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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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 degranulation, including life-threatening anaphylaxis.[4]

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

- 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.

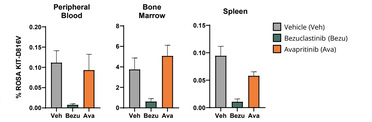
Nonclinical Data Suggests Optimal Activity Against Mastocytosis May Require Higher Exposures Than Clinically Tolerable With Available Therapy

- Mice engrafted with SCF-independent human ROSA$^{KIT\ D816V}$ cells[8] were treated daily for 8 weeks with a KIT inhibitor at doses matching clinical exposures observed in NonAdvSM patients.
- Only bezuclastinib led to statistically significant decreases ($p<0.05$) in mutant MC burden compared to vehicle.
- At exposures comparable to those achieved in NonAdvSM patients, bezuclastinib led to statistically significant decreases ($P<0.05$) in bone marrow and spleen compared to avapritinib.

Table 1. Total Drug Exposure Ratio Measured in SM Mouse Model

	Mouse Plasma $AUC_{0\text{-}24}$ (ng·hr/mL)[a]	NonAdvSM Clinical Plasma $AUC_{0\text{-}24}$ (ng·hr/mL)[b]	Total Drug Exposure Ratio (mouse/clinic)
Bezuclastinib	11775	16900	**0.7X**
Avapritinib	2118	1548	**1.4X**

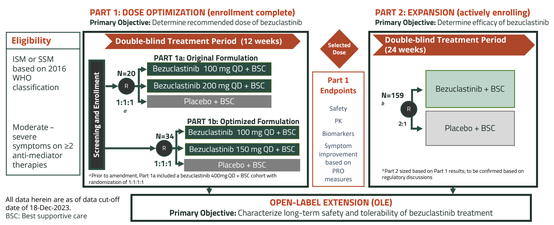
Figure 1. MC Burden in SM Mouse Model



[a]Plasma exposures were measured at study end and corrected for difference in plasma protein binding
[b]Arithmetic mean steady state AUC for bezuclastinib 100mg (Summit) or avapritinib 25mg (EPAR, table 9)

METHODS

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



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

All data herein are as of data cut-off date of 18-Dec-2023.
BSC: Best supportive care

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

- Eleven symptoms contribute to the MS2D2 Total Symptom Score (TSS).
- 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 2. Symptoms Contributing to MS2D2[a] TSS

Itching	Feeling of tiredness	Headache
Flushing	Difficulty concentrating	Bone Pain
Covered with spots	Difficulty remembering things	Nausea
Skin redness		Abdominal pain
TSS (0 – 110) Higher scores represent more severe symptoms		

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

RESULTS

Bezuclastinib 100mg QD Optimized Formulation Selected as Summit Part 2 Dose Based on Part 1 Safety, PK, Biomarker and Efficacy Results

Summit Part 1 Enrolled NonAdvSM Patients with Moderate to Severe Disease

Table 3. Patient Demographics, Characteristics, and Disposition

Patient Demographics	Part 1a (N=20)	Part 1b (N=34)
Female, n (%)	15 (75)	21 (61.8)
Median Age in years, n (range)	50.5 (38 – 75)	52.0 (27-76)
ECOG PS, n (%)		
0	3 (15)	16 (47.1)
1	15 (75)	17 (50.0)
2	2 (10)	1 (2.9)
Clinical Characteristics	**Part 1a (N=20)**	**Part 1b (N=34)**
NonAdv Subtype per PI, n (%)		
Indolent SM (ISM)	18 (90)	33 (97)
Smoldering SM (SSM)	2 (10)	1 (3)
Median (range) MAS Total Score at Eligibility	45.56 (26.3 – 71.6)	43.44 (28.6 – 65.4)
Mast Cell Burden	**Part 1a (N=20)**	**Part 1b (N=34)**
KIT D816V in Whole Blood, Positive, n (%)	15 (75)	28 (82.4)
Median KIT D816V VAF, % (range)	0.49 (BLD – 32.48)	0.085 (BLD - 19.58)
Median Bone Marrow MC Burden, % (range)	22.5 (1 – 80)	15 (2 – 50)
Median Serum Tryptase, ng/mL (range)	74.35 (10.2- 592.0)	37.15 (9.2 - 206.0)
<20 ng/mL, n (%)	3 (15)	7 (20.6)
≥20 ng/mL, n (%)	17 (85)	27 (79.4)

SM Therapy	Part 1a (N=20)	Part 1b (N=34)
Prior avapritinib, n (%)	1 (5.0)	1 (2.9)
Baseline Supportive Care Medications, Median (range)	3 (2-7)	2.5 (2 – 9)
H1 blockers, n (%)	19 (95)	30 (88.2)
H2 blockers, n (%)	18 (90)	27 (79.4)
Leukotriene receptor antagonists, n (%)	8 (40)	14 (41.2)
Proton pump inhibitors, n (%)	7 (35)	9 (26.5)
Cromolyn sodium, n (%)	4 (20)	3 (8.8)
Omalizumab, n (%)	3 (15)	1 (2.9)
Corticosteroids, n (%)	1 (5)	1 (2.9)
Patient Disposition	**Part 1a (n=20)**	**Part 1b (N=34)**
Months on Study (Part 1 + OLE), median (range)	7.03 (2.8 – 16.0)	4.09 (2.7-6.6)
Completed Part 1 (a or b), n (%)	20 (100)	34 (100)
On Study as of Data Cut-off, n (%)	18 (90)	33 (97.1)
Discontinued study, n (%)	2 (10)	1 (2.9)
AE, n (%)	1 (5)	1 (2.9)
Patient Decision, n (%)	1 (5)	0

BLD, below the limit of detection

Encouraging Safety and Tolerability Profile for Bezuclastinib 100mg Dose in Part 1b

Table 4. All Treatment-Emergent Adverse Events (TEAEs) Occurring >1 Patient in Any Cohort in Part 1b

	Placebo (n=12)		Bezuclastinib 100mg QD (n=11)		Bezuclastinib 150mg QD (n=11)	
Preferred Term	Gr 1/2	Gr 3+	Gr 1/2	Gr 3+	Gr 1/2	Gr 3+
Hair color changes	-	-	3	-	7	-
Diarrhea	2	-	2	-	2	-
Nausea	3	-	3	-	1	-
Taste disorder[#]	-	-	1	-	2	-
Dizziness	2	-	-	-	2	-
Fatigue	1	-	-	-	2	-
Noncardiac chest pain	1	-	-	-	2	-
ALT/AST increased[#]	1	-	-	-	1	1*
Neutropenia[#]	-	-	-	-	1	1*
COVID-19	3	-	1	-	-	-
Insomnia	2	-	-	-	-	-
Decreased appetite	2	-	-	-	-	-
Vomiting	2	-	-	-	-	-
Urticaria	2	-	-	-	-	-
Palpitations	2	-	-	-	-	-

- The majority of TEAEs were low grade and reversible without dose modification
- No bleeding or cognitive impairment events reported across bezuclastinib cohorts
- No dose reductions at 100mg cohort; two dose reductions at 150mg: Gr1 ALT, Gr2 abdominal pain
- Only one SAE reported in bezuclastinib cohorts (150mg patient experienced ALT/AST increase that led to discontinuation)

*Events occurred in a single patient
Pooled PTs

Bezuclastinib Demonstrated Dose Dependent Increase in Mean Steady State Exposure

Figure 3. Summit Part 1b: Mean (± SD) Concentration on C2D1 (Steady State)

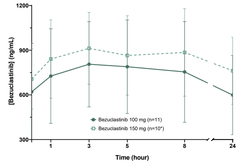


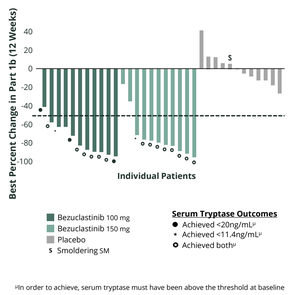
Table 5. Comparable Exposures for Low and High Dose Across Part 1a and 1b

	Dose (mg), Study Part	N	Mean S.S. $AUC_{0\text{-}24h}$ (ng.h/mL)
Low Dose	**100, 1a**	7	16900
	100, 1b	11	16900
High Dose	**200, 1a**	5	19200
	150, 1b	10*	19700

*Excludes one patient with undetectable trough and anomalous low C2D1 exposure

Bezuclastinib Elicited Deep Reductions Across Markers of Mast Cell Burden Within 12 Weeks

Figure 4. Serum Tryptase (n=34)



[a]In order to achieve, serum tryptase must have been above the threshold at baseline

Serum Tryptase

- Of patients with baseline tryptase ≥20ng/mL, nearly all patients treated with bezuclastinib achieved <20ng/mL (100% on 100 mg, 89% on 150 mg, 0% on placebo)
  - Overall, mean time to tryptase <20ng/mL was 4.5 weeks for patients treated with bezuclastinib
- Of patients with baseline tryptase ≥11.4ng/mL: 70% on 100mg, 90% on 150mg and 0% on placebo achieved <11.4ng/mL

KIT D816V VAF

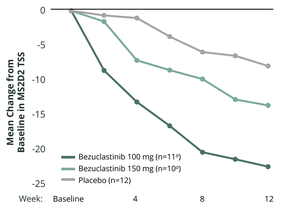
- Among patients with detectable KIT D816V at baseline: 100% on 100mg, 89% on 150mg and 0% on placebo achieved at least 50% reduction or undetectable KIT D816V at Week 12

Bone Marrow Mast Cells (BM MC)

- Among patients with evaluable BM: 86% on 100mg, 78% on 150mg and 40% on placebo achieved ≥50% reduction in BM MC at Week 12
  - Mean % change from baseline in BM MC at Week 12 for patients treated with bezuclastinib 100mg was -70% vs -30% on placebo

Patients Treated With Bezuclastinib 100mg Reported Rapid and Significant Improvement in Symptom Severity

Figure 5. Symptom Severity Measured by MS2D2

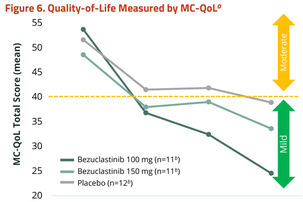


- 51% mean improvement in overall symptom severity (MS2D2 TSS) from baseline at Week 12 for patients receiving 100 mg bezuclastinib vs. 18% improvement for placebo patients
- Patients treated with 100 mg bezuclastinib reported a significant reduction in total symptom severity vs. placebo at Week 12 (-23.78 vs. -9.03; p=0.0003)
- 70% of patients treated with 100 mg bezuclastinib achieved ≥50% reduction in MS2D2 TSS at Week 12 vs. 8% placebo patients

[a]Data are unavailable for 1 patient at selected timepoints

Patients Treated With Bezuclastinib 100mg Reported Rapid and Significant Improvement in Quality of Life

Figure 6. Quality-of-Life Measured by MC-QoL[a]



- 49% mean improvement in quality of life (MC-QoL) from baseline at Week 12 in patients treated with 100 mg bezuclastinib vs 24% for placebo
- Patients reported a significant improvement in quality of life after 12 weeks of bezuclastinib 100mg QD compared to placebo (–24.86 vs. -12.39, p=0.046)

[a]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]
[a]Data are unavailable for 2 patients at selected timepoints

Bezuclastinib 100mg QD Demonstrated Improvement Compared to Placebo Across Symptoms of SM

Figure 7. Greater Improvement Observed in the MS2D2 TSS With 12 Weeks of Bezuclastinib 100 mg vs Placebo

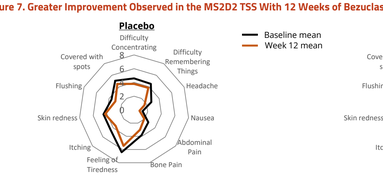
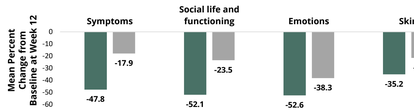
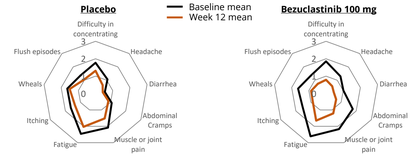


Figure 8. Health-Related QoL Across All MC-QoL[a] Domains Improved With 12 Weeks of Bezuclastinib 100mg vs Placebo



[a]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.[9]

Figure 9. Bezuclastinib 100 mg Improved Symptom Severity, As Measured by the Mastocytosis Activity Score[a] (MAS), Compared to Placebo



- 41% mean improvement from baseline in MAS at Week 12 for patients receiving 100 mg bezuclastinib vs. 21% improvement for placebo
- 50% of patients treated with 100 mg bezuclastinib achieved ≥50% improvement in MAS at week 12 vs. 0% placebo patients

[a]MAS is a disease-specific PROM used to assess symptom severity and consists of 9 items.[10] Severity of each item is rated from not at all (0) to very severe (4). For the Week 12 assessment, items are scored daily for 14 consecutive days prior to the end of the 12-week treatment period. The scores shown here are a mean for subjects in the 100mg cohort (N=10) versus the placebo cohort (N=12)

CONCLUSIONS

Totality of Results from Summit Part 1 Support 100 mg QD as the Optimal Dose of Bezuclastinib for Patients With NonAdvSM

In Part 1b, bezuclastinib 100mg QD resulted in:

- Safety and tolerability profile generally consistent with placebo results
  - No bleeding, cognitive impairment, or edema AEs reported
  - No dose reductions or discontinuations due to AEs
- Rapid reductions across markers of mast cell burden, supported by KIT D816V mechanism and exposure evidence from nonclinical studies
- Significant improvement versus placebo at 12 weeks in both symptom severity and quality of life, based on mean change from baseline in MS2D2 and MC-QoL total scores which corresponds to:
  - 51% reduction in symptom severity (measured by MS2D2)
  - 49% improvement in health-related quality-of-life (measured by MC-QoL)
- 70% of patients achieving ≥50% improvement in symptom severity versus 8% on placebo, as measured by MS2D2

Summit Part 2 is actively enrolling patients

SOHO Annual Meeting
Houston, TX
September 4-7, 2024

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