Initial Results from Summit: An Ongoing, 3-Part, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Study of Bezuclastinib in Adult Patients with NonAdvanced Systemic Mastocytosis (NonAdvSM)

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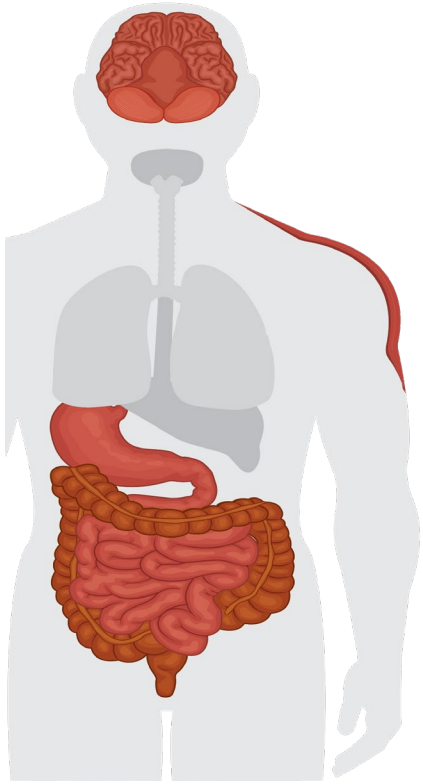
Summit
NONADVANCED SM

Systemic Mastocytosis (SM) is a Rare Disease Characterized by Neoplastic Mast Cell Infiltration of Extracutaneous Tissues and Symptoms of Mast Cell Activation

- SM is primarily driven by D816V *KIT* mutation[1]
- Subtypes range from non-advanced to advanced disease
- Nonadvanced SM (NonAdvSM) accounts for ~90% of all SM cases[2] and includes:
  - Indolent SM (ISM; ~85%) Characterized by symptoms related to mast cell mediator release[3]
  - Smoldering SM (SSM; ~5%) Characterized by a higher systemic mast cell burden: increased levels of serum tryptase and high degrees of bone marrow involvement[3]

Patients with NonAdvSM experience a variety of disabling, potentially serious and severe symptoms caused by mast cell degranulation, including life-threatening anaphylaxis[4]



Neurological
Headache, brain fog,
cognitive dysfunction, anxiety, depression

Systemic
Anaphylaxis

Cutaneous (skin)
Flushing of the face/neck/chest, hives, skin rashes, itching with or without rash

Gastrointestinal
Diarrhea, nausea, vomiting

Other
Cardiovascular
Ear/Nose/Throat/Respiratory
Osteoporosis/Bone fractures
Skeletal
Gynecological
Urinary

1. Pardanani A. AmJ Hematol 2021; 96(4):508-525. 2. NORD 2021. Mastocytosis; available at: https://rarediseases.org/rare-diseases/mastocytosis/. 3. Trizuljak J, et al. Allergy 2020 Aug;75(8):1927-1938. 4. Pyatilova P and Siebenhaar F. Immunol Allergy Clin North Am 2023; 43(4):751-762.

Bezuclastinib is an Oral, Potent, and Selective Type 1 Tyrosine Kinase Inhibitor With Activity Against KIT D816V

- Agents targeting KIT D816V in exon 17 have been used to treat AdvSM and NonAdvSM, but unmet need remains.[1-3]
  - High frequency of adverse events, such as cognitive effects and edema, may limit dosing to optimal efficacy
  - No therapies are approved for patients with Smoldering SM
- Bezuclastinib has minimal brain penetration and high selectivity[4], which may allow for more complete inhibition of KIT D816V with reduced cognitive side effects and reduced edema.
- The Summit study (NCT05186753) is designed to explore the use of bezuclastinib as a therapy for patients diagnosed with NonAdvSM, including Indolent SM (ISM) and Smoldering SM (SSM).

1. DeAngelo D, et al. Nat Med, 2021, 27(12):2183-2191. 2. Ayvakit (avapritinib) [product information]. Cambridge, MA: Blueprint Medicines Corporation. (2021).
3. DeAngelo et al. [abstract] In: Blood (ASH) 2022; 140 (Supplement 1): 1512-13. 4. Gaurnieri, A. et al, AACR, 2022.

Summit: Phase 2 Clinical Study Evaluating Bezuclastinib in NonAdvSM

Eligibility

ISM or SSM based on 2016 WHO classification

Moderate – severe symptoms on ≥2 anti-mediator therapies

BSC: Best supportive care

PART 1: DOSE OPTIMIZATION (fully enrolled)

Primary Objective: Determine the recommended dose of bezuclastinib

Double-blind Treatment Period (12 weeks)

Screening and Enrollment

PART 1a: Formulation A

N=20

R

1:1:1[a]

- Bezuclastinib 100 mg QD + BSC
- Bezuclastinib 200 mg QD + BSC
- Placebo + BSC

PART 1b: Formulation B[b]

N=34

R

1:1:1

- Bezuclastinib 100 mg QD + BSC
- Bezuclastinib 150 mg QD + BSC
- Placebo + BSC

[a] Prior to amendment, Part 1a included a bezuclastinib 400mg QD + BSC cohort with randomization of 1:1:1:1

[b] Formulation B is an optimized formulation with improved bioavailability

Selected Dose

Part 1 Endpoints

Safety

PK

Biomarkers

Symptom improvement based on PRO measures

PART 2: EXPANSION

Primary Objective: Determine the efficacy of bezuclastinib

Double-blind Treatment Period (24 weeks)

N=TBD[c]

R

2:1

- Bezuclastinib (Formulation B) Selected Dose + BSC
- Placebo + BSC

[c] Part 2 will be sized based on Part 1 results and regulatory discussions

OPEN-LABEL EXTENSION (OLE)

Primary Objective: Characterize safety and tolerability of bezuclastinib

Summit Part 1a Enrolled Highly Symptomatic SM Patients with Moderate to Severe Disease

Patient Demographics	All patients (N=20)
Female, n (%)	**15 (75)**
Median Age in years, n (range)	**50.5 (38 – 75)**
ECOG PS, n (%)	
0	**3 (15)**
1	**15 (75)**
2	**2 (10)**
Clinical Characteristics	**All patients (N=20)**
NonAdv Subtype per PI, n (%)	
Indolent SM (ISM)	**18 (90)**
Smoldering SM (SSM)	**2 (10)**
Median (range) MAS Total Score at Eligibility	**45.56 (26.3 – 71.6)**
Mast Cell Burden	**All patients (N=20)**
***KIT* D816V in Whole Blood, Positive, n (%)**	**15 (75)**
Median *KIT* D816V VAF, % (range)	**0.49 (0 – 32.48)**
Median Bone Marrow MC Burden, % (range)	**22.5 (1 – 80)**
Median Serum Tryptase, ng/mL (range)	**74.35 (10.2- 592.0)**
<20 ng/mL, n (%)	**3 (15)**
≥20 ng/mL, n (%)	**17 (85)**

SM Therapy	All patients (N=20)
Prior avapritinib, n (%)	**1 (5.0)**
Baseline Supportive Care Medications, Median (range)	**3 (2-7)**
H1 blockers, n (%)	**19 (95)**
H2 blockers, n (%)	**18 (90)**
Leukotriene receptor antagonists, n (%)	**8 (40)**
Proton pump inhibitors, n (%)	**7 (35)**
Cromolyn sodium, n (%)	**4 (20)**
Omalizumab, n (%)	**3 (15)**
Corticosteroids, n (%)	**1 (5)**
Patient Disposition	**All patients (N=20)**
Months on Study (Part 1a + OLE), median (range)	**7.03 (2.8 – 16.0)**
Completed Part 1a, n (%)	**20 (100)**
On Study as of Data Cut-off, n (%)	**18 (90)**
Discontinued study, n (%)	**2 (10)**
AE, n (%)	**1 (5)**
Patient Decision, n (%)	**1 (5)**

As of Data Cut-off of 25-Oct-2023

Encouraging Safety at 100-200 mg QD in Patients from Summit Part 1a

All cause TEAEs > 1 patient in bezuclastinib cohorts

	Bezuclastinib 100mg QD n= 7		Bezuclastinib 200mg QD n=5		Placebo n=7	
Preferred Term	**Gr 1 / 2**	**Gr 3**	**Gr 1 / 2**	**Gr 3**	**Gr 1 / 2**	**Gr 3**
Hair color changes	4	-	4	-	1	-
Nausea	3	-	1	-	2	-
Peripheral edema	3	-	-	-	-	-
Diarrhea	2	-	-	-	3	-
GERD	2	-	-	-	-	-
Taste disorder [a]	1	-	2	-	-	-
Neutropenia [a]	1	1	1	-	-	-
Fatigue	1	-	1	1	-	-
Hypophosphatemia	1	-	1	-	-	-
Alopecia	-	-	2	-	-	-
AST / ALT increased	-	1	-	-	-	-

[a] Pooled PTs

As of Data Cut-off of 25-Oct-2023

- The majority of TEAEs were low grade and reversible
- No related SAEs reported
- No bleeding or cognitive impairment events reported
- Dose reductions due to TEAEs included Fatigue (n=2) and 1 patient dose reduced and subsequently discontinued due to ALT increased

Safety in patient assigned to 400 mg QD bezuclastinib

- One patient with SSM was enrolled into 400 mg cohort which was subsequently closed to further enrollment
- Patient experienced Gr 4 neutropenia, dose reduced to 200mg (Cycle 4). Other TRAEs included Gr 3 WBC decreased and Gr 1 anemia

Safety and Tolerability Profile in Open-Label Extension (OLE) Supports Potential for Chronic Dosing

All Cause TEAEs > 1 patient

Open-Label Extension (n=18) *[assigned doses]*								
	Active treatment[a] (n=11)				Placebo → Active treatment (n=7)			
Preferred Term	*100mg* n= 6		*200mg* n= 5		*[Placebo→100mg]* n= 3		*[Placebo→200mg]* n= 4	
	Gr1/2	Gr3+	Gr1/2	Gr3+	Gr1/2	Gr3+	Gr1/2	Gr3+
Hair color changes	1	-	1	-	2	-	1	-
Arthralgia	2	-	-	-	-	-	1	-
URTI	1	-	1	-	-	-	-	-
Weight increased	-	-	1	-	-	-	1	-

[a] Patients on active treatment in Part 1 continued on the same dose in OLE

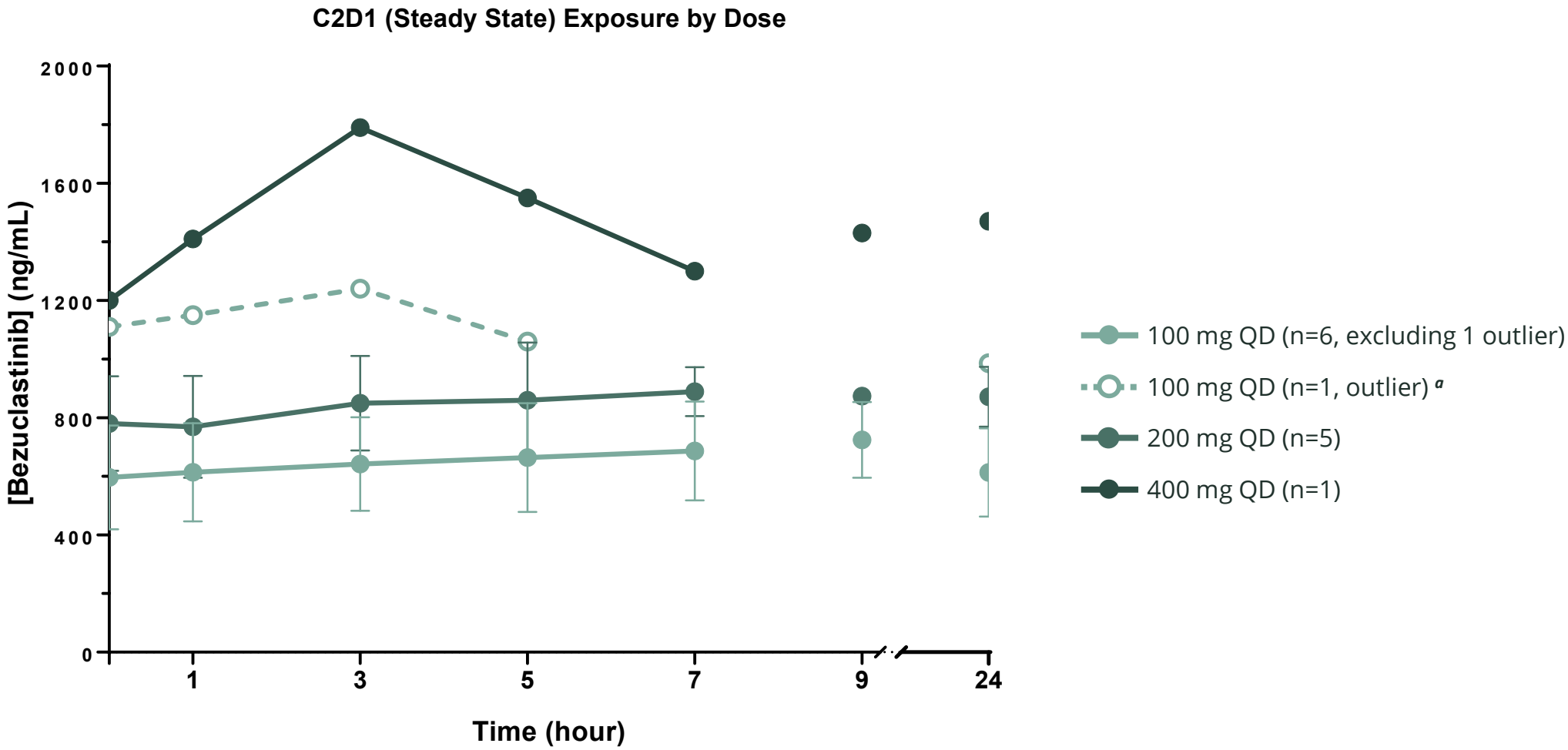
As of Data Cut-off of 25-Oct-2023

- Following completion of Part 1, patients received a median duration of active treatment in OLE of 16 weeks (range: 3.3-53.7)
- Consistent safety profile observed for patients starting bezuclastinib treatment following placebo

Safety in SSM patient reduced from 400 mg → 200 mg QD

- In OLE, TRAEs included: Gr1 taste disorder, Gr1 hair color changes, Gr2 WBC decreased, Gr2 anemia, Gr3 neutropenia and Gr3 fatigue (requiring dose reduction)
- Patient remains on study >400 days

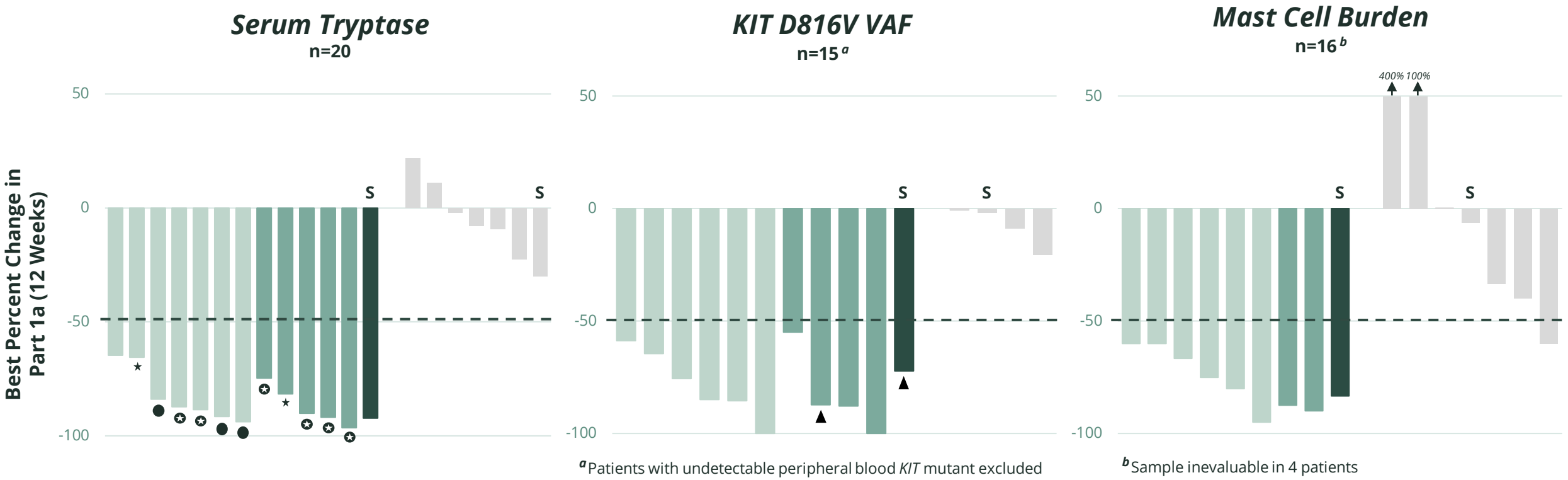
Dose Dependent Increase in Steady State Bezuclastinib Exposure



[a] Patient with outlier PK had a Gr3 ALT elevation leading to dose reduction and subsequent dose discontinuation

As of Data Cut-off of 25-Oct-2023

Within 12 Weeks, 100% of Bezuclastinib Treated Patients Achieved >50% Reduction in Markers of Mast Cell Burden



[a] Patients with undetectable peripheral blood *KIT* mutant excluded

[b] Sample inevaluable in 4 patients

- 90% (9/10) of patients with baseline serum tryptase ≥20ng/mL achieved <20ng/mL after 12 weeks of bezuclastinib
- 67% (8/12) of patients with baseline serum tryptase ≥11.4ng/mL achieved <11.4ng/mL after 12 weeks of bezuclastinib

Dose
- 100 mg QD bezuclastinib
- 200 mg QD bezuclastinib
- 400 mg QD bezuclastinib
- Placebo

Serum Tryptase Outcomes
- ● Achieved <20ng/mL[μ]
- ★ Achieved <11.4ng/mL[μ]
- ✪ Achieved both[μ]

***KIT* D816V VAF Outcomes**
- ▲ Achieved <0.03% (LLD)

S SSM

[μ]In order to achieve, serum tryptase must have been above the threshold at baseline
LLD, lower limit of detection

As of Data Cut-off of 25-Oct-2023

Patient Reported Outcome Measures (PROMs) Used to Assess Severity of Symptoms, HRQoL, and Treatment Benefit [a]

Mastocytosis Quality of Life (MC-QoL) [b]

Disease-specific health-related quality of life measure
PRO Target: Cutaneous & Indolent SM
Range: 0 – 100 total score
Domains: Symptoms, Social life/functioning, Emotions and Skin
Measured in Summit: Baseline and every 4 weeks

Patient Global Impression of Severity (PGIS)

Anchor measure designed to assess patient's impression of symptom severity
PRO Target : NonAdvSM
Range: 5-point scale from 0 (none) to 4 (very severe)
Domains: Overall, dermatological, gastrointestinal, pain, fatigue, cognitive
Measured in Summit: Baseline and every 4 weeks

Mastocytosis Activity Score (MAS) [c]

Disease-specific PROM used to assess symptom severity
PRO Target: Cutaneous & Indolent SM
Range: 0 – 100 total score
Domains: Skin (itching, wheals, flushing); GI (diarrhea, abdominal pain); Other (muscle/joint pain, fatigue, headache, concentration)
Measured in Summit: Baseline and Week 12

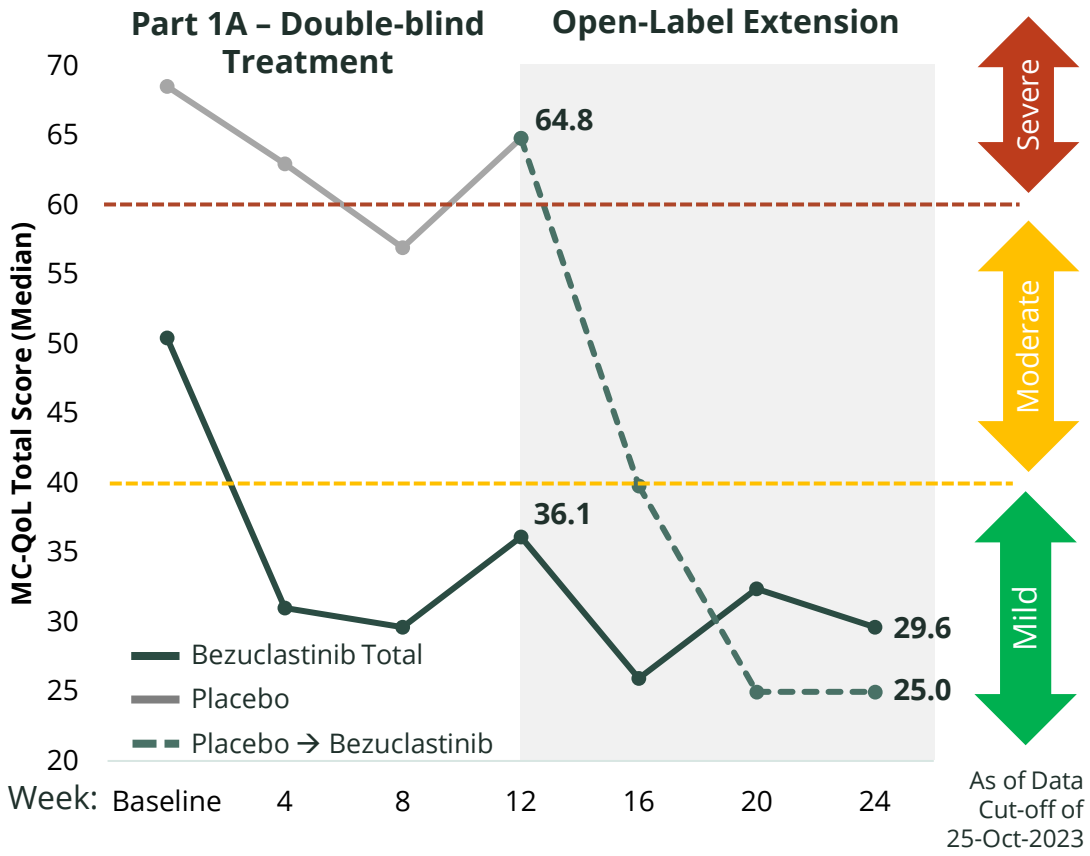
Patient Global Impression of Change (PGIC)

Anchor measure designed to assess patient's impression of the change in symptoms since start of treatment
PRO Target : NonAdvSM
Range: 7-point scale from -3 (very much worse) to 3 (very much better)
Domains: Overall, dermatological, gastrointestinal, pain, fatigue, cognitive
Measured in Summit: Every 4 weeks

[a] Trizuljak J, et al. Allergy 2020 Aug;75(8):1927-1938; [b] Siebenhaar et al. Allergy 2016 71(6):869-77; [c] Siebenhaar F, Sander B, Tram H, Ellrich A, Maurer M, Weller K. Development and validation of the mastocytosis activity score. Allergy. 2018;00:1–8. https://doi.org/10.1111/all.13425. HRQoL – Health-Related Quality of Life

Encouraging Signs of Rapid Improvement in Quality of Life and Symptom Severity

Quality-of-life assessed by MC-QoL



- Median best percent improvement in patients treated with bezuclastinib (n=8) was 37% in Part 1a and 57% in OLE
- After placebo crossover to bezuclastinib in OLE (n=5), the median best percent improvement was 75%

Symptom Severity assessed by MAS

Mastocytosis Activity Score (MAS) % change from baseline at week 12[a]		
	Total Bezuclastinib (N=8)	**Placebo (N=4)**
Median	-35.53	-27.76
Min, Max	-60.1, -5.0	-73.1, 3.3

[a] Not collected in OLE

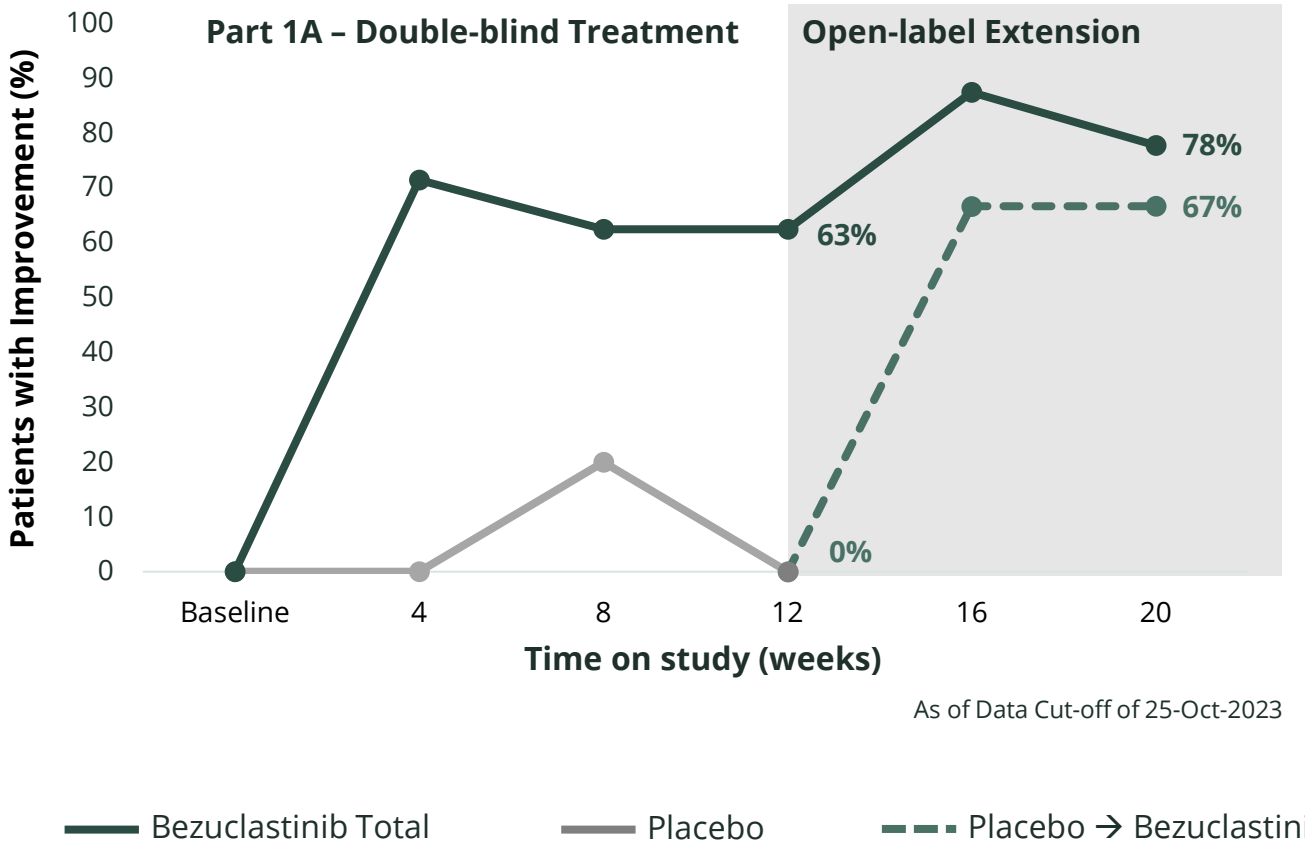
As of Data Cut-off of 25-Oct-2023

- 49% median decrease in MAS for patients treated with 100 mg QD dose level

Bezuclastinib Treatment Provided Rapid and Continued Improvement in Overall Symptom Severity

Patient Global Impression of Severity (PGIS)

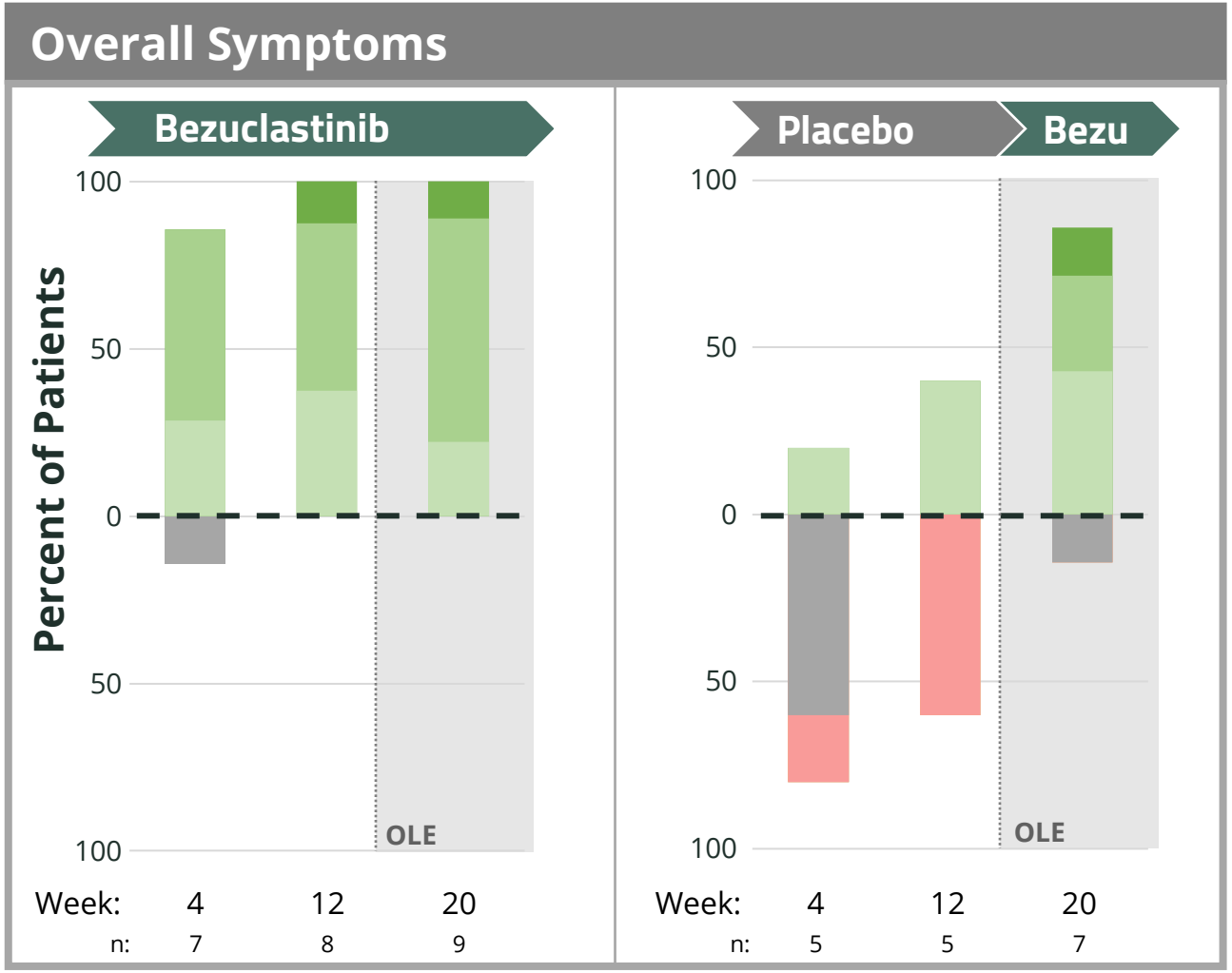
Patients with ≥1 point improvement on PGIS



As of Data Cut-off of 25-Oct-2023

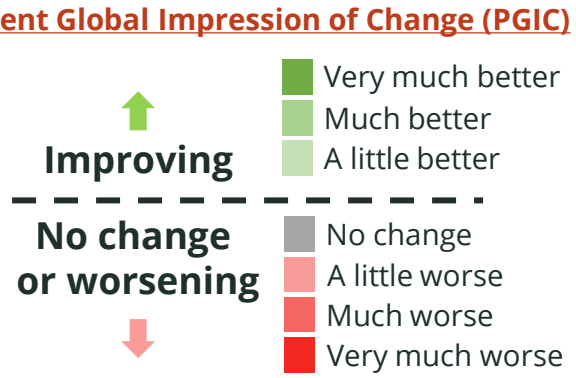
- By the first assessment (4 weeks), 71% (5/7) of patients who received bezuclastinib had ≥1 point improvement in PGIS compared to 0% (0/5) on placebo.
- At 20 weeks, 78% (7/9) of bezuclastinib-treated patients had a ≥1 point improvement.
- During the OLE, 67% (4/6) patients starting bezuclastinib had ≥1 point improvement in overall symptom severity after 4 weeks on active treatment.

100% Bezuclastinib-Treated Patients Reported Overall Symptom Improvement During Part 1a Which Was Sustained During OLE



As of Data Cut-off of 25-Oct-2023

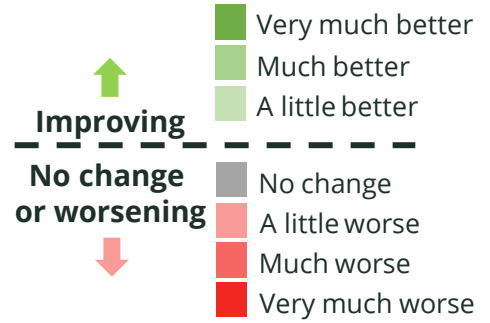
- At week 12, 63% of patients receiving bezuclastinib reported overall symptoms were much better to very much better. After an additional 8 weeks of bezuclastinib in OLE, this increased to 78%.
- At week 12, no patients receiving placebo reported overall symptoms were much better to very much better; after transitioning to bezuclastinib for 8 weeks in OLE, 43% of these patients reported overall symptoms were much better or very much better.

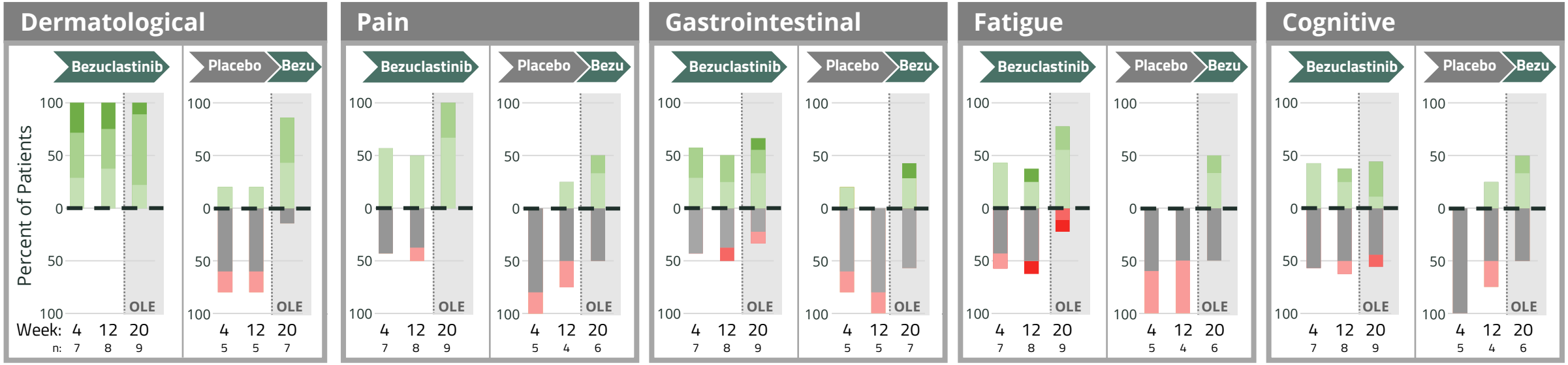


Bezuclastinib-treated Patients Reported Symptomatic Improvement Across Domains During Part 1a Which Deepened During OLE

- With extended treatment (at 20 weeks), 100% of patients reported pain symptoms were better and 78% of patients reported fatigue was improving.
- After 20 weeks of bezuclastinib treatment, more patients compared to week 12 reported dermatological (78%), gastrointestinal (33%), and cognitive symptoms (33%) were much to very much better.

Patient Global Impression of Change (PGIC)



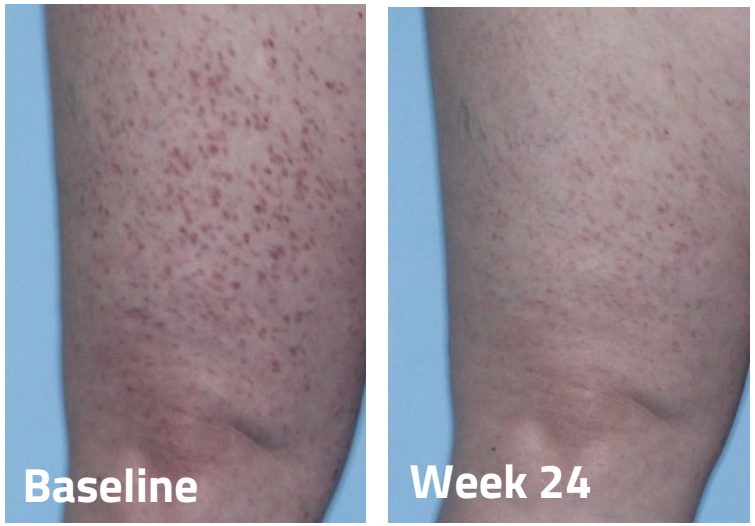


As of Data Cut-off of 25-Oct-2023

Normalization of Serum Tryptase and Concurrent Improvement in Symptoms After 4 Weeks of Bezuclastinib 100mg QD

46 yo woman diagnosed with ISM

- Moderate symptoms despite use of 2 anti-mediator therapies
  - Baseline MAS 32; MC-QoL 58
  - Baseline BSC: fexofenadine/pseudoephedrine; famotidine
- Randomized to bezuclastinib 100mg QD
- All TRAEs were Grade 1 and included hair color changes, taste disorder, peripheral edema, pruritus, skin exfoliation, dry skin



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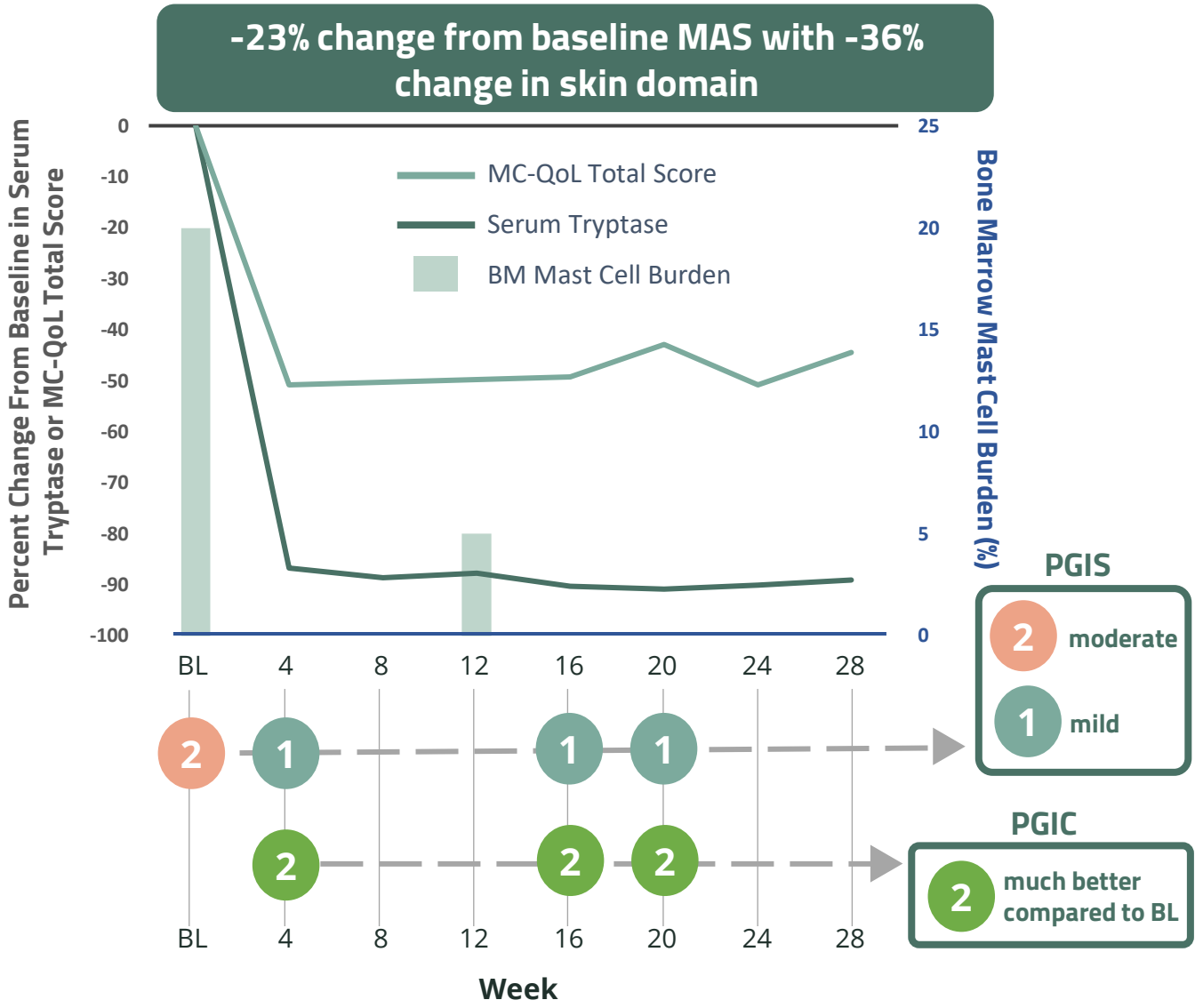

Bezuclastinib treatment demonstrated rapid reduction in mast cell burden, evidence of clinical activity and an encouraging safety profile

- The majority of TEAEs were low grade and reversible with no related SAEs reported
- Safety and tolerability profile in OLE supports potential for chronic dosing
- Within 12 weeks, 100% of patients achieved a ≥50% reduction in markers of mast cell burden (serum tryptase, *KIT* D816V VAF, and bone marrow MC burden)
- Patients reported rapid symptomatic improvement with bezuclastinib treatment that was sustained and deepened over time
  - MC-QoL best improvement was 37% in 12 weeks of Part 1a and 57% during additional 8 weeks in OLE
  - 63% of patients receiving bezuclastinib had ≥1 point improvement in PGIS during Part 1a vs. 0% of placebo patients. This increased to 78% after an additional 8 weeks of bezuclastinib in OLE. After crossing over to bezuclastinib in the OLE 67% of placebo patients had ≥1 point improvement after 4 weeks on active treatment
  - 63% of patients receiving bezuclastinib reported overall symptoms were much to very much better on PGIC at week 12. This increased to 78% of patients after an additional 8 weeks of bezuclastinib in OLE
- Bezuclastinib shows promise as a potential disease modifying therapy for patients with NonAdvSM
  - Additional clinical data from patients in Part 1b expected early 2024; Part 2 initiation planned for 1H2024

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