

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)

Brian D. Modena¹, Lindsay A. M. Rein², Stephen T. Oh³, Daniel J. DeAngelo⁴, Anthony M. Hunter⁵, Cem Akin⁶, Mariana Castells⁷, Michael Manning⁸, Richard Herrscher⁹, Celalettin Ustun¹⁰, Arnold Kirshenbaum¹¹, Cristina Bulai Livideanu¹², Nathan A. Boggs¹³, Cecilia Arana Yi¹⁴, Frank Siebenhaar^{15,16}, Tracy I. George¹⁷, Jay Patel¹⁷, Lei Sun¹⁸, Benjamin Exter¹⁸, Jenna Zhang¹⁸, Amanda Pilla¹⁸, Hina A. Jolin¹⁸, Rachael Easton¹⁸, Prithviraj Bose¹⁹

1. Modena Allergy & Asthma, San Diego, CA, USA; 2. Duke University, Durham, NC, USA; 3. Washington University School of Medicine, St. Louis, Missouri, USA; 4. Dana-Farber, Boston, MA, USA; 5. Emory University School of Medicine, Atlanta, GA, USA; 6. University of Michigan, Ann Arbor, MI, USA; 7. Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; 8. Allergy, Asthma, & Immunology Associates, Scottsdale, AZ, USA; 9. AirCare, Plano, TX, USA; 10. Rush University Medical Center, Chicago, IL; 11. Allervie Clinical Research, Glenn Dale, MD; 12. CEREMAST Toulouse, Dermatology Department, Toulouse University Hospital, Toulouse, France; 13. Walter Reed National Military Medical Center, Bethesda, MD; 14. Mayo Clinic Arizona, Phoenix, AZ; 15. Institute of Allergology, Charité - Universitätsmedizin Berlin, Berlin, Germany; 16. Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology IA, Berlin, Germany; 17. University of Utah, ARUP Laboratories, Salt Lake City, UT, USA; 18. Cogent Biosciences Inc., Waltham, MA, USA; 19. MD Anderson Cancer Center, Houston, Texas, USA

Poster Number: 694

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 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 cells⁸ were treated daily for 8 weeks with a KIT inhibitor at doses matching clinical exposures observed in NonAdvSM patients.

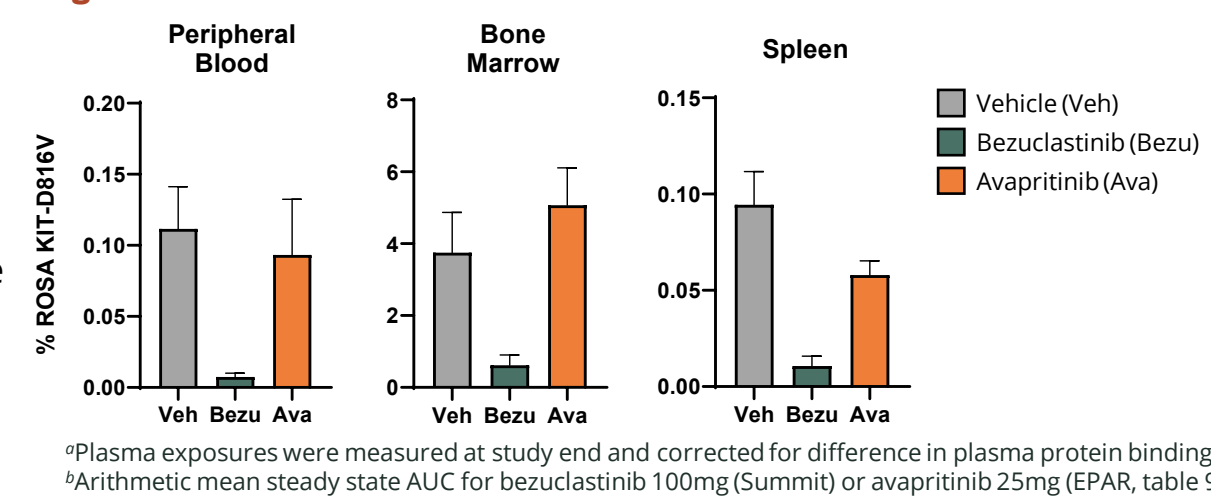
- Only bezuclastinib led to statistically significant decreases (p<0.05) in mutant MC burden compared to vehicle.

- 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

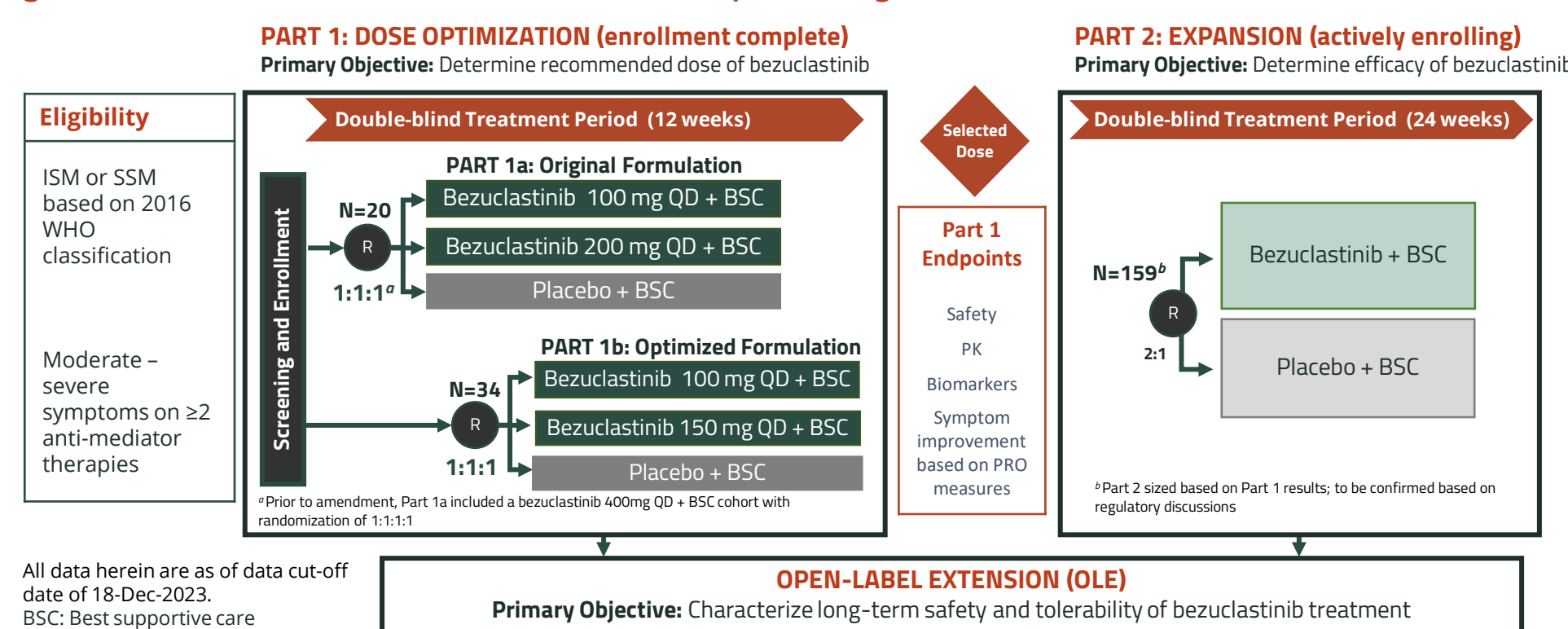
	Mouse Plasma AUC ₀₋₂₄ (ng·hr/mL) ^a	NonAdvSM Clinical Plasma AUC ₀₋₂₄ (ng·hr/mL) ^b	Total Drug Exposure Ratio (mouse/clinic)
Bezuclastinib	11775	16900	0.7X
Avapritinib	2118	1548	1.4X

Figure 1. MC Burden in SM Mouse Model



METHODS

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



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 MS2D2² 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		

^aMS2D2 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)	SM Therapy	Part 1a (N=20)	Part 1b (N=34)
Female, n (%)	15 (75)	21 (61.8)	Prior avapritinib, n (%)	1 (5.0)	1 (2.9)
Median Age in years, n (range)	50.5 (38 – 75)	52.0 (27-76)	Baseline Supportive Care Medications, Median (range)	3 (2-7)	2.5 (2 – 9)
ECOG PS, n (%)			H1 blockers, n (%)	19 (95)	30 (88.2)
0	3 (15)	16 (47.1)	H2 blockers, n (%)	18 (90)	27 (79.4)
1	15 (75)	17 (50.0)	Leukotriene receptor antagonists, n (%)	8 (40)	14 (41.2)
2	2 (10)	1 (2.9)	Proton pump inhibitors, n (%)	7 (35)	9 (26.5)
Clinical Characteristics	Part 1a (N=20)	Part 1b (N=34)	Cromolyn sodium, n (%)	4 (20)	3 (8.8)
NonAdv Subtype per PI, n (%)			Omalizumab, n (%)	3 (15)	1 (2.9)
Indolent SM (ISM)	18 (90)	33 (97)	Corticosteroids, n (%)	1 (5)	1 (2.9)
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)	Patient Disposition	Part 1a (n=20)	Part 1b (N=34)
NonAdv Subtype per PI, n (%)			Months on Study (Part 1 + OLE), median (range)	7.03 (2.8 – 16.0)	4.09 (2.7-6.6)
Indolent SM (ISM)	18 (90)	33 (97)	Completed Part 1 (a or b), n (%)	20 (100)	34 (100)
Smoldering SM (SSM)	2 (10)	1 (3)	On Study as of Data Cut-off, n (%)	18 (90)	33 (97.1)
Median (range) MAS Total Score at Eligibility	45.56 (26.3 – 71.6)	43.44 (28.6 – 65.4)	Discontinued study, n (%)	2 (10)	1 (2.9)
NonAdv Subtype per PI, n (%)			AE, n (%)	1 (5)	1 (2.9)
Indolent SM (ISM)	18 (90)	33 (97)	Patient Decision, n (%)	1 (5)	0
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
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)			
NonAdv Subtype per PI, n (%)					