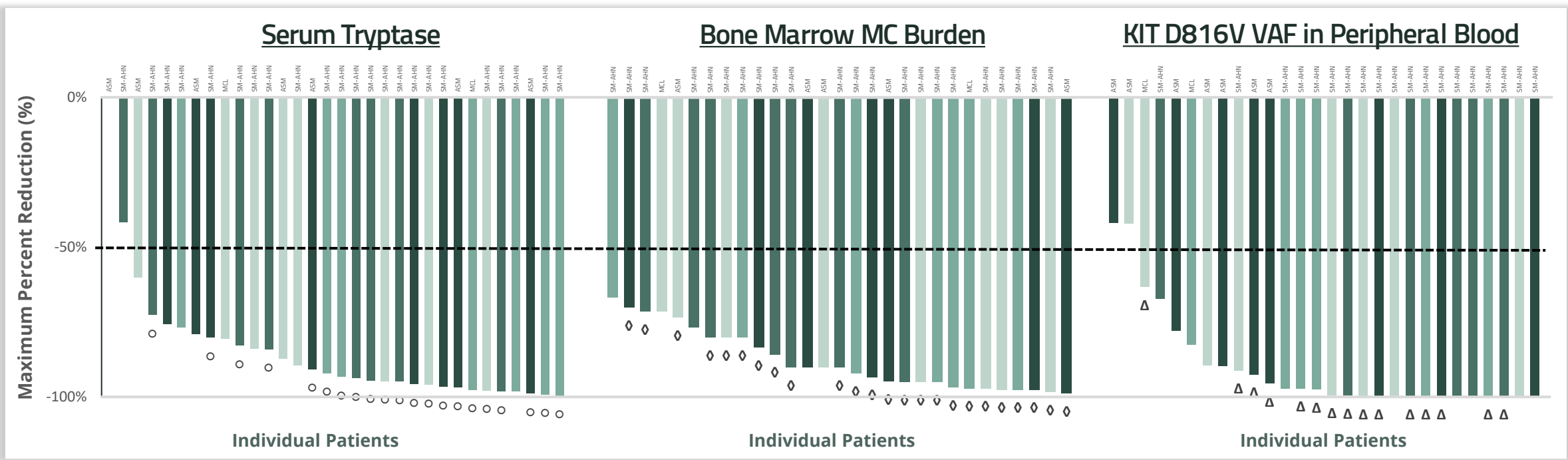
Pure Pathologic Response (PPR)^a: Objective measure evaluating mast cell burden, serum tryptase level, and CBC results without challenges of C-finding (organ damage) assessments

Best PPR ^a Response, n (%)	All
	N=32
Overall response rate (CR + PR)	28 (88)
Complete Response (CR/CRh)	14 (44)
Partial Response (PR)	14 (44)
Stable Disease (SD)	1 (3)
Not Evaluable	3 (9)

- Median (range) time to achieve PPR response of PR or better (CR, CRh, or PR) was 2.1 (1.8-10.2) months

^aPPR is derived based on local hematology and central pathology assessments.
1. Shomali and Gotlib. Int J Mol Sci. 2021; 22(6):2983.
Data as of: 11Oct2024
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Bezacclastinib Demonstrates Deep Reductions in Markers of Mast Cell Burden



- 94% (30/32) achieved $\geq 50\%$ reduction
- 100% (29/29) with at least 2 cycles of treatment achieved $\geq 50\%$ reduction
- 66% (21/32) achieved < 20 ng/mL
- 100% (29/29) with baseline and ≥ 1 post-baseline assessment achieved $\geq 50\%$ reduction
- 83% (24/29) achieved complete clearance of mast cell aggregates by central review
- 93% (26/28) achieved a $\geq 50\%$ reduction
- 71% (15/21) achieved VAF $< 1\%$

50 mg BID

100 mg BID

200 mg BID

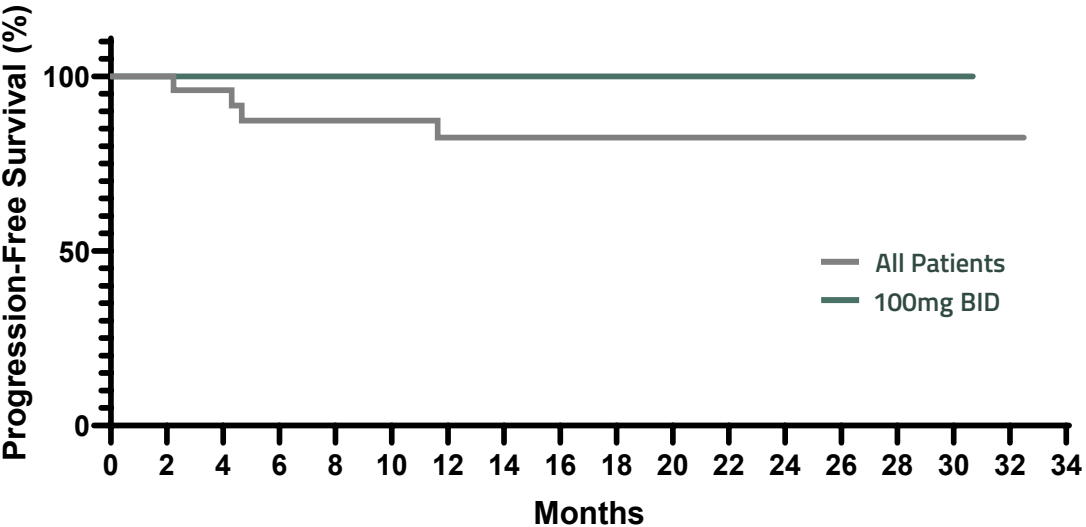
400 mg QD

Milestone Achieved

- < 20 ng/mL serum tryptase
- ◇ Complete clearance of mast cell aggregates
- △ $< 1\%$ KIT D816V VAF

Median PFS and Duration of Response Were Not Reached

Progression-free survival (PFS^a) in mIWG-MRT-ECNM-evaluable population (n=27)



- Median PFS not yet reached at median study follow-up of 20 months
- PFS rate was 82% at 24 months

Duration of response (DOR) (N=27)

- Median duration of response not yet reached
- Median (range) time to achieve mIWG-MRT-ECNM confirmed response of PR or better (CR, CRh, PR) was 2.2 (1.9-7.5) months

Disease Progression in Overall Population (N=32)

- No patients had SM progression
- 7 patients developed progression of AHN
 - AML transformation (3), progression of MDS (2), worsening of CMML (2)
- 3 patients remained on bezuclastinib and began treatment with azacitidine in the rollover cohort

^aPFS progression includes death or CRRC assessment of progressive disease
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Bezaclastinib Continues to Demonstrate an Encouraging Safety Profile

Treatment Related Adverse Events in > 10% Patients

	Total (n=32) n (%)		50 mg BID (n=8) n (%)	100 mg BID (n=7) n (%)	200 mg BID (n=8) n (%)	400 mg QD (n=9) n (%)
Preferred Term	All grade	Grade ≥3	All grade	All grade	All grade	All grade
Hair color changes	11 (34)	-	-	4 (57)	3 (38)	4 (44)
ALT/AST increased*	10 (31)	2 (6)	4 (50)	2 (29)	2 (25)	2 (22)
Thrombocytopenia*	9 (28)	3 (9)	1 (13)	4 (57)	2 (25)	2 (22)
Neutropenia*	9 (28)	5 (16)	1 (13)	3 (43)	2 (25)	3 (33)
Taste disorder*	6 (19)	-	1 (13)	1 (14)	1 (13)	3 (33)
Fatigue	5 (16)	-	3 (38)	-	2 (25)	-
Peripheral edema	4 (13)	-	-	1 (14)	1 (13)	2 (22)
Periorbital edema	4 (13)	1 (3)	-	-	3 (38)	1 (11)
Anemia	4 (13)	1 (3)	-	1 (14)	2 (25)	1 (11)
Blood ALP increased	4 (13)	-	1 (13)	-	1 (13)	2 (22)

*Includes pooled terms.

- Median duration of treatment 16.2 months (range: 0.1-32.2)
- The majority of hematological adverse events were low grade, reversible, and did not require dose reduction
- No intracranial bleeding events were reported
- SAEs reported as at least possibly related in 4 patients including Gr4 Thrombocytopenia, Gr 4 GGT increased (confounded by cholelithiasis and underlying ampullary lesion), Gr3 Hypersensitivity (mediator flare), and Gr3 Leishmaniasis
- 12 patients required dose reduction due to AEs, 8 of which were at 400 mg total daily dose
- 2 patients discontinued due to treatment related adverse events of transaminase increased
- 100mg BID tolerability: 2 patients required dose reductions for thrombocytopenia and no discontinuations due to AEs.

100mg BID of Bezuclastinib Original Formulation Resulted in Optimal Efficacy

Confirmed mIWG-MRT-ECNM Responses in All Patients (n=27) and By Dose

Best Response, n (%) ^a	All (N=27)	50 BID (n=7)	100 BID (n=6)	200 BID/400 QD (n=14)
Overall response rate				
CR + CRh + PR + CI ^b	14 (52)	4 (57)	5 (83)	5 (36)
CR + CRh + PR	13 (48)	3 (43)	5 (83)	5 (36)
Complete Response (CR + CRh)	7 (26)	2 (29)	3 (50)	2 (14)
Partial Response (PR)	6 (22)	1 (14)	2 (33)	3 (21)
Clinical Improvement (CI)	1 (4)	1 (14)	0	0
Stable Disease (SD)	10 (37)	3 (43)	1 (17)	6 (43)
Not evaluable	3 (11)	0	0	3 (21)

^a 5 patients without measurable C-findings per mIWG-MRT-ECNM at baseline were excluded; one additional patient was excluded due to discontinuation prior to first dose (not dosed [ND]).

^b Primary endpoint of Apex study

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Bezuclastinib Has an Encouraging Safety Profile With Deep, Durable Responses in Patients with AdvSM

- **Bezuclastinib continues to demonstrate an encouraging safety and tolerability profile while providing durable responses**
 - 52% ORR per mIWG-MRT-ECNM and 88% ORR per PPR criteria
 - Deep reductions demonstrated across commonly used biomarkers of mast cell activity
 - Median DOR and median PFS were not reached and PFS rate was 82% at 24 months
 - The majority of hematological adverse events were low grade, reversible, and did not require dose reduction
- **100mg BID dose resulted in optimal efficacy and safety outcomes**
 - 83% overall response rate per mIWG-MRT-ECNM
 - All patients receiving 100mg BID achieved PR or better based on PPR criteria
 - No discontinuations due to AEs with 100mg BID dose
 - Exposures at 100mg BID dose are similar to selected dose for Part 2
- **Enrollment to Part 2 is ongoing**
 - A cohort evaluating bezuclastinib with concurrent AHN therapy is enrolling

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