# Efficacy and Safety Results From the Pivotal Summit Trial: Bezuclastinib in Adults with Non-Advanced Systemic Mastocytosis

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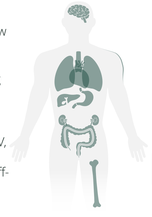
## INTRODUCTION

**Bezuclastinib (CGT9486) is an oral, potent, and selective type 1 TKI with activity against *KIT* p.D816V, the activating mutation in most patients with systemic mastocytosis (SM)[1-5]**

- Nonadvanced SM (NonAdvSM), including indolent SM, smoldering SM, and bone marrow mastocytosis subtypes, is the most prevalent form of SM[3,6,7]
- NonAdvSM can be associated with debilitating symptoms, including life-threatening anaphylaxis, which can significantly impair quality of life[5,8,9]
- Bezuclastinib is highly active against KIT D816V, has minimal brain penetration, and spares closely related kinases, which may minimize off-target toxicities, such as bleeding, cognitive impairment, edema, and pleural effusion[1,2,10]



Symptoms of NonAdvSM

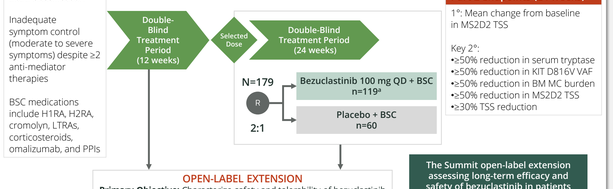
- **Neurocognitive** — Difficulty concentrating, difficulty remembering, brain fog, cognitive dysfunction, anxiety, depression
- **Fatigue** — Tiredness
- **Cardiovascular** — Hypotension, tachycardia, palpitations, chest tightness
- **Skin** — Itching, flushing, skin redness, spots
- **Gastrointestinal** — Nausea, abdominal pain, diarrhea, vomiting, bloating, GERD
- **Pain** — Headache, bone pain, joint pain

GERD, gastroesophageal reflux disease; SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor.

1. DeAngelo DJ, et al. *Hemasphere.* 2022; 6(suppl). 2. Guarnieri A, et al. Poster presented at: AACR Annual Meeting; April 8-13, 2022; Orleans, LA. 3. Ungerstedt J, et al. *Cancers.* 2022;14(16):3942.doi:10.3390/cancers14163942. 4. Li JY, et al. *Cancers (Basel).* 2023;15(23). 5. Tse KY, et al. *J Allergy Clin Immunol Glob.* 2024;3(4):100316. 6. Scherber RM and Borate U. *Br J Haematol.* 2018;180(1):11-23. 7. Gilreath JA, et al. *Clin Pharmacol.* 2019;11:77-92. 8. Pardanani A. *Am J Hematol.* 2021;96(4):508-25. 9. Piris-Villaespesa M and Alvarez-Twose I. *Front Pharmacol.* 2020;11(443): doi:10.3389/fphar.2020.00443. 10. Das A, et al. *Crit Rev Oncol Hematol.* 2021;157:103186.

## METHODS

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




Data cutoff: May 22, 2025.
[a]One patient withdrew consent and did not receive treatment.
BM, bone marrow; BMM, bone marrow mastocytosis: BSC, best supportive care; H1RA; histamine receptor type 1 antagonist; HR2A, H2RA, histamine receptor type 2 antagonist; ISM, indolent SM; LTRA, leukotriene receptor antagonists; MC, mast cell; MS2D2, mastocytosis symptom severity daily diary; NonAdvSM, nonadvanced SM; PPI, proton pump inhibitors; QD, once daily; R, randomized; SM, systemic mastocytosis; SSM, smoldering SM; TSS, total symptom score; VAF, variant allele frequency; WHO, World Health Organization.

**MS2D2: A comprehensive patient-reported outcome measure of symptom severity in patients across the spectrum of NonAdvSM**

- The MS2D2[a] is a 17-item measure addressing signs and symptoms of NonAdvSM
- 11 symptoms within 4 domains are included in MS2D2 TSS
- Severity of each of these symptoms is assessed daily from 0 (none) to 10 (worst possible)
- TSS is analyzed as a 14-day average
- Data from Summit Part 1 support MS2D2 as a reliable, valid and "fit for purpose" PRO measure to assess treatment efficacy as the primary endpoint in Summit Part 2[a]

MS2D2 Total Symptom Score (TSS)

| Domain | Symptom |
|---|---|
| Neurocognitive | • Difficulty concentrating<br>• Difficulty remembering |
| Fatigue | • Tiredness |
| Skin | • Itching<br>• Flushing<br>• Skin redness<br>• Spots |
| Other | Gastrointestinal<br>• Nausea<br>• Abdominal pain<br>Pain<br>• Headache<br>• 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.
FDA, US Food and Drug Administration; MS2D2, mastocytosis symptom severity daily diary; NonAdvSM, nonadvanced systemic mastocytosis; PRO, patient-reported outcome.

## RESULTS

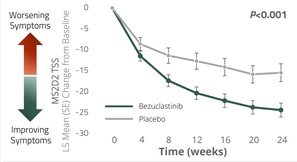
**Patient characteristics are representative of a broad NonAdvSM population**

| Baseline Characteristics | Bezuclastinib (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) |
| BSC medications, median (range) | 3 (0–6) | 3 (1–7) |

| Disease Severity | Bezuclastinib (N=119) | Placebo (N=60) |
|---|---|---|
| Mean MS2D2 TSS, (range) | 57.1 (18–105.2) | 52.6 (12.8–91.3) |
| *KIT*D816V[b] in whole blood, detected, n (%) | 91 (76.5) | 48 (80.0) |
| Median *KIT* p.D816V VAF[b], % (range) | 0.22 (0^–32.28) | 0.30 (0^–33.59) |
| Median BM 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, masitinib. [b]Limit of detection equals 0.03%. †Undetected.
BSC, best supportive care; BM, bone marrow; MC, mast cell; MS2D2, mastocytosis symptom severity daily diary; NonAdvSM, nonadvanced SM; SM, systemic mastocytosis; TSS, total symptom score; VAF, variant allele frequency.

**Primary endpoint was achieved through rapid, durable, statistically significant, and clinically meaningful symptom improvement**



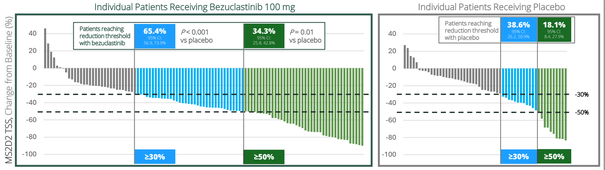

| Mean Change in TSS at Week 24 [95% CI] | | |
|---|---|---|
| Bezuclastinib | Placebo | *P* Value |
| -24.32 (-27.56, -21.08) | -15.41 (-19.58, -11.24) | <0.001 |
| -8.91 (-13.56, -4.26) | | |

- Significant improvement observed as early as 6 weeks

CI, confidence interval; LS, least squares; MS2D2, mastocytosis symptom severity daily diary; SE, standard error; TSS, total symptom score.

**Bezuclastinib achieves robust symptom reduction**

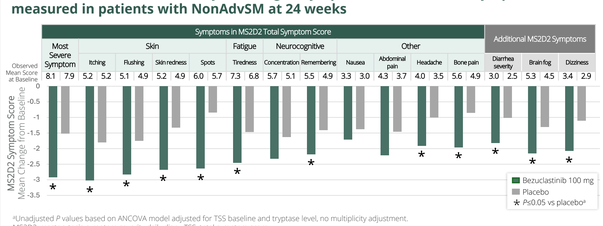
- A significantly greater proportion of patients treated with bezuclastinib achieved ≥30%[a] and ≥50% reductions in MS2D2 TSS compared with placebo




- In patients receiving bezuclastinib with detectable *KIT* p.D816V mutation in blood, 71.2% and 42.6% of patients had reductions of ≥30% and ≥50%, respectively

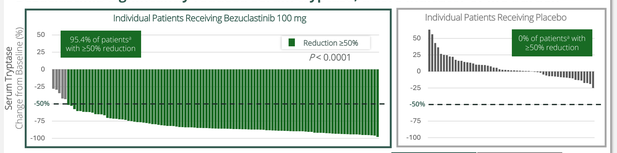
[a]Symptom reductions of ≥30% represent clinically meaningful change as determined by anchor-based analyses.
MS2D2, mastocytosis symptom severity daily diary; TSS, total symptom score.

**Bezuclastinib delivers clinically meaningful symptom relief across all symptoms measured in patients with NonAdvSM at 24 weeks**



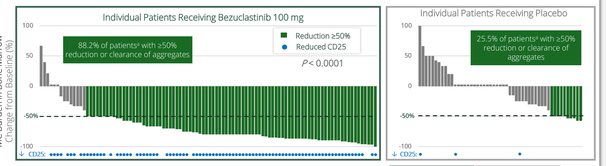

[a]Unadjusted *P* values based on ANCOVA model adjusted for TSS baseline and tryptase level, no multiplicity adjustment.
MS2D2, mastocytosis symptom severity daily diary; TSS, total symptom score.

**Bezuclastinib significantly reduced serum tryptase, a core indicator of MC burden**



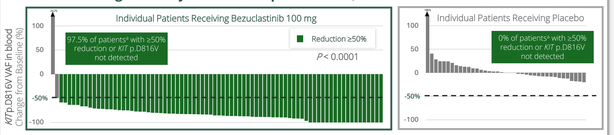

| | | Bezuclastinib | Placebo |
|---|---|---|---|
| Median serum tryptase at 24 weeks, ng/mL (range) | | 6.1 (2.1-97.7) | 42.5 (6.4-298.0) |
| Patients reaching ≥50% reduction in serum tryptase at 24 weeks, % (n/N) | ITT population[b] | 87.4 (104/119) | 0 (0/60) |
| | Patients with data at 24 weeks | 95.4 (104/109) | 0 (0/57) |
| Patients achieving threshold[c], % (n/N) | <20ng/mL | 83.1 (74/89) | 0 (0/47) |
| | <11.4ng/mL | 77.9 (81/104) | 0 (0/55) |

**Bezuclastinib significantly reduced BM MC burden and abnormal MC phenotype**




| | | Bezuclastinib | Placebo |
|---|---|---|---|
| Median MC burden at 24 weeks (range) | | 3.0 (0-50) | 10.0 (1-75) |
| Patients reaching ≥50% reduction in MC burden or clearance of aggregates at 24 weeks, % (n/N) | ITT population[b] | 75.6 (90/119) | 21.7 (13/60) |
| | Patients with data at 24 weeks | 88.2 (90/102) | 25.5 (13/51) |

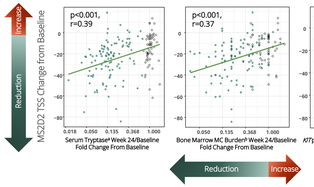
**Bezuclastinib significantly reduced *KIT* p.D816V VAF, a molecular driver of disease**




| | | Bezuclastinib | Placebo |
|---|---|---|---|
| KIT p.D816V VAF in blood at 24 weeks, % | Median (range) | 0.05 (0-3.5) | 0.33 (0-32.8) |
| Patients reaching ≥50% reduction in *KIT* p.D816V VAF in blood or undetectable mutation at 24 weeks, % (n/N) | ITT population[b] | 85.7% (78/91) | 0% (0/48) |
| Patients achieving milestone[d], % (n/N) | 50% reduction or KIT p.D816V not detected | 97.5% (78/80) | 0% (0/39) |
| | KIT p.D816V not detected | 22.5% (18/80) | 0% (0/39) |

[a]Patients with data at 24 weeks. [b]ITT population: patients missing data at baseline and/or week 24 are treated as nonresponders for this analysis.
[c]Of patients with baseline serum tryptase above threshold. [d]Limit of detection equals 0.03%.
BM, bone marrow; ITT, intention to treat; MC, mast cell; VAF, variant allele frequency.

**Magnitude of symptom improvement correlates with degree of MC burden improvement**




- Greater reduction in serum tryptase, bone marrow MCs, and *KIT* p.D816V VAF was significantly correlated with greater reduction in symptom severity, as assessed with the MS2D2 TSS

[a]Bezuclastinib (n=107) and placebo (n=56).
[b]Bezuclastinib (n=99) and placebo (n=51).
[c]Bezuclastinib (n=62) and placebo (n=38). [d]Limit of detection equals 0.03%.
MC, mast cell; MS2D2, mastocytosis symptom severity daily diary; TSS, total symptom score; VAF, variant allele frequency.

**Smoldering SM and prior avapritinib subgroups demonstrate meaningful improvements in symptoms and objective measures of disease**

| | Patients Receiving Bezuclastinib | | |
|---|---|---|---|
| | Overall population (N=119) | Smoldering SM (N=8) | Prior avapritinib exposure (N=11) |
| Symptom severity at 24 weeks, change from baseline LS mean (95% CI) | | | |
| MS2D2 TSS | -24.3 (-27.6, -21.1) | -35.6 (-48.1, -23.1) | -21.6 (-32.6, -10.6) |
| Markers of MC burden at 24 weeks with ≥50% reduction from baseline or reaching other threshold, % (n/N) | | | |
| *KIT* p.D816V in whole blood[a] | 85.7 (78/91) | 100 (8/8) | 83 (5/6) |
| Bone marrow MC burden[b] | 75.6 (90/119) | 75 (6/8) | 63.6 (7/11) |
| Serum tryptase | 87.4 (104/119) | 100 (8/8) | 82 (9/11) |

[a]For *KIT* p.D816V in whole blood, patients could reach ≥50% reduction from baseline or undetectable; limit of detection equals 0.03%.
[b]For bone marrow mast cell burden, patients could reach ≥50% reduction from baseline or clearance of aggregates.
CI, confidence interval; LS, least squares; MC, mast cell; MS2D2, mastocytosis symptom severity daily diary; SM, systemic mastocytosis; TSS, total symptom score.

**Bezuclastinib demonstrated a favorable and manageable safety profile**

| | Bezuclastinib (N=118) | Placebo (N=60) |
|---|---|---|
| TEAEs, n (%) | 116 (98.3) | 53 (88.3) |
| Serious TEAEs, n (%) | 5 (4.2) | 3 (5.0) |
| Reductions due to drug-related TEAEs, n (%) | 13 (11.0) | 0 |
| DCs due to drug-related TEAEs, n (%) | 7 (5.9)[b] | 0 |
| TEAEs >10% that occurred in greater frequency in bezuclastinib arm , n (%) | | |
| Hair color changes | 82 (69.5) | 3 (5.0) |
| Altered taste[a] | 28 (23.7) | 0 |
| Nausea | 26 (22.0) | 8 (13.3) |
| ALT/AST increased[a] | 26 (22.0) | 4 (6.6) |
| Headache | 21 (17.8) | 7 (11.7) |
| Alopecia | 14 (11.9) | 2 (3.3) |
| ALP increased | 12 (10.2) | 2 (3.3) |

- Majority of TEAEs were of low grade (70% grade 1) and reversible
- Variety of AEs occurred more often in the placebo group (vs the bezuclastinib group): dizziness (10% vs 12%), fatigue (7% vs 12%), arthralgia (6% vs 15%), diarrhea (13% vs 18%)
- Low rate of cognitive impairment AEs reported in bezuclastinib group compared to placebo, including disturbance in attention (0% vs 5%) and memory impairment (1% vs 7%)
- The only hepatic events reported were lab abnormalities
  - Transaminase elevation AEs reported were transient and there were no significant changes in liver function as measured by coagulation parameters (INR, PT, PTT) or bilirubin
  - 5.9% of patients experienced ≥grade 3 transaminase elevation AEs and no patient required hospitalization
- All treatment-related DCs were due to transaminase elevations and all events fully resolved

Adverse events per CTCAE v5.0.
[a]Includes pooled terms. [b]1 additional patient discontinued after the data cutoff.
AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DC, discontinuation; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; TEAE, treatment-emergent AE.

## CONCLUSIONS

**Bezuclastinib represents a promising new treatment with evidence of disease modification in patients with NonAdvSM**

- Patients receiving bezuclastinib achieved clinically meaningful symptom improvement, with a mean TSS reduction of -24.32 at Week 24 vs -15.41 for placebo, alongside improvements across all 14 patient- reported symptoms
- Significant reductions in objective disease markers:
  - Serum tryptase: ↓ ≥50% in 95.4% of patients
  - Bone marrow mast cell burden: ↓ ≥50% in 88.2%
  - *KIT* p.D816V variant allele frequency: ↓ ≥50% in 97.5%
- First demonstration of significant correlation between reduction in objective measures of disease and improvement in symptom severity, consistent with the pathogenetic link between the neoplastic mast cell and clinical symptomatology
- Bezuclastinib was well tolerated, with most TEAEs being low grade and reversible
- NDA for a broad NonAdvSM population has been submitted with Breakthrough Therapy Designation granted by the FDA for patients with NonAdvSM previously treated with avapritinib and with smoldering SM
- Bezuclastinib SM Expanded Access Program (NCT06915766) is currently open to requests from treating physicians in the United States

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