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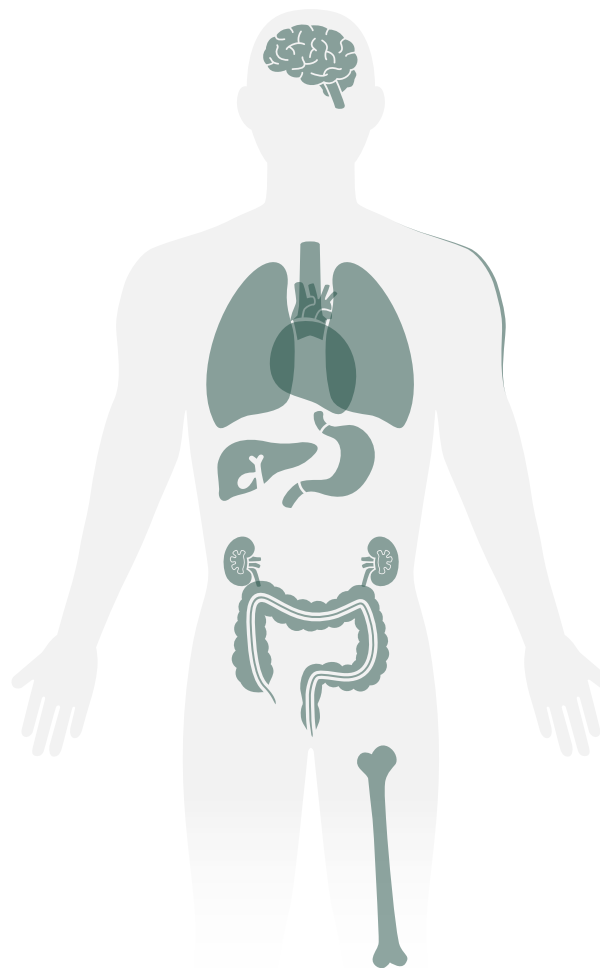
Efficacy and Safety Results From the Pivotal Summit Trial: Bezucclastinib in Adults with Non-Advanced Systemic Mastocytosis

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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 mastocytosis¹⁻⁵

- Non-advanced 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* p.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



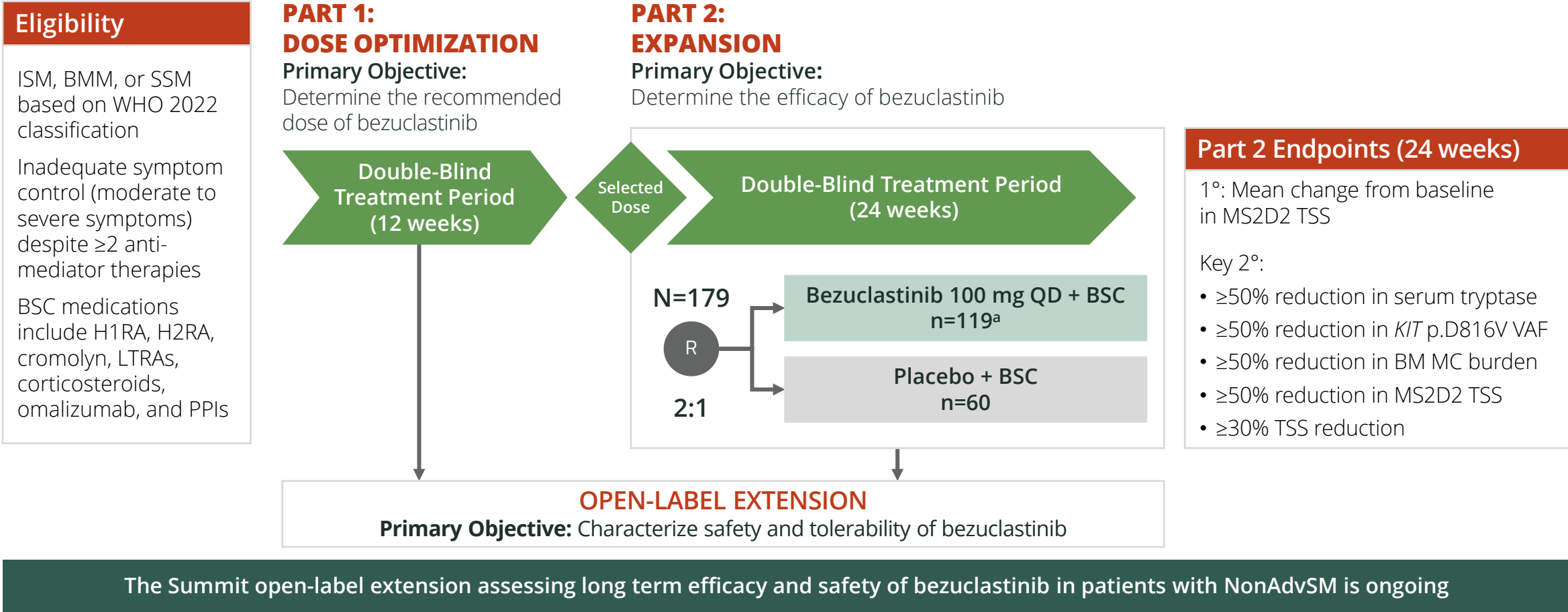
Pain

Headache, bone pain, joint pain

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

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



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
- Eleven 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 • Difficulty remembering
Fatigue		• Tiredness
Skin		• Itching • Flushing • Skin redness • Spots
Other	 	Gastrointestinal • Nausea • Abdominal pain Pain • Headache • Bone pain

^aMS2D2 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, non-advanced systemic mastocytosis; PRO, patient-reported outcome.

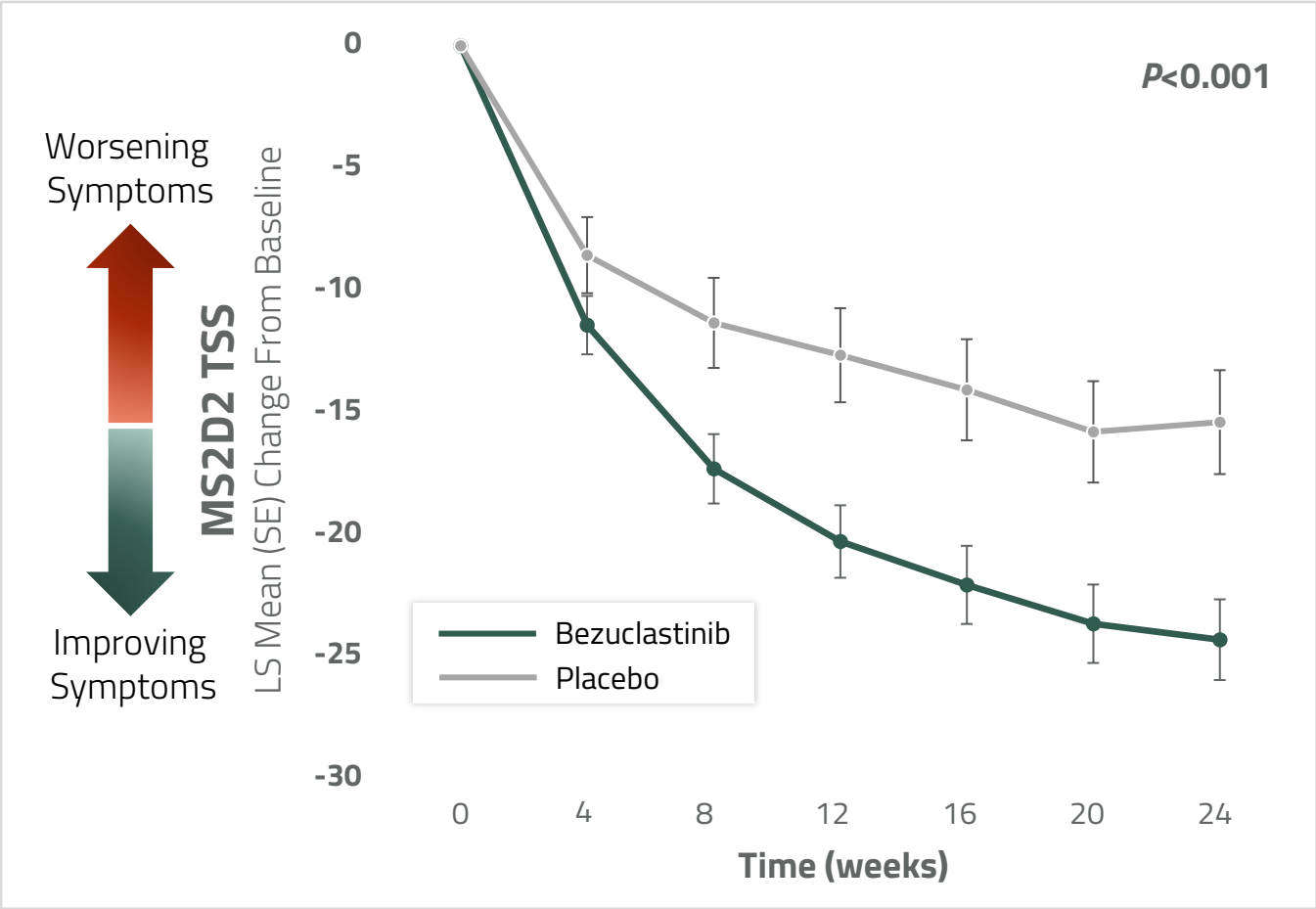
Patient demographics and characteristics were representative of a broad NonAdvSM population

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 –32.28)	0.30 (0 ^c –33.59)
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)

^aKIT inhibitors included: avapritinib, imatinib, midostaurin, dasatinib, masitinib. ^bLimit of detection equals 0.03%. ^cUndetected.
BM, bone marrow; MC, mast cell; MS2D2, mastocytosis symptom severity daily diary; NonAdvSM, nonadvanced SM; QD, once daily; 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

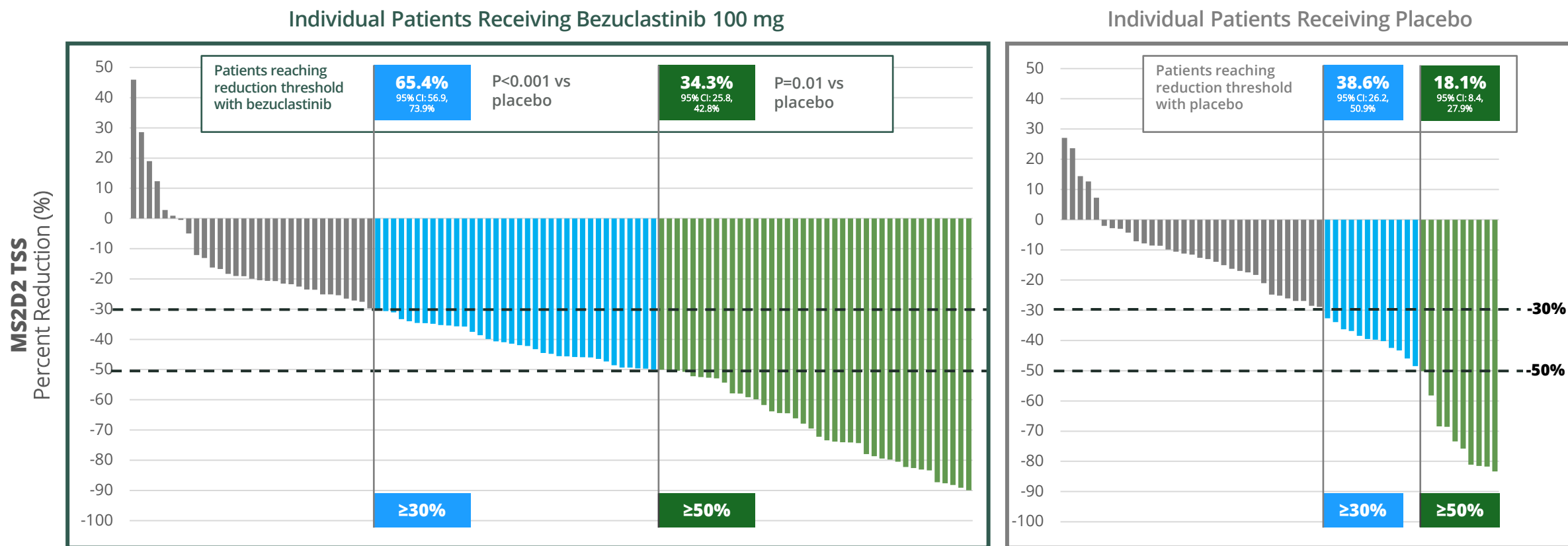


Mean Change in TSS at Week 24 [95% CI]		
Bezuclastinib	Placebo	P Value
-24.32 (-27.56, -21.08)	-15.41 (-19.58, -11.24)	<0.001
-8.91 (-13.56, -4.26)		

- Significant improvement observed as early as 6 weeks

Bezuclastinib achieves robust symptom reduction

A significantly greater proportion of patients treated with bezuclastinib achieved $\geq 30\%^a$ and $\geq 50\%$ reductions in MS2D2 TSS compared with placebo



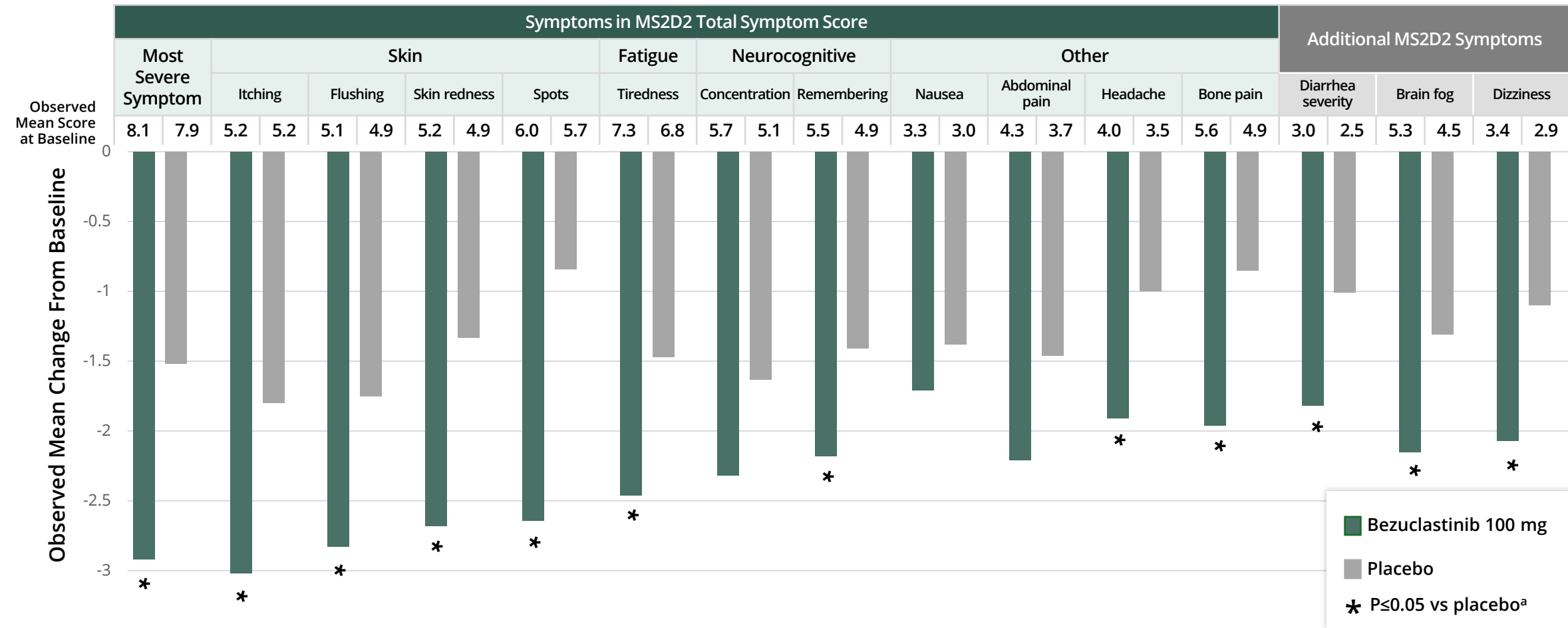
- In patients receiving bezuclastinib with detectable *KIT* p.D816V mutation in blood, 71.2% and 42.6% of patients had reductions of $\geq 30\%$ and $\geq 50\%$, respectively

^aSymptom reductions of $\geq 30\%$ represent clinically meaningful change as determined by anchor-based analyses.

MS2D2, mastocytosis symptom severity daily diary; TSS, total symptom score.

Data cutoff: May 22, 2025.

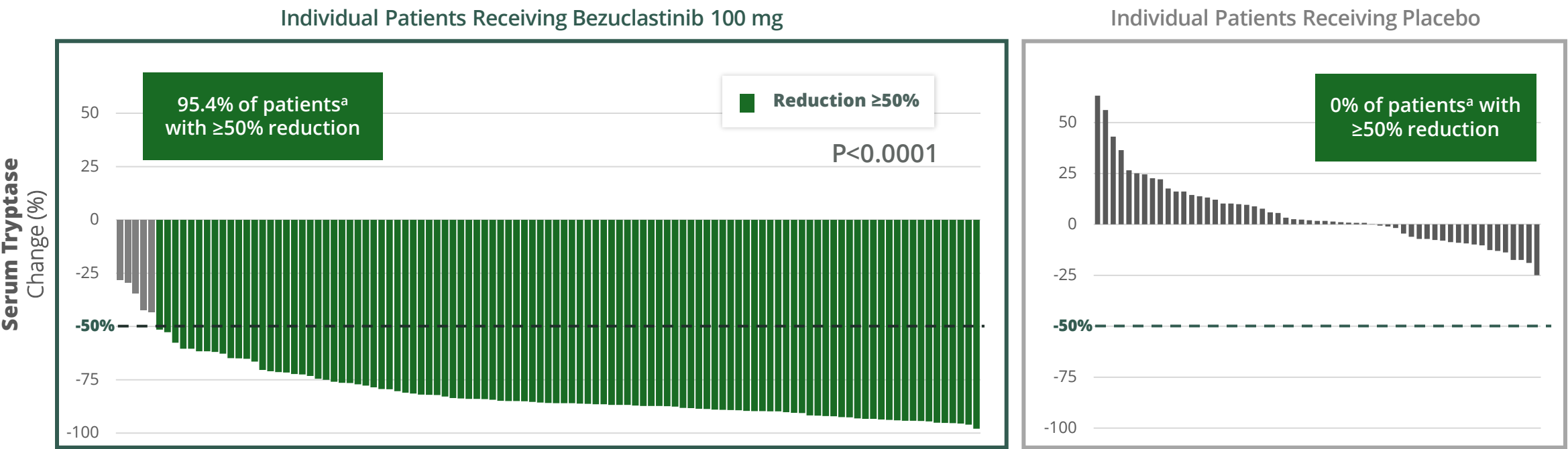
Bezuclastinib delivers clinically meaningful symptom relief across all symptoms measured in patients with NonAdvSM at 24 weeks



^aUnadjusted *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.

Data cutoff: May 22, 2025. 8

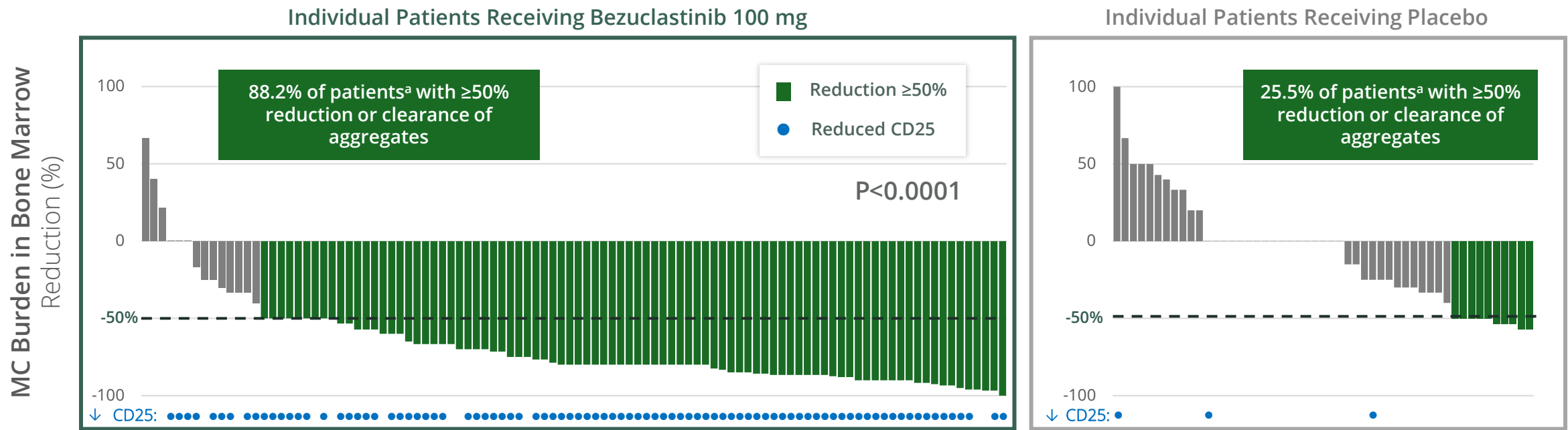
Bezuclastinib significantly reduced serum tryptase, a core indicator of mast cell burden



		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)

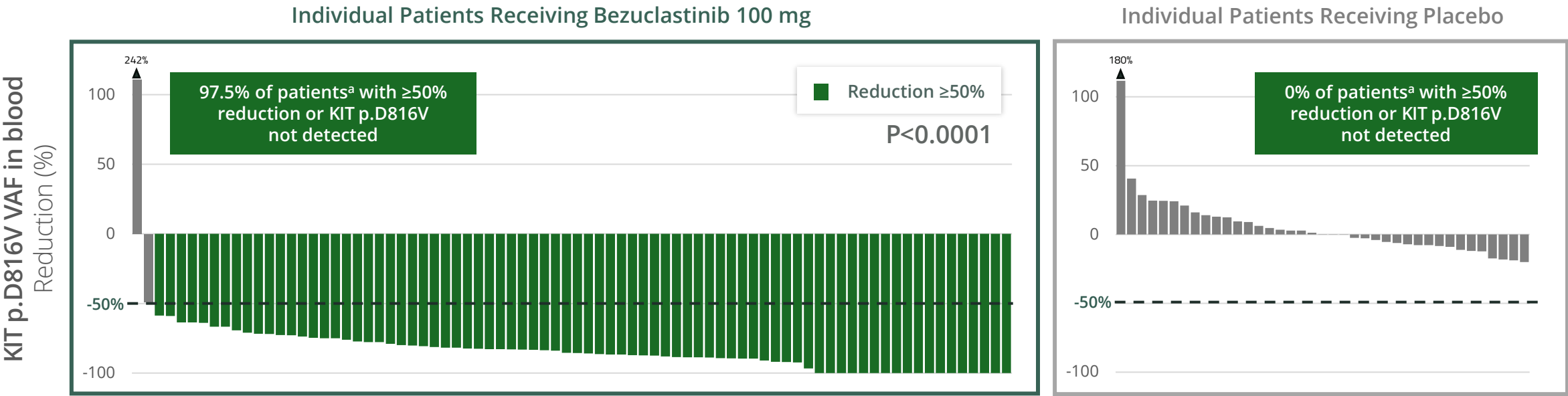
^aPatients with data at 24 weeks. ^bITT population: patients missing data at baseline and/or week 24 are treated as nonresponders for this analysis.
^cOf patients with baseline serum tryptase above threshold.
ITT, intention to treat.

Bezuclastinib significantly reduced bone marrow mast cell burden and abnormal mast cell phenotype



		Bezuclastinib	Placebo
Median mast cell burden at 24 weeks (range)		3.0 (0-50)	10.0 (1-75)
Patients reaching ≥50% reduction in mast cell 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 variant allele frequency, 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 <i>KIT</i> p.D816V VAF in blood ^b or undetectable mutation at 24 weeks, % (n/N)	ITT population ^c	85.7% (78/91)	0% (0/48)
Patients achieving milestone, % (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)

^aPatients with data at 24 weeks. ^bLimit of detection equals 0.03%. ^cITT population: patients missing data at baseline and/or week 24 are treated as nonresponders for this analysis. ITT, intention to treat; 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)	With prior avapritinib exposure (N=11)
Symptom severity at 24 weeks, change from baseline LS mean (95% CI)			
MS2D2 total symptom score	-24.3 (-27.6, -21.1)	-35.6 (-48.1, -23.1)	-21.6 (-32.6, -10.6)
Markers of mast cell 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 mast cell 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)

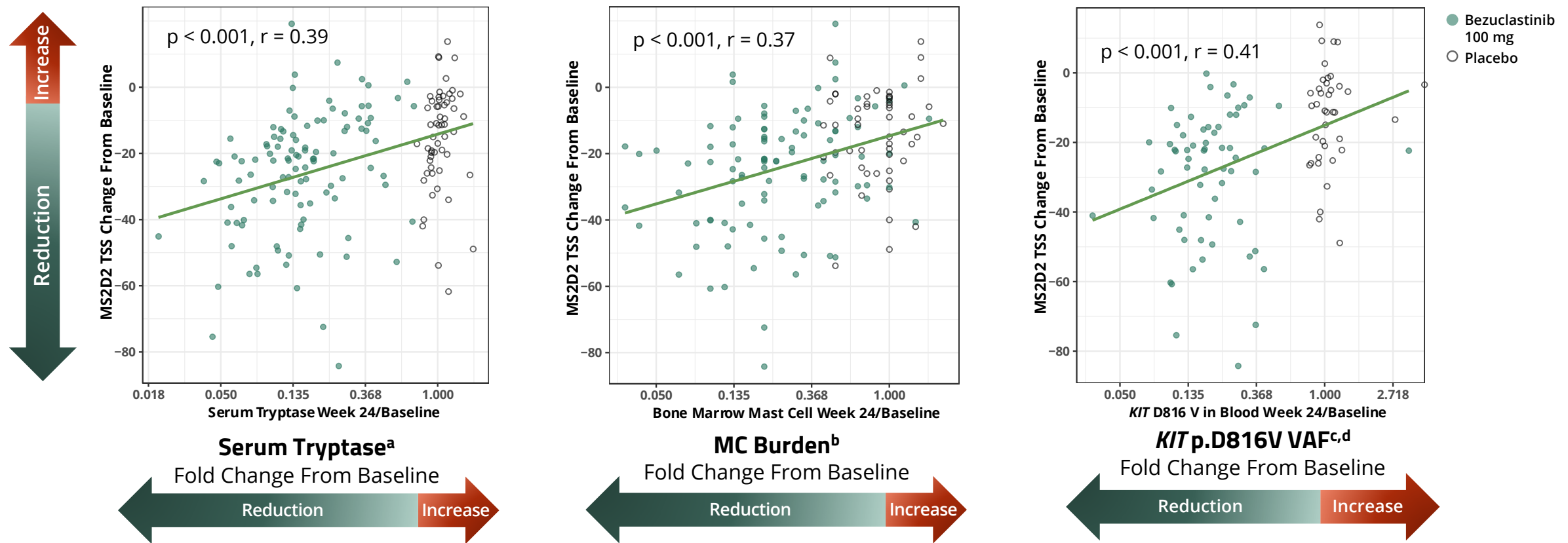
^aFor KIT p.D816V in whole blood, patients could reach ≥50% reduction from baseline or undetectable; limit of detection equals 0.03%.

^bFor bone marrow mast cell burden, patients could reach ≥50% reduction from baseline or clearance of aggregates.

CI, confidence interval; LS, least squares; MS2D2, mastocytosis symptom severity daily diary; SM, systemic mastocytosis.

The magnitude of symptom improvement correlates with the degree of mast cell 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



^aBezuclastinib (n=107) and placebo (n=56). ^bBezuclastinib (n=99) and placebo (n=51). ^cBezuclastinib (n=62) and placebo (n=38). ^dLimit of detection equals 0.03%.

MC, mast cell; MS2D2, mastocytosis symptom severity daily diary; TSS, total symptom score; VAF, variant allele frequency.

Data cutoff: May 22, 2025.

Bezuclastinib demonstrated a favorable and manageable safety profile

	Bezuclastinib 100 mg QD (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 $\geq$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)

Adverse events per CTCAE v5.0.

^aIncludes pooled terms. ^bOne 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; QD, once daily; TEAE, treatment-emergent adverse event.

- The 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
 - The 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 $\geq$ grade 3 transaminase elevation AEs and no patient required hospitalization
- All treatment-related DCs were due to transaminase elevations and all events fully resolved

Data cutoff: May 22, 2025.

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
- Bezucastinib was well tolerated, with most TEAEs being low grade and reversible
- NDA submission for a broad NonAdvSM population is expected by end of 2025 with Breakthrough Therapy Designation recently granted by the FDA for patients with NonAdvSM previously treated with avapritinib and with smoldering SM

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For additional information on bezucastinib in systemic mastocytosis:

- **The Effect of Bezucastinib on the Pathobiology of Mastocytosis: Changes in BM Mast cells, Tryptase, and KIT p.D816V Variant Allele Frequency From the Pivotal Summit Trial**
 - **Oral Presentation by Dr Tracy I George**
December 8, 2025, 5 PM (*session begins at 4:30pm*)
West Hall D2
- **Relationship Between KIT Inhibition by Bezucastinib and Effects on Disease Burden in Mouse Models of Systemic Mastocytosis**
 - **Poster Presentation by Michelle Crow**
December 8, 2025, 6–8 PM
West Halls B3-B4

**Bezucastinib Systemic Mastocytosis Expanded Access Program (NCT06915766)
is currently open to requests from treating physicians in the United States**