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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BACKGROUND

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 midostaurin[3-6]
  - Reported toxicities for approved D816V-targeted tyrosine kinase inhibitor (TKI) therapies also include nausea, vomiting, diarrhea, edema, intracranial bleeding, and cognitive effects[7-8]

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 properties[9]
  - Inhibition of closely related kinases have been linked to off-target toxicities, such as bleeding, edema, and pleural effusions[10-11]

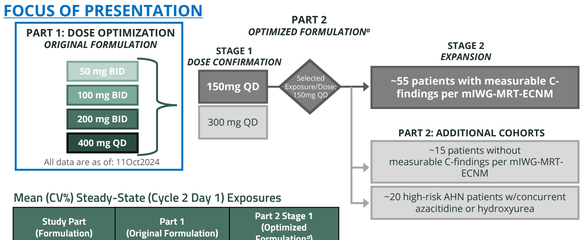
Kinase Inhibition Profile of Clinical Stage and Approved KIT D816V Agents; Cell IC_{50} (nM)

Compound	KIT V560G/D816V (HMC 1.2)	PDGFRα	PDGFRβ	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.

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)
$AUC_{D-24hr,ss}$ (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

[a]The original formulation was modified to improve bioavailability.

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 ≥50 x 10^9/L

ASM, aggressive SM; SM-AHN, SM with an associated hematologic neoplasm; MCL, mast cell leukemia; AE, adverse events; SAE, serious adverse events; PK, pharmacokinetics; ORR, overall response rate; CR, complete response; CRh, complete remission with partial hematologic recovery; PR, partial response; CI, clinical improvement; CRRC, central response review committee; PRO, patient reported outcomes; PD, pharmacodynamics; BM, bone marrow; PPR, pure pathologic response

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

RESULTS

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 Naive[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)
***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 (35-1578)**	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)

[a]One patient never dosed was excluded
[b]CMML [n=18]; MDS and/or MPN [n=5]
[c]Additional therapies included cytoreductives and biologics
[d]Patients 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[a] 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

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RESULTS, continued

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

Pure Pathologic Response (PPR)[12]: 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)**

[a] PPR is derived based on local hematology and central pathology assessments.

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

Bezuclastinib Demonstrates Deep Reductions in Markers of Mast Cell Burden

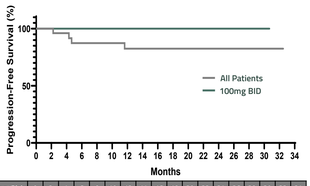
Serum Tryptase
- 94% (30/32) of patients achieved ≥50% reduction
- 100% (29/29) of patients with at least 2 cycles of treatment achieved ≥50% reduction
- 66% (21/32) of patients achieved <20 ng/mL

Bone Marrow Mast Cell Burden
- 100% (29/29) of patients with baseline and ≥1 post-baseline assessment achieved ≥50% reduction
- 83% (24/29) of patients achieved complete clearance of mast cell aggregates by central review

KIT D816V VAF in Peripheral Blood
- 93% (26/28) of patients achieved a ≥50% reduction
- 71% (15/21) of patients achieved VAF <1%

Median PFS and Duration of Response Were Not Reached

Progression-free survival (PFSa) 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



Pts at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
All Pts	27	25	22	19	19	19	17	15	12	9	9	7	6	6	2	2	1	0
100 BID	7	7	7	7	7	7	7	7	6	5	4	4	3	3	3	2	0	0

[a]PFS progression includes death or CRRC assessment of progressive disease

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

100mg BID of Bezuclastinib Original Formulation Resulted in Optimal Efficacy

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

SUMMARY

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

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