Symptom-focused Results from Summit Part 1: 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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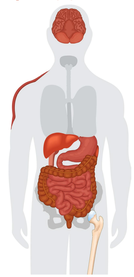
INTRODUCTION

Systemic Mastocytosis (SM) is a Rare and Debilitating Disease Characterized by Neoplastic Mast Cell Infiltration of Extracutaneous Tissues and Symptoms of Mast Cell Activation[1]

- Nonadvanced SM (NonAdvSM)[2] includes smoldering SM (SSM),[3] for which no therapies are approved, as well as indolent SM (ISM).
- Patients with NonAdvSM experience a variety of disabling, potentially serious and severe symptoms caused by mast cell reactions, including life-threatening anaphylaxis.[4]

Figure 1. Symptoms of Nonadvanced Systemic Mastocytosis



Neurocognitive
Difficulty Concentrating, Difficulty Remembering, Brain Fog, Cognitive Dysfunction, Anxiety, Depression

Fatigue
Tiredness

Skin
Itching, Flushing, Skin Redness, Spots

Gastrointestinal/Pain
Nausea, Abdominal pain, Headache, Bone Pain, Diarrhea, Vomiting, Bloating, Gastroesophageal Reflux Disease (GERD)

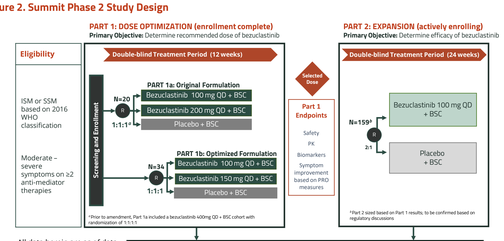
Bezuclastinib is an Oral, Potent, and Selective Type 1 Tyrosine Kinase Inhibitor (TKI) With Activity Against KIT D816V and Encouraging Safety and Tolerability Profile

- Agents targeting KIT D816V are used to treat Advanced SM (AdvSM) and NonAdvSM, but unmet need remains.[5-7]
- Adverse events, such as cognitive impairment, bleeding, and edema, may limit dosing of other agents, resulting in suboptimal symptom control.
- Part 1 of the Summit trial was designed to determine the recommended dose of bezuclastinib on a composite of safety, PK, and PD data. In addition, the study was designed to explore the effects of bezuclastinib on the signs and symptoms of NonAdvSM, including assessment of disease-specific symptom severity using a novel patient-reported outcome measure, the Mastocytosis Symptom Severity Daily Diary (MS2D2).
  - Totality of results from Summit Part 1 support 100 mg QD as the optimal dose of bezuclastinib for patients with NonAdvSM.[8]
  - Bezuclastinib demonstrated an encouraging safety and tolerability profile
  - Data from Part 1 of the Summit trial demonstrated that patients randomized to 100mg Original Formulation and 100 mg Optimized Formulation (the phase 2 selected dose) had similar exposure and PK profiles and significant positive impact on HRQoL measures, skin manifestations, and other symptoms as measured by the MS2D2.[9]

METHODS

Summit (NCT05186753): Phase 2 Clinical Study Evaluating Bezuclastinib in NonAdvSM

Figure 2. Summit Phase 2 Study Design



Mastocytosis Symptom Severity Daily Diary (MS2D2) – A Novel Patient-Reported Outcome Measure (PROM) Designed to Assess Disease-Specific Symptom Severity in NonAdvSM Patients

- The MS2D2[α] is a 17-item measure addressing signs & symptoms of NonAdvSM
- Eleven symptoms within 4 domains are included in MS2D2 Total Symptom Score (TSS) (Table)
  - Severity of each of these symptoms is assessed daily from 0 (none) – 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" PROM to assess treatment efficacy as the primary endpoint in Summit Part 2.

Table 1. MS2D2 Total Symptoms Score (TSS) Domains and Symptoms

Domain	Symptom
Neurocognitive	Concentration Remembering
Fatigue	Tiredness
Skin	Itching Flushing Skin redness Spots
Gastrointestinal /Pain	Nausea Abdominal pain Headache Bone pain

[α]MS2D2 developed according to FDA Guidance for Industry PROMs and regulatory agency feedback; pending alignment with regulatory agency

RESULTS

PATIENT DEMOGRAPHICS, CLINICAL CHARACTERISTICS, AND PK

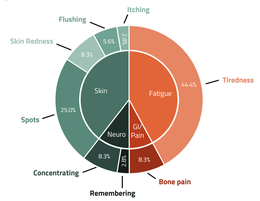
Summit Part 1 Enrolled NonAdvSM Patients with Moderate to Severe Disease

Table 2. Patient Demographics, Baseline Clinical and QOL Characteristics, and Steady State PK at C2D1

Patient Demographics	Part 1a 100mg (N=7)	Part 1b 100mg (N=11)	100mg (1a+1b) (N=18)	Placebo (N=19)
Female, n (%)	6 (85.7)	7 (63.6)	13 (72.2)	13 (68.4)
Median Age in years, (range)	51 (38-72)	61 (39-76)	57.5 (38-76)	56 (36-76)
ECOG PS at screening, n (%)				
0	3 (42.9)	5 (45.5)	8 (44.4)	7 (36.8)
1	4 (57.1)	5 (45.5)	9 (50)	11 (57.9)
2	0 (0)	1 (9.1)	1 (5.6)	1 (5.3)
Clinical Characteristics	**Part 1a 100mg (N=7)**	**Part 1b 100mg (N=11)**	**100mg (1a+1b) (N=18)**	**Placebo (N=19)**
NonAdv Subtype per PI, n (%)				
Indolent SM (ISM)	7 (100)	11 (100)	18 (100)	18 (94.7)
Smoldering SM (SSM)	0	0	0	1 (5.3)
Number of Baseline Supportive Care Meds, n (%)				
2	2 (28.6)	6 (54.5)	8 (44.4)	8 (42.1)
3	2 (28.6)	2 (18.2)	4 (22.2)	5 (26.3)
4+	3 (42.9)	3 (27.3)	6 (33.3)	6 (31.6)
Baseline Mast Cell Burden	**Part 1a 100mg (N=7)**	**Part 1b 100mg (N=11)**	**100mg (1a+1b) (N=18)**	**Placebo (N=19)**
KIT D816V in Whole Blood, Positive, n (%)	6	8	14	15
Median Bone Marrow MC Burden, % (range)	15 (3-25)	15 (2-30)	15 (2-30)	20 (1-80)
Median Serum Tryptase at baseline, ng/mL (range)	77 (10.2-275)	37 (9.8-191)	42.4 (9.8-275)	46.8 (14.8-423)
< 20 ng/mL, n (%)	2	2	4	3
≥ 20 ng/mL, n (%)	5	9	14	16

Baseline QoL Measures	Part 1a 100mg (N=7)	Part 1b 100mg (N=11)	100mg (1a+1b) (N=18)	Placebo (N=19)
Median (range) MS2D2 TSS at Baseline	47.5 (31.6-86.9)	42.3 (24-92.1)	43.6 (24-92.1)	43.4 (22.7-79.8)
Median (range) MCQoL at Baseline	57.4 (27.8-77.8)	52.8 (28.7-90.7)	54.6 (27.8-90.7)	57.4 (31.5-85.2)
PK at Steady State (C2D1)	**Part 1a 100mg (N=7)**	**Part 1b 100mg (N=11)**	**100mg (1a+1b) (N=18)**	**Placebo (N=19)**
Mean (SD) S.S. $AUC_{0\text{-}24h}$ (ng*h/mL)	16900 (29.2)	16900 (41.2)	16900 (36.1)	--

Figure 3. Percentage of Patients with MS2D2 TSS Symptom Identified as the Most Severe



- Skin symptoms and tiredness/fatigue were most commonly identified as the most severe symptom

SAFETY AND TOLERABILITY

Encouraging Safety and Tolerability Profile for Bezuclastinib 100mg (1a+1b)

- The majority of TEAEs were low grade and reversible without dose modification
- No SAEs reported on bezuclastinib
- No bleeding or cognitive impairment events reported
- One dose reduction due to TEAE (100 mg original formulation) and subsequent discontinuation occurred for ALT increased

Table 3. All Cause TEAEs Occurring >10% in active and All Grade 3 events

	Placebo (n=19)		Bezuclastinib					
			Total (n=18)		100mg Original Form (n=7)		100mg Optimized Form (n=11)	
Preferred Term	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3	Gr 1/2	Gr 3
Hair color changes/ hair disorder	1	-	7	-	4	-	3	-
Nausea	5	-	6	-	3	-	3	-
Diarrhea	5	-	4	-	2	-	2	-
Edema peripheral	-	-	3	-	3	-	-	-
GERD	-	-	2	-	2	-	-	-
Taste disorder[#]	-	-	2	-	1	-	1	-
ALT/AST increased	1	-	-	1	-	1	-	-
Neutropenia	-	-	1	1	1	1	-	-
Acute myocardial infarction	-	1	-	-	-	-	-	-

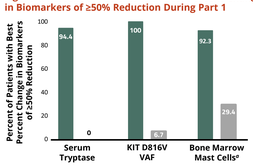
[#] Pooled PTs
GERD, gastroesophageal reflux disease; ALT, alanine transaminase; AST, aspartate transaminase

BIOMARKERS OF MAST CELL BURDEN

Nearly All Patients Experienced At Least 50% Reduction in Biomarkers of Mast Cell Burden During Treatment with Bezuclastinib 100 mg (1a+1b)

- Overall, mean time to first ≥ 50% reduction in tryptase from baseline was 4.8 weeks in those treated with bezuclastinib
- Overall, mean time to first ≥ 50% reduction in KIT D816V VAF from baseline was 6.3 weeks in those treated with bezuclastinib

Figure 4. Percent of Patients with Best Percent Change in Biomarkers of ≥50% Reduction During Part 1

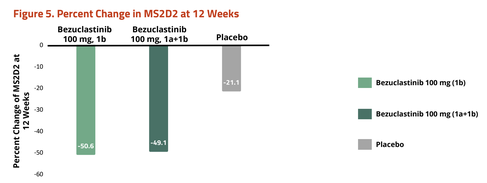


[α]Bone marrow mast cell assessment in systemic mastocytosis is characteristically variable

PATIENT-REPORTED OUTCOME MEASURES

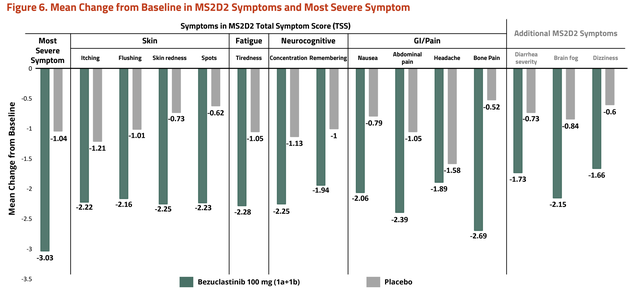
Symptomatic Improvement on 12 Week MS2D2 TSS Consistent Across All Part 1 Patients Treated With 100 mg

Figure 5. Percent Change in MS2D2 at 12 Weeks



Bezuclastinib 100 mg (1a+1b) Treatment Resulted in Improvement Across All Symptoms of NonAdvSM Within 12 Weeks as Measured by MS2D2

Figure 6. Mean Change from Baseline in MS2D2 Symptoms and Most Severe Symptom



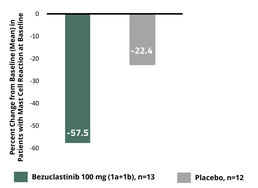
- Bezuclastinib treatment resulted in broad improvement in all symptoms included in the MS2D2 TSS, as well as patients' most severe baseline symptom.
- The most severe symptom at baseline for patients receiving bezuclastinib 100mg decreased 41.74% (vs. 14.24% for placebo).
- Symptoms not included in the MS2D2 TSS also improved among patients receiving bezuclastinib 100mg, including diarrhea severity, dizziness and brain fog.
- Bezuclastinib 100mg demonstrated clinically meaningful changes compared to placebo in patients' symptoms related to NonAdvSM.

Patients Report Fewer Days With a Mast Cell Reaction After 12 Weeks of Bezuclastinib 100 mg (1a+1b)

- During the 14 days prior to the start of the study:
  - 72% (13/18) of patients in the bezuclastinib cohort and 67% (12/18) of patients in the placebo cohort reported at least 1 mast cell reaction.
  - In the patients reporting mast cell reactions at baseline, mast cell reactions were reported on an average (range) of 8.5 (1 – 14) days and 10.9 (1 – 14) days in the bezuclastinib and placebo groups, respectively,
- During the 14 days prior to Week 12, patients treated with bezuclastinib reported a mast cell reaction on average on 3.5 days vs 8.3 days for placebo.

[α]In the MS2D2 assessment, patients are asked if they experienced a mast cell reaction in the past 24 hours. Mast cell reaction is defined as "an increase in your symptoms of mastocytosis, which may be sudden and/or severe."

Figure 7. Percent Change from Baseline in Patients with Mast Cell Reaction at Baseline



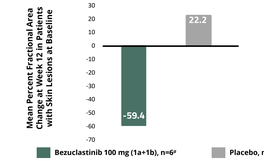
OBJECTIVE SKIN ASSESSMENT

Surface Area of Mastocytosis Skin Lesions Were Significantly Reduced at 12 Weeks in Patients Treated With Bezuclastinib 100mg (1a+1b)

- Digital skin photography assessment:
  - Affected body surface area centrally analyzed using novel technology by Canfield Scientific, Inc., specializing in assessment of Mastocytosis skin lesions
  - Independent committee review at baseline and 12w
- Patients on bezuclastinib 100mg had ~60% reduction in skin lesions compared to an increase of 22% in those on placebo during Part 1 of Summit

[α]Skin photography was an optional assessment.

Figure 8. Mean Percent Fractional Area Change at Week 12 in Patients with Skin Lesions at Baseline



PATIENT CASE

65 Year Old Male Treated With Bezuclastinib 100mg QD (Part 1b) Has Significant Skin, QoL, and Mast Cell Burden Response

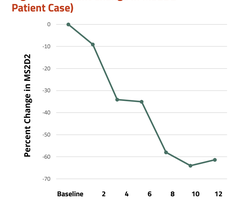
Safety
- No related adverse events reported

Efficacy
- 42% reduction in surface area skin lesions of most affected area (back)

Table 4. Measures of Efficacy (Patient Case)

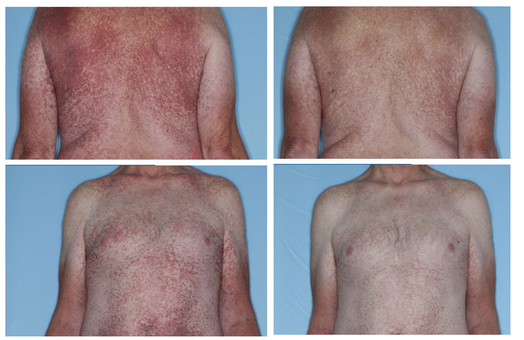
	Baseline	Week 12	Percent Change
Markers of Mast Cell Burden			
Serum Tryptase (ng/mL)	102	10.9	-89.3
KIT D816V VAF (%)	1.9	0.37	-80.5
BM MC Burden (%)	20	0.7	-96.5
PRO and QoL Measures			
MC-QoL Total Score[α]	33.3	10.2	-69.4
MS2D2 Total Symptom Score	29.8	11.5	-61.4

Figure 9. Percent Change in MS2D2 Patient Case)



[α]MC-QoL is a disease-specific HRQoL questionnaire with 27 items in 4 domains. Total score is linearly transformed to a 0 to 100 scale.[10]

Figure 10. Skin Photography at Baseline and Week 12



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CONCLUSIONS

Further Characterization of Clinical Benefit in Patients Treated With 100 mg Bezuclastinib Across All of Part 1 Supports Bezuclastinib as a Promising Therapy for Patients With NonAdvSM

- Consistent with previous results:
  - Favorable safety and tolerability profile, as previously reported
    - No bleeding or cognitive impairment AEs reported
    - No SAEs
  - Significant and deep reductions (>90%) across all markers of mast cell burden
- Additional data show meaningful reduction in symptom severity and objective measures of disease:
  - Substantial reduction in mast cell reactions (>50%) and patients' most severe symptoms as measured by MS2D2
  - Clinically meaningful reduction in all individual MS2D2 TSS symptoms and across domains, as well as additional symptoms including dizziness, diarrhea severity, and brain fog
  - Clinically meaningful improvement in skin symptoms as well as objective reduction in skin lesions
- Summit Part 2 is actively enrolling patients

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REFERENCES 1. Pardanani A. Am J 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. 5. DeAngelo D, et al. Nat Med, 2021, 27(12):2183-2191. 6. Ayvakit (avapritinib) [product information]. Cambridge, MA: Blueprint Medicines Corporation; May 2023. 7. DeAngelo et al. [abstract] In: Blood (ASH) 2022; 140 (Supplement 1): 1512-13. 8. Modena et al. JACI (AAAAI). 153(2)_suppl. [abstract AB224]. 9. Modena et al. J Allergy Clin Immunol (AAAAI) 2024. Poster 694. 10. Siebenhaar et al. Allergy 2016 71(6):869-77.