Safety and Efficacy of Bezuclastinib (CGT9486), a Novel, Highly Selective, Potent KIT D816V Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis (AdvSM): Results From Part 1 of the Phase 2 Apex Trial

Apex ADVANCED SM

MPN-334

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INTRODUCTION

Unmet Need Remains for Advanced Systemic Mastocytosis Patients

- Advanced Systemic Mastocytosis (AdvSM) is an aggressive and life-threatening form of systemic mastocytosis (SM) that is primarily driven by KIT D816V mutation and leads to uncontrolled proliferation of mast cells (MC)[1,2]
  - Subtypes: aggressive SM (ASM); SM with associated hematologic neoplasm (SM-AHN); mast cell leukemia (MCL)[1]
  - Based on subtype, the median overall survival ranges from <6 months to 3-4 years[3,4]
- Unmet need remains for approved therapies without associated clinically significant toxicities
  - Reported toxicities for marketed tyrosine kinase inhibitor (TKI) therapies include nausea, vomiting, diarrhea, edema, intracranial bleeding, and cognitive effects[5-7]

Bezuclastinib: Highly Selective and Potent KIT D816V Inhibitor

- Oral, selective type I tyrosine kinase inhibitor (TKI) with potent activity against KIT D816V, the driving mutation in 95% of SM
- Preclinically, highly active with specificity for mutations in KIT exons 9, 11, 17, and 18
- Spares closely related kinases and has minimal brain penetration and favorable PK properties[8]
  - Inhibition of closely related kinases have been linked to off-target toxicities, such as bleeding, edema, and pleural effusions[9,10]

Nonclinical Models Provide Strong Support for Bezuclastinib and Azacitidine[∂] Concomitant Therapy

- Colony-forming assays (CFU-Mk) were performed to determine the likelihood of drug-induced thrombocytopenia in patients when combining bezuclastinib with azacitidine
- Bezuclastinib plus azacitidine is **non-interactive** based on Bliss Synergy Score (-5.98), supporting clinical investigation as a concomitant therapy for SM-AHN patients[11]

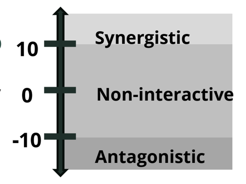
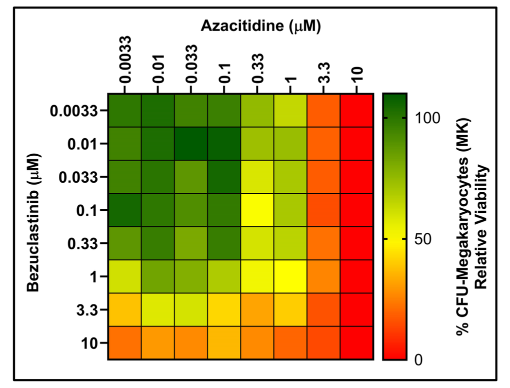


Figure 1. CFU-Mk Assay Predicts No Synergistic Drug-Induced Thrombocytopenia

Drug	Human CFU-Mk Single Agent IC_{50} (nM)	Fold Change Above Primary Target KIT D816V
Bezuclastinib	5,000	357x
Azacitidine	1,200	n/a
Avapritinib	330	25x

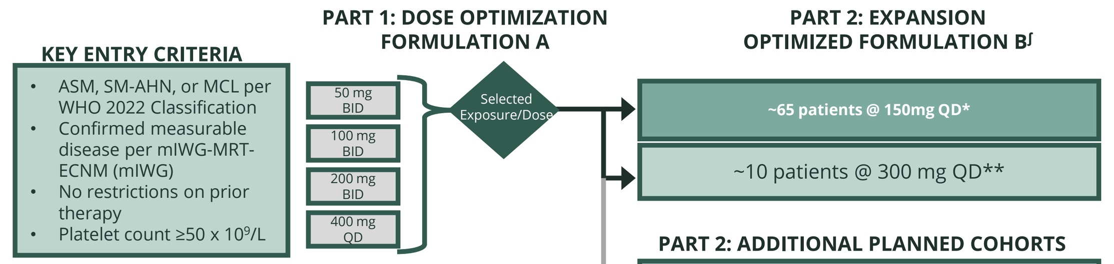
The effect of bezuclastinib combined with azacitidine was assessed using CFU-Mk assays. The table reflects single agent IC_{50}s for each drug tested alone in the CFU-Mk assay. The heatmap represents human megakaryocyte viability following a dose matrix of increasing concentrations of bezuclastinib and azacitidine. Viable colonies were scored after 2 weeks of exposure to drugs (ReachBio, Seattle, WA). Colors in the dose inhibition heatmap indicate low viability (red) and high viability (green).



[∂]Refer to the Additional Planned Cohorts on the Apex Study Design for information on this cohort that is now enrolling

STUDY DESIGN

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



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

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

∫ Formulation B is an optimized formulation with improved bioavailability
* Part 2 specifics subject to regulatory authority feedback
** Designed to explore the effect of exceeding IC90 KIT D816V engagement in AdvSM patients.

RESULTS

Table 1. Patient Demographics and Characteristics

33 patients enrolled[§]; 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 0-1, n (%)	**27 (84.4)**	8 (100)	5 (71.4)	7 (87.5)	7 (77.8)
AdvSM Subtype per Central Eligibility Review, n (%)					
ASM	**7 (21.9)**	2 (25)	0	0	5 (55.6)
SM-AHN	**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 therapy for AdvSM, n (%)[∫]					
TKI Naïve*	**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)
***KIT* D816V in Whole Blood, Positive, n (%)**	**29 (90.6)**	8 (100)	6 (85.7)	7 (87.5)	8 (88.9)
Median KIT D816V 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 (35.0-1578.0)**	178.0 (130.0-605.0)	233.0 (53.6-1578.0)	97.1 (35.0-131.0)	182.0 (50.2-370.0)

[§]One patient never dosed was excluded
[∫]Additional therapies included cytoreductives and biologics
*Patients who have received no prior SM-directed therapy with midostaurin and/or avapritinib

Data as of: 25Sep2023

Figure 3. Dose Dependent Increase in Bezuclastinib Steady State Exposure with 100 mg BID (200 mg per day) Identified as Optimal

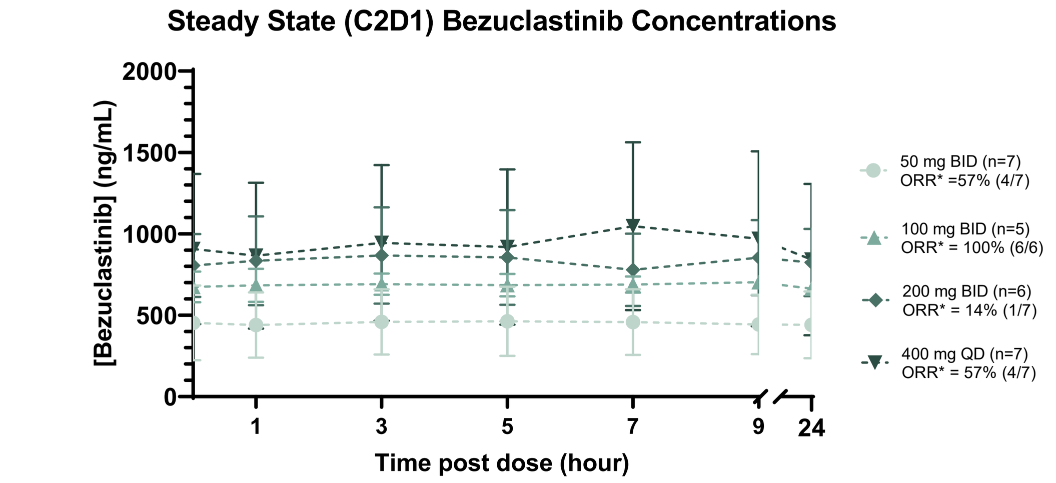


*Figure was derived from mIWG population with PK available at C2D1 (n=25)
*Overall response rate (ORR; CR+CRh+PR+CI) was assessed in all mIWG evaluable patients (n=27)
Data as of: 25Sep2023

Bezuclastinib Continues to Demonstrate a Differentiated Safety Profile

Table 2. 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)**	**0**	0	4 (57)	3 (38)	4 (44)
Thrombocytopenia*	**7 (22)**	**2 (6)**	0	4 (57)	1 (13)	2 (22)
Transaminase increased*	**7 (22)**	**1 (3)**	3 (38)	2 (29)	1 (13)	1 (11)
Neutropenia*	**6 (19)**	**3 (9)**	1 (13)	2 (29)	1 (13)	2 (22)
Taste disorder*	**6 (19)**	**0**	1 (13)	1 (14)	1 (13)	3 (33)
Peripheral edema	**4 (13)**	**0**	0	1 (14)	1 (13)	2 (22)
Periorbital edema	**4 (13)**	**1 (3)**	0	0	3 (38)	1 (11)

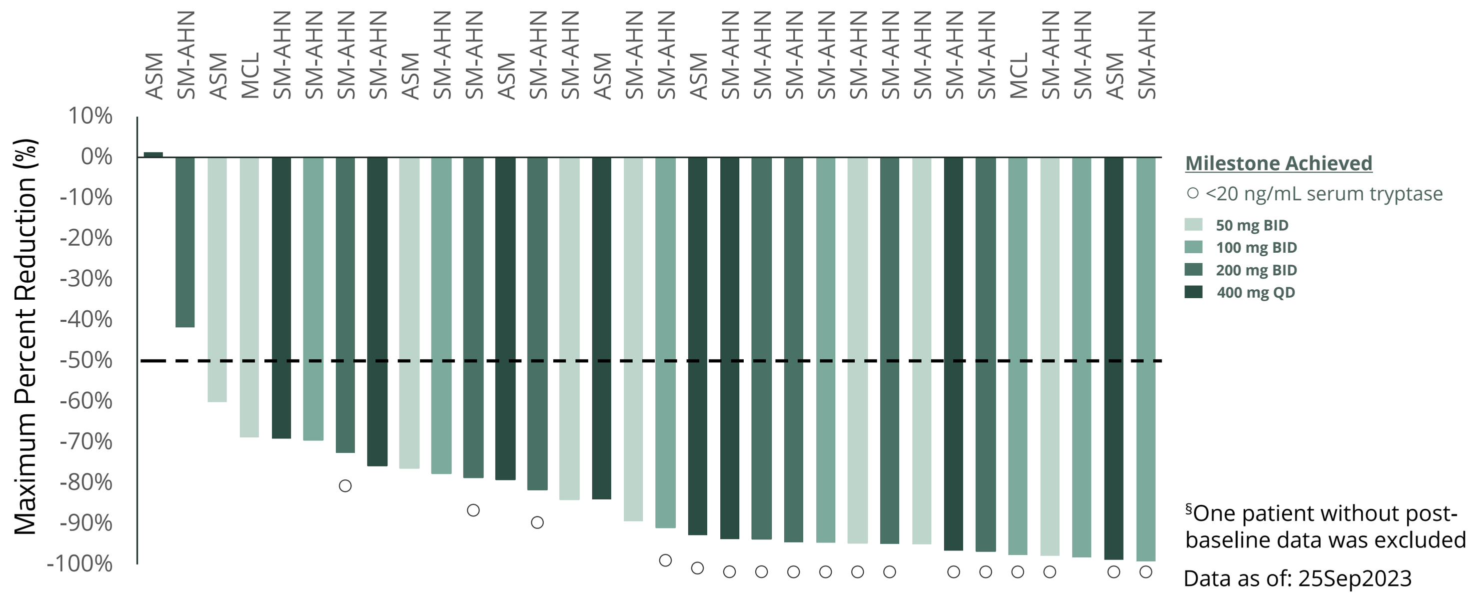
*Includes pooled preferred terms

Data as of: 25Sep2023

- The majority of adverse events were of low grade and reversible.
- No related cognitive impairment or bleeding events reported.
- The majority of hematological adverse events were of low grade, reversible and did not require dose reduction.
- Related SAEs reported in 4 patients including Gr4 Thrombocytopenia, Gr3 Hypersensitivity (mediator flare), Gr3 Leishmaniasis, and Gr3 DILI (presented with late onset [day 488] and mixed cholestatic pattern of injury and subject was subsequently found to have biliary outflow tract obstruction).
- 9/32 patients required dose reduction due to adverse events, 6 of whom were at 400 mg; 3/32 patients discontinued due to adverse events.

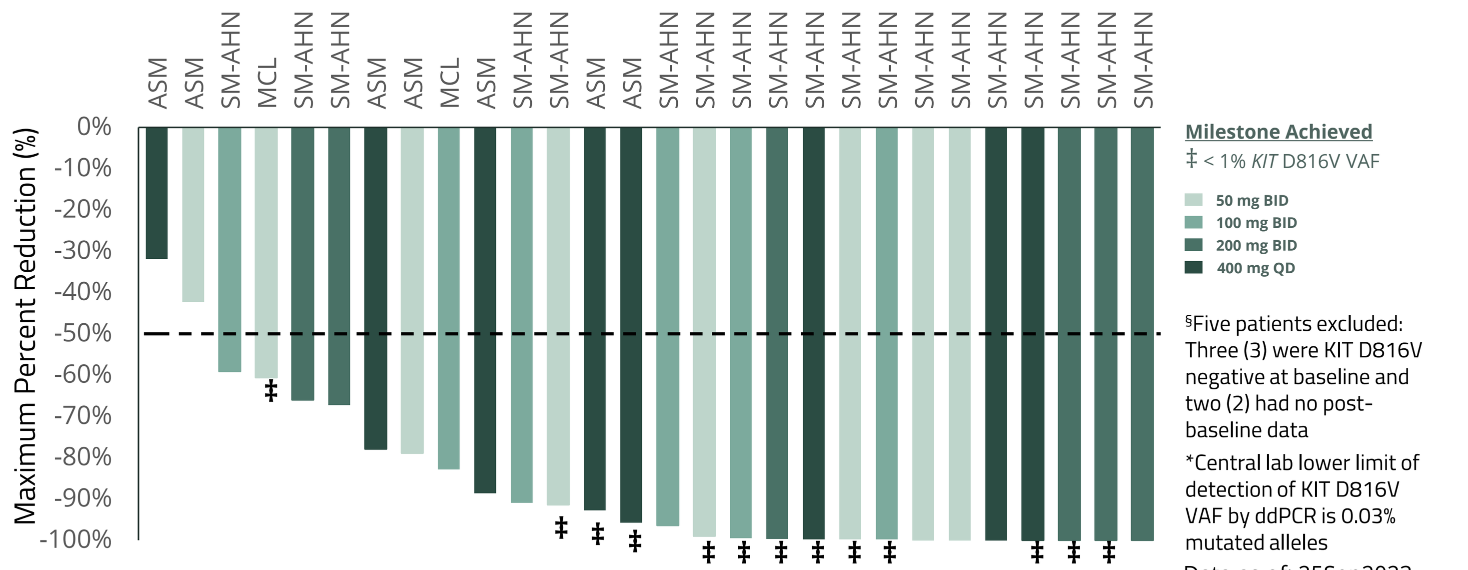
Bezuclastinib Demonstrates Deep Reductions in Markers of Mast Cell Burden

Figure 4. Deep Reductions in Serum Tryptase, (n=32[§])



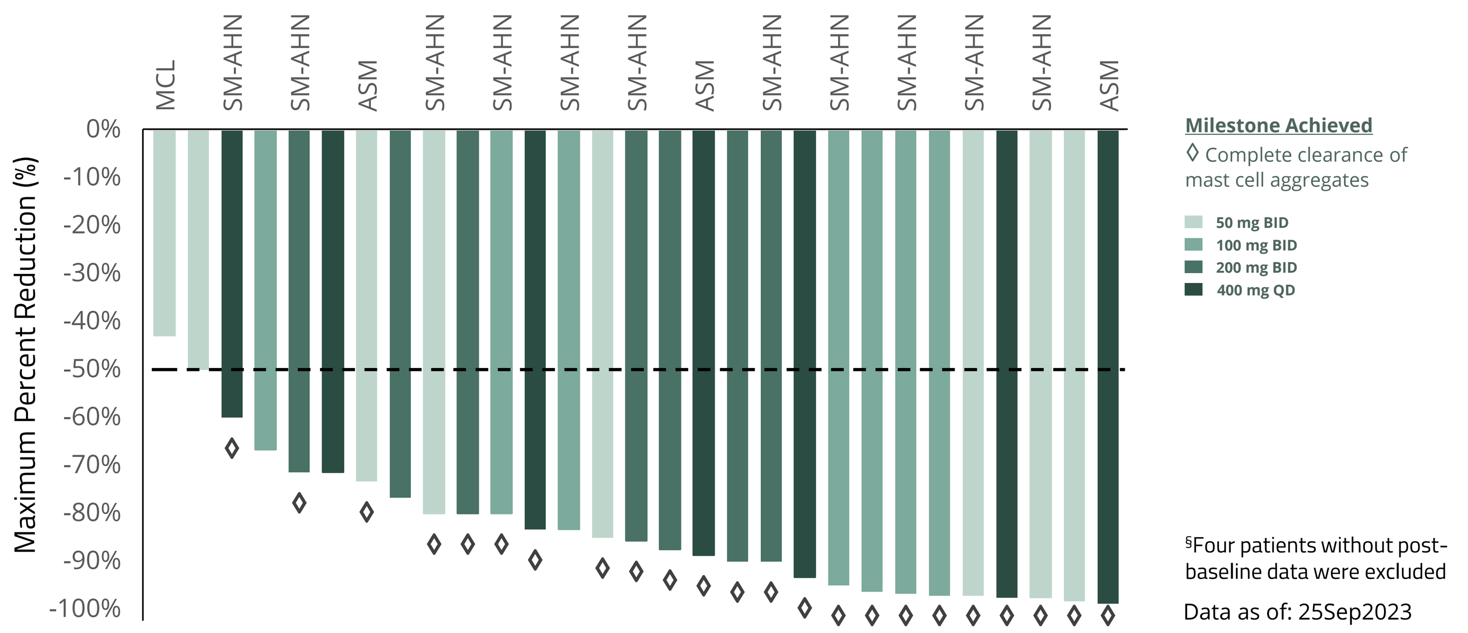
- 94% (30/32) of patients achieved a ≥ 50% reduction
- 100% (29/29) of patients with at least 2 cycles of treatment achieved a ≥ 50% reduction
- 53% (17/32) achieved below 20 ng/mL
- Median time to first serum tryptase <20 ng/mL was 4.0 weeks (range: 1.1-66.9)

Figure 5. Deep Reductions in *KIT* D816V VAF* in Peripheral Blood, (n=28[§])



- 93% (26/28) of patients achieved a ≥ 50% reduction
- Median time to first VAF below 1% was 9.0 weeks (range: 6.0-85.3)

Figure 6. Deep Reductions in Mast Cell Burden, (n=29[§])



- 97% (28/29) of patients with baseline and at least 1 post-baseline assessment achieved a ≥ 50% reduction
- 79% (23/29) achieved complete clearance of mast cell aggregates by central review
- Median time to first clearance of mast cell aggregates was 9.0 weeks (range: 7.3-34.3)

Early and Sustained Responses Observed by mIWG-MRT-ECNM and PPR

Table 3. Apex Part 1: Responses Observed by mIWG-MRT-ECNM

Best Response, n (%)[Ω]	Total* Confirmed and unconfirmed mIWG-MRT-ECNM Responses per CRRC Assessment (n=27)	Confirmed mIWG-MRT-ECNM Responses per CRRC Assessment (n=27)	mIWG-MRT-ECNM per CRRC Assessment* (TKI[‡] Therapy Naïve) (n=18)	mIWG-MRT-ECNM per CRRC Assessment* (Prior TKI[‡] Exposure) (n=9)
Overall response rate				
CR + CRh + PR + CI[†]	**15 (56)**	12 (44)	11 (61)	4 (44)
CR + CRh + PR	**14 (52)**	10 (37)	10 (56)	4 (44)
Complete Response (CR + CRh)	**6 (22)**	6 (22)	6 (33)	0 (0)
Partial Response (PR)	**8 (30)**	4 (15)	4 (22)	4 (44)
Clinical Improvement (CI)	**1 (4)**	2 (7)	1 (6)	0 (0)
Stable Disease (SD)	**9 (33)**	12 (44)	6 (33)	3 (33)
Not evaluable	**3 (11)**	3 (11)	1 (6)	2 (22)

[Ω]5 patients without measurable C-finding at baseline were Not mIWG-MRT-ECNM Evaluable (NE) and therefore are excluded; one additional patient was excluded due to discontinuation prior to first dose (Not Dosed [ND]).
*4 patients who remain on therapy but have not yet reached the 12-week confirmation duration for partial response (PR) are included
‡ SM-directed therapy with midostaurin and/or avapritinib
† Primary endpoint of Apex study

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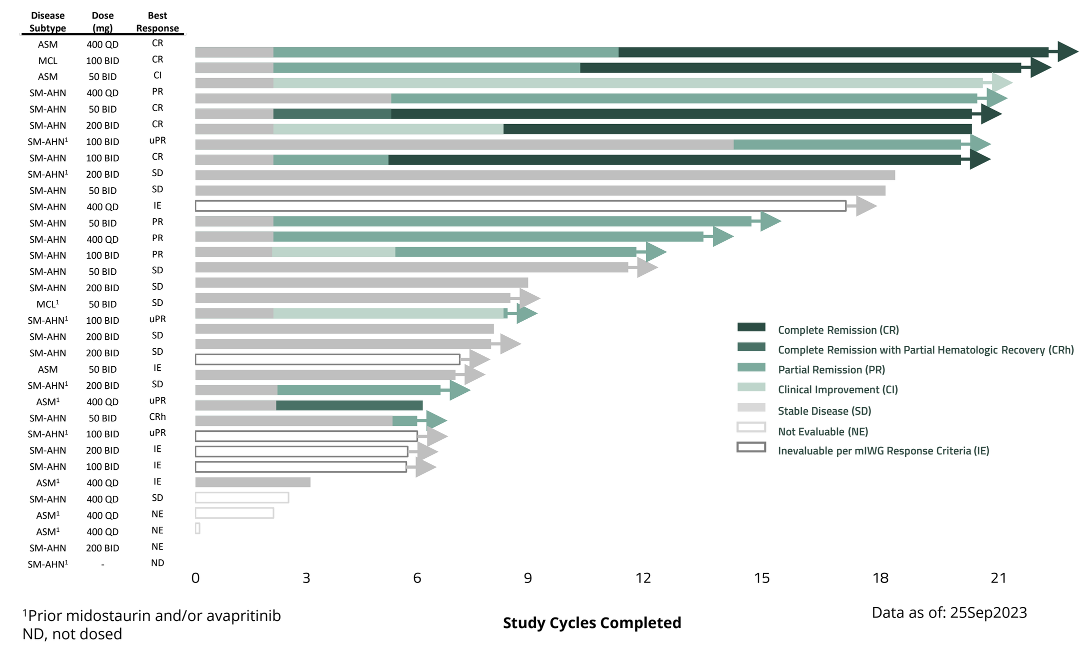
Table 4. Apex Part 1: Responses Observed by PPR Criteria

Best Response, n (%)[α]	Total (n=32)	PPR per Investigator Assessment (TKI[‡] Therapy Naïve) (n=22)	PPR per Investigator Assessment (Prior TKI[‡] Therapy) (n=10)
Overall response rate (CR + PR)	**24 (75)**	19 (86)	5 (50)
Complete Response (CR)	**13 (41)**	12 (55)	2 (20)
Partial Response (PR)	**11 (34)**	7 (32)	3 (33)
Stable Disease (SD)	**5 (16)**	2 (9)	3 (33)
Not Evaluable	**3 (9)**	1 (5)	2 (20)

[α] One patient was excluded due to discontinuation prior to first dose (Not Dosed [ND]).
[‡] SM-directed therapy with midostaurin and/or avapritinib

Data as of: 25Sep2023

Figure 7. Early and Sustained Responses Observed by mIWG-MRT-ECNM Criteria



[1]Prior midostaurin and/or avapritinib
ND, not dosed

Data as of: 25Sep2023

- Median duration on study = 34.7 (range: 0.43-89) weeks
- Median time to confirmed response (CR+CRh+PR+CI) = 2.02 (range 1.9-4.8) months
- First confirmed CRh by mIWG documented as early as 8 weeks and first confirmed CR as early as 20 weeks

CONCLUSIONS

- **Bezuclastinib continues to demonstrate a differentiated safety profile**
  - The majority of adverse events reported were of low grade and reversible
  - No related cognitive impairment or bleeding events reported
  - 28% of patients required dose reduction due to adverse events; 9% of patients discontinued due to adverse events
- **Treatment with bezuclastinib resulted in encouraging signs of clinical activity**
  - 56% overall response rate (CR + CRh + PR + CI; confirmed and unconfirmed) per mIWG-MRT-ECNM and 75% ORR (CR +PR) per PPR criteria
  - Deep reductions demonstrated across commonly used biomarkers of mast cell activity:

≥50% Serum Tryptase	≥50% KIT D816V VAF	≥50% Bone Marrow MC Burden
94% of patients	93% of patients	97% of patients

- **Exposure achieved with 100 mg BID (200 mg per day) dose resulted in optimal efficacy and safety outcomes**
  - All patients receiving 100mg BID achieved PR or better and remain on trial with 3 patients at ≥20 cycles
  - Dose of 100mg BID was well tolerated; majority of dose reductions occurred in patients receiving 400mg total daily dose (200 mg BID or 400 mg QD)
- **Enrollment to Part 2 is ongoing**
  - 150 mg QD of the optimized formulation expected to deliver exposures consistent with 200 mg total daily dose of the original formulation
  - A cohort evaluating bezuclastinib with concomitant AHN therapy, which is supported by nonclinical data, is open for enrollment

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