

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 Activation¹

- Nonadvanced SM (NonAdvSM)² includes smoldering SM (SSM),³ for which no therapies are approved, as
- Patients with NonAdvSM experience a variety of disabling, potentially serious and severe symptoms

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

- Mice engrafted with SCF-independent human ROSAKIT D816V cells8 were treated daily for 8 weeks with a KIT inhibitor at doses matching clinical exposures
- Only bezuclastinib led to statistically significant decreases (p<0.05) in mutant MC burden compared to
- At exposures comparable to those achieved in NonAdvSM patients, bezuclastinib led to statistically marrow and spleen compared to

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

37.15 (9.2 - 206.0)

27 (79.4)

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

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, %	22.5 (1 – 80)	15 (2 – 50)

17 (85)

Table 4. All Treatment-Emergent Adverse Events (TEAEs) Occurring

Sivi Therapy	Part 1a (N=20)	Part 10 (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

The majority of TEAEs were low grade

No bleeding or cognitive impairment

events reported across bezuclastinib

No dose reductions at 100mg cohort;

two dose reductions at 150mg: Gr1

bezuclastinib cohorts (150mg patient

experienced ALT/AST increase that led

ALT, Gr2 abdominal pain

Only one SAE reported in

to discontinuation)

Events occurred in a single patient

and reversible without dose

modification

cohorts

>1 Patient in Any Cohort in Part 1b

<20 ng/mL, n (%)

<u>></u>20 ng/mL, n (%)

Hair color changes

Noncardiac chest pa

ALT/AST increased[#]

Decreased appetite

Taste disorder[‡]

Dizziness

Neutropenia[‡]

COVID-19

Vomiting

Urticaria

Fatigue

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

Figure 4. Serum Tryptase (n=34) 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)

Of patients with baseline tryptase ≥11.4ng/mL: 70% on 100mg, 90% on 150mg and 0% on placebo achieved <11.4ng/mL

 Overall, mean time to tryptase <20ng/mL was 4.5 weeks for patients treated with bezuclastinib

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)

placebo patients

8% placebo patients

^aData are unavailable for 1 patient at selected timepoints

mg bezuclastinib vs 24% for placebo

^bData are unavailable for 2 patients at selected timepoints

 Among patients with evaluable BM: 86% on 100mg, 78% on 150mg and 40% on placebo achieved ≥50% reduction in BM MC at Week 12

51% mean improvement in overall symptom severity

(MS2D2 TSS) from baseline at Week 12 for patients

receiving 100 mg bezuclastinib vs. 18% improvement for

Patients treated with 100 mg bezuclastinib reported a

achieved ≥50% reduction in MS2D2 TSS at Week 12 vs.

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

 Mean % change from baseline in BM MC at Week 12 for patients treated with bezuclastinib 100mg was -70% vs -30% on placebo

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

Figure 5. Symptom Severity Measured by MS2D2

Bezuclastinib 100 mg (n=11

Bezuclastinib 150 mg ($n=10^a$)

● Achieved < 20ng/mL^µ

◆ Achieved both^µ

★ Achieved <11.4ng/mL^µ

Bezuclastinib 100 mg

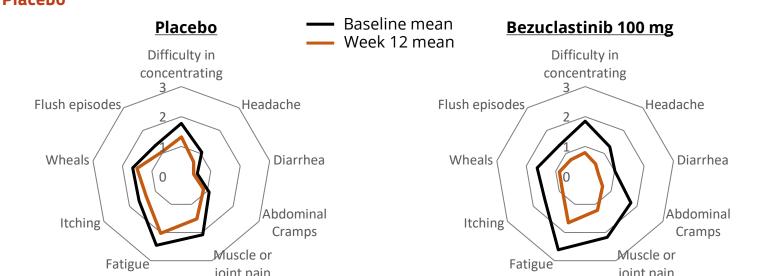
Bezuclastinib 150 mg

Placebo

Symptom Severity

Smoldering SM

Figure 9. Bezuclastinib 100 mg Improved Symptom Severity, As Measured by the Mastocytosis Activity Score^a (MAS), Compared to Patients Treated With Bezuclastinib 100mg Reported Rapid and Significant Improvement in



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

Bezuclastinib 100 mg (n=9)

omains. Total score is linearly

transformed to a 0 to 100 scale

Placebo (n=11)

patients 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

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

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

- caused by mast cell degranulation, including life-threatening anaphylaxis.⁴

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**
- observed in NonAdvSM patients.
- significant decreases (P<0.05) in bone

	0-24 (AUC	₀₋₂₄ (ng·hr/ml	_)"	(mouse/clinic)	
Bezuclastinib	11775		16900		0.7X	
Avapritinib	2118		1548		1.4X	
gure 1. MC B	urden in SM Mouse N	/lodel				
Peripher Blood	al Bone Marrow		Spleen			
0.207	87	0.15			Vehicle (Veh)	

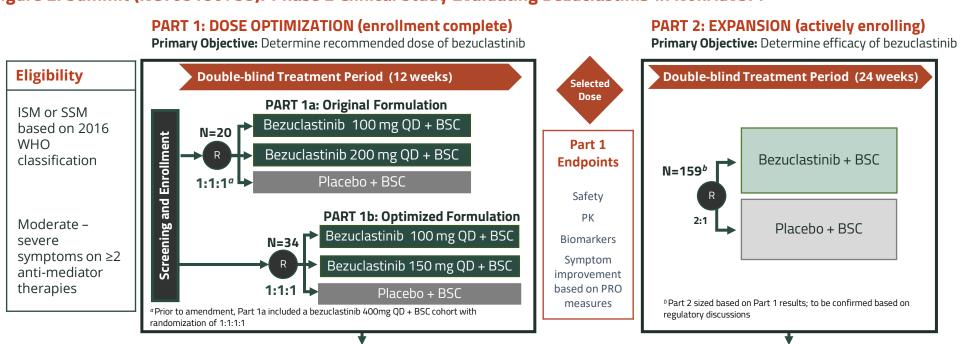
Bezuclastinib (Bezu)

Avapritinib (Ava)

^bArithmetic 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



All data herein are as of data cut-off 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

OPEN-LABEL EXTENSION (OLE)

Primary Objective: Characterize long-term safety and tolerability of bezuclastinib treatment

feedback; pending alignment with regulatory agency

- Eleven symptoms contribute to the MS2D2 Total Symptom Score (TSS).
- Severity of each of these symptoms is assessed daily from 0 (none) – 10 (worst
- 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.

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Table 2 Symptoms Contributing to MS2D2ªTSS

Table 2. Symptoms Contributing to MS2D2" 155			
Itching	Feeling of tiredness	Headache	
Flushing	Difficulty concentrating	Bone Pain	
Covered with spots	Difficulty remembering	Nausea	
Skin redness	things	Abdominal pain	
TSS (0 – 110) Higher scores represent more severe symptoms			

^oMS2D2 developed according to FDA Guidance for Industry PROMs and regulatory agency

Bezuclastinib Demonstrated Dose Dependent Increase in Mean Steady State Exposure

Figure 3. Summit Part 1b: Mean (± SD) Concentration

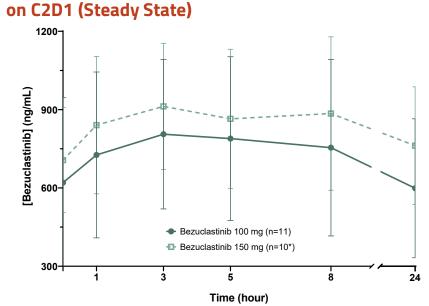


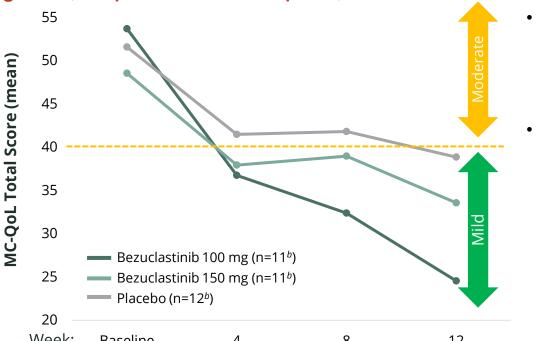
Table 5. Comparable Exposures for Low and High Dose Across

	Dose (mg), Study Part	N	Mean S.S. AUC _{0-24h} (ng.h/mL)
Law Daga	100, 1a	7	16900
Low Dose	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

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

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



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)

49% mean improvement in quality of life (MC-QoL) from

baseline at Week 12 in patients treated with 100

^aMC-OoL is a disease-specific HRQoL questionnaire with 27 items in 4 domains. Total score is linearly transformed to a 0 to 100 scale. 10

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BLD, below the limit of detection