Expanded Results From the Phase 2 Summit Trial: Bezuclastinib in Adults With Nonadvanced Systemic Mastocytosis

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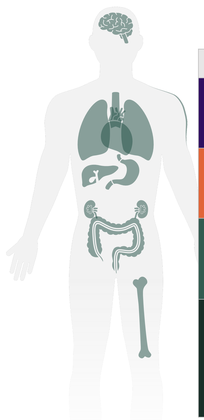
INTRODUCTION

Bezuclastinib (CGT9486) is an oral, potent, and selective type 1 TKI that reduces symptoms of nonadvanced systemic mastocytosis (NonAdvSM)[1-5]

- NonAdvSM is the most prevalent form of SM and is associated with debilitating symptoms that significantly impair quality of life[3,5-10]
- Bezuclastinib is highly active against KIT D816V, has minimal brain penetration and spares closely related kinases, which minimizes off-target toxicities, such as bleeding, cognitive impairment, edema, and pleural effusion[1,2,11]
- The MS2D2[a] is a comprehensive PRO measure of symptom severity in patients across the spectrum of NonAdvSM
  - Severity of each symptom within the Total Symptom Score (TSS) is assessed daily from 0 (none) to 10 (worst possible)
  - TSS is analyzed as a 14-day average



Eleven symptoms within 4 domains are included in MS2D2 TSS

Domain	Symptom
Neurocognitive	• Difficulty concentrating • Difficulty remembering
Fatigue	• Tiredness
Skin	• Itching • Flushing • Skin redness • Spots
Other	Gastrointestinal • Nausea • Abdominal pain Pain • Headache • Bone pain

[a]MS2D2 developed according to FDA Guidance for Industry PRO measures and regulatory agency feedback and reached alignment with FDA for use of MS2D2 TSS in Part 2 of the registration-directed Summit trial.

METHODOLOGY

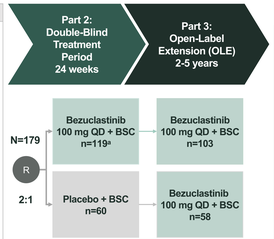
Summit (NCT05186753): Pivotal phase 2 multicenter, randomized, double-blind, placebo-controlled study evaluating bezuclastinib in NonAdvSM

Eligibility

ISM, BMM, or SSM based on WHO 2022 classification

Inadequate symptom control (moderate to severe symptoms) despite ≥2 antimediator therapies

BSC medications include H1RA, H2RA, cromolyn, LTRAs, corticosteroids, omalizumab, and PPIs



Part 3 OLE Objectives

- Characterize long-term safety and tolerability of bezuclastinib
- Durability of effect at the selected dose
- Change of the most severe symptom and most severe subdomain of MS2D2
- Evaluate additional efficacy parameters in patients with NonAdvSM
- Determine the effects of bezuclastinib on serum tryptase
- Explore changes in concomitant medication use for the treatment of NonAdvSM

Data cutoff: November 7, 2025
[a]One patient withdrew consent and did not receive treatment.

RESULTS

Patient demographics and characteristics were representative of a broad NonAdvSM population

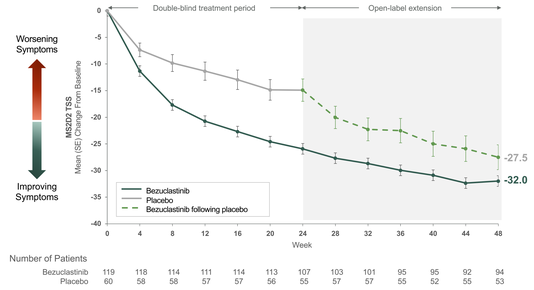
Baseline Characteristics	Bezuclastinib 100 mg QD (N=119)	Placebo (N=60)
Female, n (%)	**74 (62.2)**	**44 (73.3)**
Median age in years, (range)	**51 (24-73)**	**52 (23-78)**
NonAdv subtype, n (%)		
Indolent SM	97 (81.5)	50 (83.3)
Smoldering SM	8 (6.7)	4 (6.7)
BM mastocytosis	14 (11.8)	6 (10.0)
Region, n (%)		
North America	53 (44.5)	28 (46.7)
Europe	64 (53.8)	30 (50.0)
Asia-Pacific	2 (1.7)	2 (3.3)
SM therapy		
Prior *KIT* inhibitor[a], n (%)	17 (14.3)	5 (8.3)
Best supportive care medications, median (range)	3 (0-6)	3 (1-7)

Disease Severity	Bezuclastinib 100 mg QD (N=119)	Placebo (N=60)
Mean MS2D2 TSS, (range)	**57.1 (18-105.2)**	**52.6 (12.8-91.3)**
***KIT* p.D816V[b] in whole blood, detected, n (%)**	**91 (76.5)**	**48 (80.0)**
Median *KIT* p.D816V VAF[b], % (range)	0.22 (0[c]-32.3)	0.30 (0[c]-33.6)
Median bone marrow MC burden, % (range)	**10 (1-75)**	**10 (1-75)**
Median serum tryptase, ng/mL (range)	**39.9 (6.3-448.0)**	**41.2 (7.1-692.0)**
Serum tryptase <20 ng/mL, n (%)	22 (18.2)	10 (16.7)
Most severe MS2D2 TSS symptoms at baseline in >10% of patients, n (%)		
Tiredness	54 (45.4)	24 (40.0)
Spots	39 (32.8)	21 (35.0)
Bone pain	16 (13.4)	9 (15.0)

[a]KIT inhibitors included avapritinib, imatinib, midostaurin, dasatinib, and masitinib. [b]Limit of detection equals 0.03%. [c]Undetected.

Rapid, durable, and clinically meaningful symptom improvement that continues to deepen to 48 weeks of treatment

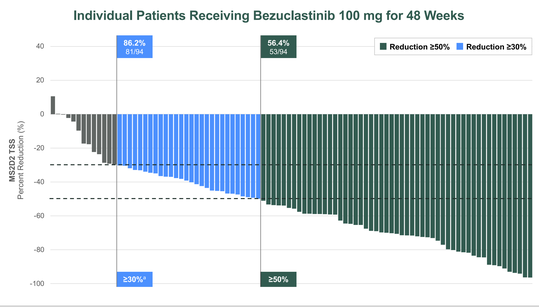
Patients crossing over to receive active treatment experience clinically meaningful symptom improvement



Bezuclastinib achieves robust symptom reduction at 48 weeks

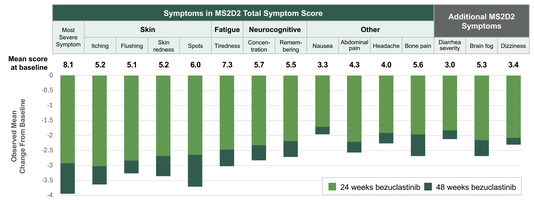
86% of patients achieve clinically meaningful symptom improvement

Individual Patients Receiving Bezuclastinib 100 mg for 48 Weeks



[a]Symptom reductions of ≥30% represent clinically meaningful change as determined by anchor-based analyses.

Bezuclastinib achieves sustained and deepening symptom improvement through 48 weeks in NonAdvSM

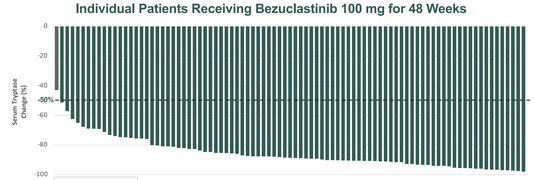


- All symptoms have deepening of improvement to 48 weeks of treatment with bezuclastinib
- At week 48, 50% of those in the bezuclastinib arm had a dose reduction or discontinuation of BSC medication

99% of patients reached ≥50% reduction in serum tryptase at 48 weeks

Serum tryptase normalization persisted to 48 weeks of bezuclastinib treatment

Individual Patients Receiving Bezuclastinib 100 mg for 48 Weeks



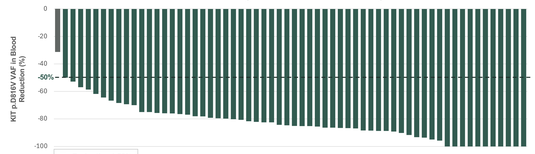
		Week 48	
		Bezuclastinib (N=89)	Placebo → Bezu (N=60)
Median serum tryptase, ng/mL (range)		**4.7** (1.0-128.0)	**5.8** (1.1-143.0)
Patients reaching ≥50% reduction in serum tryptase, % (n/N)[a]		**98.9%** (88/89)	**96.1%** (49/51)
Patients achieving threshold[b], % (n/N)	<20 ng/mL	**91.7** (66/72)	**90.5** (38/42)
	<11.4 ng/mL	**83.3** (70/84)	**77.6** (38/49)

- At week 48, the majority of placebo crossover patients achieved ≥50% serum tryptase reductions and normalization within 24 weeks of bezuclastinib treatment

[a]Patients with data at 48 weeks. [b]Of patients with baseline serum tryptase above threshold.

Bezuclastinib significantly reduced KIT p.D816V VAF, a molecular driver of disease, at 48 weeks

Individual Patients Receiving Bezuclastinib 100 mg for 48 Weeks



		Week 48	
		Bezuclastinib	Placebo → Bezu
Median KIT p.D816V VAF in blood, % (range)		**0.04** (0-10.5)	**0.07** (0-12.1)
Patients reaching ≥50% reduction in KIT p.D816V VAF[a] in blood[b] or undetectable mutation, % (n/N)	ITT population	**98.4** (61/62)	**100** (37/37)

- At week 48, placebo crossover patients achieved significant reductions in KIT p.D816V within 24 weeks of bezuclastinib treatment

[a]Patients with data at 48 weeks. [b]Limit of detection equals 0.03%.

Bezuclastinib was well tolerated and no new safety concerns observed with longer-term treatment

TEAEs during OLE	Placebo → Bezuclastinib (n=58)		Bezuclastinib (n=103)	
Median (range) duration of bezuclastinib treatment (months) in the OLE	8.8 (2.8-14.4)		8.6 (0.46-15.0)	
TEAEs, n (%)	57 (98.3)		92 (89.3)	
Serious TRAEs, n (%)	1 (1.7)		0	
Reductions due to TRAEs, n (%)	9 (15.5)		2 (1.9)	
DCs due to TRAEs, n (%)	3 (5.2)		1 (1.0)	
TEAEs >10% either arm, n (%)				
Preferred Term	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
Hair color changes	37 (63.8)	-	11 (10.7)	-
ALT/AST increased[a]	22 (37.9)	5 (8.6)	10 (9.7)	1 (1.0)
Altered taste[a]	12 (20.7)	-	2 (1.9)	-
Dizziness	9 (15.5)	-	10 (9.7)	-
Nausea	8 (13.8)	-	5 (4.9)	-
Dyspepsia	8 (13.8)	-	5 (4.9)	-
Headache	8 (13.8)	-	9 (8.7)	-
URTI	8 (13.8)	-	7 (6.8)	-
Fatigue	8 (13.8)	2 (3.4)	2 (1.9)	-
Diarrhea	7 (12.1)	-	8 (7.8)	-
ALP increased	7 (12.1)	-	1 (1.0)	-
Arthralgia	6 (10.3)	-	10 (9.7)	1 (1.0)
Insomnia	6 (10.3)	-	4 (3.9)	-

- The majority of TEAEs were low grade and reversible
- Overall median (range) duration of treatment in patients continuing bezuclastinib in the OLE was 13.4 (0.67–20.5) months
- Consistent safety and tolerability profile observed in OLE for patients crossing over to bezuclastinib, similar to the previously reported 24-week experience
- The only hepatic events reported were transient and manageable lab abnormalities, similar to the previously reported 24-week experience
- Discontinuations due to TRAEs remained limited, consistent with the previously reported 24-week experience; all were due to transaminase elevations and all events fully resolved

Only TEAEs that occurred during OLE on bezuclastinib treatment are included. Adverse events per NCI CTCAE v5.0.
[a]Includes pooled terms.

CONCLUSIONS

Bezuclastinib represents a promising new treatment for patients with NonAdvSM

Disease modification and symptom improvement continue out to 48 weeks of treatment

- Rapid, statistically significant, and clinically meaningful symptom improvement is durable and continues to deepen to 48 weeks of treatment
  - Placebo patients crossing over to receive bezuclastinib experience clinically meaningful symptom improvement
- 86% of patients achieve clinically meaningful symptom improvement
  - All symptoms have deepening of improvement to 48 weeks of treatment with bezuclastinib
- At week 48, 50% in the bezuclastinib arm had a dose reduction or discontinuation of BSC medication
- Safety and tolerability profile in OLE, with >24 weeks and up to 48 weeks of treatment, supports potential for chronic dosing
- NDA for a broad NonAdvSM population was submitted in December 2025; Breakthrough Therapy Designation granted by the FDA for patients with NonAdvSM previously treated with avapritinib and with smoldering SM
- Bezuclastinib Systemic Mastocytosis Expanded Access Program (NCT06915766) is currently open to requests from treating physicians in the United States

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Abbreviations: AE, adverse event; ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BM, bone marrow; BMM, BM mastocytosis; BSC, best supportive care; DC, discontinuation; FDA, US Food and Drug Administration; H1RA, histamine type 1 receptor agonist; H2RA, histamine type 2 receptor agonist; ISM, indolent SM; ITT, intent to treat; LTRA, leukotriene receptor agonist; MC, mast cell; MS2D2, Mastocytosis Symptom Severity Daily Diary; NDA, New Drug Application; PPI, proton pump inhibitor; PRO, patient-reported outcome; QD, once daily; R, randomized; SE, standard error; SM, systemic mastocytosis; SSM, smoldering SM; TEAE, treatment-emergent AE; TKI, tyrosine kinase inhibitor; TRAE, treatment-related AE; TSS, Total Symptom Score; URTI, upper respiratory tract infection; VAF, variant allele frequency.

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