Efficacy and Safety Results of Adult Patients with NonAdvanced Systemic Mastocytosis Receiving Bezuclastinib 100 mg in the Ongoing Summit Trial:
A Randomized, Double-Blind, Placebo Controlled Phase 2 Clinical Trial of Bezuclastinib

Nathan A. Boggs[1], Daniel J. DeAngelo[2], Lindsay Rein[3], Prithviraj Bose[4], Stephen Oh[5], Cristina Bulai Livideanu[6], Celalettin Ustun[7], Michael Manning[8], Anthony M. Hunter[9], Cem Akin[10], Arnold Kirshenbaum[11], Ingunn Dybedal[12], Cecilia Arana Yi[13], Richard Herrscher[14], Mariana Castells[15], Frederick Lansigan[16], Tracy I. George[17], Jay Patel[17], Lei Sun[18], Nisha Shah[18], Jenna Zhang[18], Amanda Pilla[18], Priya Singh[18], Rachael Easton[18], Frank Siebenhaar[19,20], Brian Modena[21]

1. Walter Reed, Bethesda, MD, USA; 2. Dana-Farber Cancer Institute, Boston, MA, USA; 3. Duke University, Durham, NC, USA; 4. MD Anderson Cancer Center, Houston, TX, USA; 5. Washington University School of Medicine, St. Louis, MO, USA; 6. CEREMAST Toulouse, Dermatology Department, Toulouse University Hospital, Toulouse, France; 7. Rush University Medical Center, Chicago, IL, USA; 8. Allergy, Asthma, & Immunology Associates, Scottsdale, AZ, USA; 9. Emory University School of Medicine, Atlanta, GA, USA; 10. University of Michigan, Ann Arbor, MI, USA; 11. AllerVie Clinical Research, Glenn Dale, MD; 12. Oslo University Hospital, Oslo, Norway; 13. Mayo Clinic Arizona, Phoenix, AZ; 14. AirCare, Plano, TX, USA; 15. Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; 16. Dartmouth Hitchcock Medical Center, Lebanon, NH, USA; 17. University of Utah, ARUP Laboratories, Salt Lake City, UT, USA; 18. Cogent Biosciences Inc., Waltham, MA, USA; 19. Charité–Universitaetsmedizin Berlin, Berlin, Germany; 20. Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology IA, Berlin, Germany. 21. Modena Allergy & Asthma, San Diego, CA, USA

Summit NONADVANCED SM

Poster #520

INTRODUCTION

Systemic Mastocytosis is a Rare, Debilitating Disease Characterized by Neoplastic Mast Cell Infiltration of Skin and/or Extracutaneous Tissues and Symptoms of Mast Cell Activation[1]

- Nonadvanced SM (NonAdvSM)[2] includes indolent SM (ISM) as well as smoldering SM (SSM),[2] for which no disease-modifying therapies are approved
- Patients with NonAdvSM experience a variety of disabling, potentially serious and severe symptoms including neurocognitive, fatigue, skin, gastrointestinal, pain, respiratory, cardiovascular, and systemic
  - Symptoms may significantly reduce health-related quality of life and require polypharmacy to manage[4]
  - Symptoms are caused by mast cell reactions and can include life-threatening anaphylaxis[5]
- Agents targeting KIT D816V are used to treat Advanced SM (AdvSM) and NonAdvSM, but unmet need remains[6-8]
  - AEs like cognitive impairment, bleeding, and edema can limit dosing of other agents, resulting in poor symptom control

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

Totality of results from Summit Part 1 supported 100mg QD as the optimal dose of bezuclastinib[9]
- Encouraging safety and tolerability profile[10]
- Significant improvements versus placebo at 12 weeks in symptom severity (MS2D2 TSS), quality of life, and mast cell burden[10]

Results After 24 Weeks of Active Treatment with 100mg Bezuclastinib in Summit:[1]
- Favorable safety and tolerability profile with continued treatment
- 76% of patients achieved at least a 50% reduction in symptom severity (MS2D2 TSS)
- Substantial reduction in the patients' most severe symptom
- 89% of patients with a ≥50% decrease in serum tryptase levels
- 31% of patients with reductions or discontinuations of BSC medications

METHODS

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[a] is a 17-item measure addressing signs and symptoms of NonAdvSM
- Eleven symptoms within 4 domains are included in MS2D2 Total Symptom Score (TSS)
  - Severity of each of these symptoms is assessed daily from 0 (none) to 10 (worst possible)
  - TSS is analyzed as a 14-day average
  - TSS ranges from 0 to 110
- 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[a]

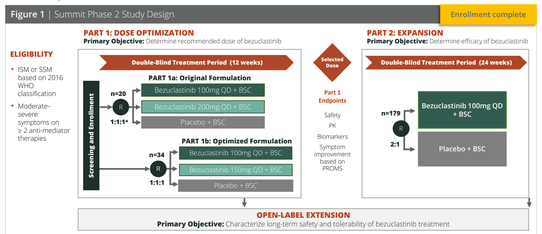
Table 1 | MS2D2 Total Symptom Score (TSS)

Domain	Symptom
Neurocognitive	• Difficulty concentrating • Difficulty remembering
Fatigue	• Tiredness
Skin	• Itching • Redness • Flushing • Spots
Other	Gastrointestinal • Nausea • Abdominal pain Pain • Headache • Bone pain

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

Summit (NCT05186753) | Phase 2 Double-Blind, Placebo-Controlled Randomized Clinical Study Evaluating Bezuclastinib in NonAdvSM

Figure 1 | Summit Phase 2 Study Design — Enrollment complete

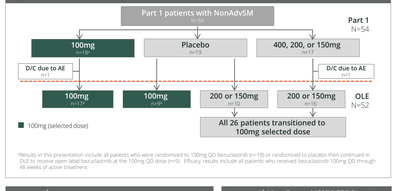


[a]Prior to amendment, Part 1a included a bezuclastinib 400mg QD + BSC cohort with randomization of 1:1:1:1.
All data herein are as of data cut-off date of 29-Aug-2024.
BSC: Best supportive care

RESULTS

Disposition and Characteristics | Part 1 Patients Receiving 100mg QD Bezuclastinib

Figure 2 | Summit Patient Disposition



*Results in this presentation include all patients who were randomized to 100mg QD bezuclastinib (n=18) or randomized to placebo then continued in OLE to receive open label bezuclastinib at the 100mg QD dose (n=9). Efficacy results include all patients who received bezuclastinib 100mg QD through 48 weeks of active treatment.

Table 2 | Patient Baseline Characteristics

Double-Blind + Open-Label Extension 100mg		Total Active (n=27)
Patient Demographics		
Female, n (%)		18 (66.7)
Median age in years, (range)		52 (36-76)
ECOG PS at screening, n (%)	0	12 (44.4)
	1	14 (51.9)
	2	1 (3.7)
Clinical Characteristics		
Number of supportive care meds at baseline, n (%)	2	12 (44.4)
	3+	15 (55.6)
Prior avapritinib, n (%)		1 (3.7)
Baseline Mast Cell Burden		
KIT D816V in Whole Blood, Positive, n (%)		21 (77.7)
Median Bone Marrow MC Burden, % (range)		10 (1-30)
Median Serum Tryptase at baseline, ng/mL (range)		37 (9.8-275)
< 20 ng/mL, n (%)		6 (22.2)
≥ 20 ng/mL, n (%)		21 (77.7)
Baseline QoL Measures		
Mean (SD) MS2D2 TSS at Baseline		48.3 (19.3)
Mean (SD) MCQoL at Baseline		52.7 (16.1)

Figure 3 | BSC at Baseline by Class (n=27)

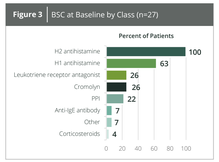
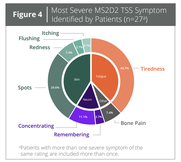


Figure 4 | Most Severe MS2D2 TSS Symptom Identified by Patients (n=27*)



*Patients with more than one severe symptom of the same rating are included more than once.

Safety and Tolerability in Patients Randomized to 100mg in Part 1 + OLE

Table 3 | All Cause Treatment-Emergent Adverse Events (TEAE) ≥ 15%

Double-Blind + OLE 100mg		
Preferred Term	**Total Active[a] (n=27)**	
	Grade 1/2	Grade 3
Hair color changes	21	-
ALT/AST increased	6	3
Nausea	7	-
URTI	7	-
Diarrhea	6	-
Headache	6	-
Pruritus	5	-
Arthralgia	5	-
GERD	5	-
Peripheral edema	4	-
Alopecia	4	-

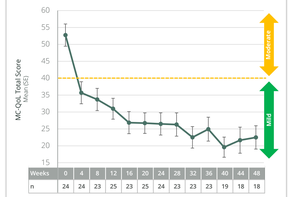
[a]Among the nine patients randomized to placebo, only TEAEs that occurred after crossover to bezuclastinib treatment are included. ALT, alanine transaminase; AST, aspartate transaminase; GERD, gastroesophageal reflux disease; LFT, liver function test; OLE, open label extension; TEAE, treatment-emergent adverse events; SAE, serious adverse event; URTI, upper respiratory tract infection

- Median (range) duration on bezuclastinib:
  - Active (N=18): 56 weeks (9.3-80.9)
  - Placebo → Active (N=9): 40 weeks (30.3-72.1)
- The majority of TEAEs were low grade and reversible
- No treatment-related bleeding or cognitive impairment events reported
- Among patients experiencing LFT elevations:
  - 5 patients resolved without dose modification and remain on study
  - 2 patients resolved with dose reduction, including one patient with a possibly related Gr 3 SAE who subsequently re-escalated to original dose, and remains on study (72 weeks)
  - 2 patients with Gr 3 events resolved following discontinuation

Significant and Sustained Improvements in Health-Related Quality of Life, Mast Cell Reactions, and Baseline Supportive Care Medications

MC-QoL Total Score

Figure 9 | Mean Total Score in MC-QoL



- Patients improved to mild as early as week 4 and sustained that improvement through 48 weeks

Mast Cell Reactions (MCR) and BSC Medication Use[a]

- During the 14 days prior to the start of study treatment, patients reported MCR on an average (range) of 7.3 (0 – 14) days
  - After ~12 weeks, patients reported 2.5 days on average with MCR
  - After ~24 weeks, patients reported 2.6 days on average with MCR
  - After ~48 weeks, patients reported 1.9 days on average with MCR

Figure 10. | Percentage of Patients Reporting Mast Cell Reactions Over 14 Days

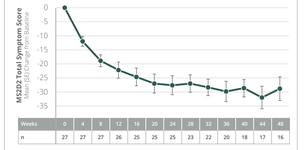
- Percentage of patients with reductions or discontinuations in BSC medications[b]:
  - 31% at 24 weeks
  - 47% at 48 weeks

[a]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."
[b]Per protocol, best supportive care (BSC) modification was only allowed in the OLE.

Significant and Sustained Improvements in the MS2D2 Total Symptom Score, Domains, and Symptoms Including Most Severe Symptom in Patients Receiving Active Treatment with 100mg QD Bezuclastinib

MS2D2 Total Symptom Score

Figure 5 | Mean Change from Baseline in MS2D2 Total Symptom Score



- MS2D2 Total Symptom Score reduced from baseline by a mean of 27.6 points and 55.8% at 24 weeks
- MS2D2 Total Symptom Score reduced from baseline by a mean of 28.8 points and 64.6% at 48 weeks

MS2D2 Total Symptom Score Domains

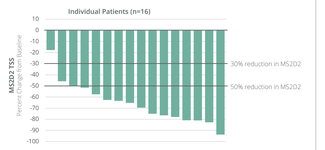
Table 4 | MS2D2 Domain Severity Scores

Domain	Baseline Mean Absolute Score	48 Weeks Mean Change from Baseline	48 Weeks Mean % Change from Baseline
Neuro	4.77	-2.84	-69.8
Fatigue	6.41	-3.55	-57.6
Skin	4.44	-2.45	-61.9
Other (GI/Pain)	3.66	-2.45	-67.0

- Significant improvement in Neurocognitive, Fatigue, Skin, and Other (GI/Pain) Symptoms were reported by patients at 48 weeks of treatment

MS2D2 Total Symptom Score in Individual Patients

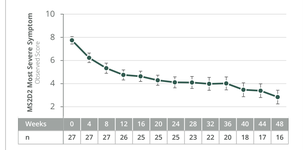
Figure 6 | Percent Change from Baseline in MS2D2 Total Symptom Score at 48 Weeks



- 94% (15/16) of patients reached at least 30% reduction in MS2D2 TSS
- 88% (14/16) of patients reached at least 50% reduction in MS2D2 TSS

Severity of Most Severe Symptom

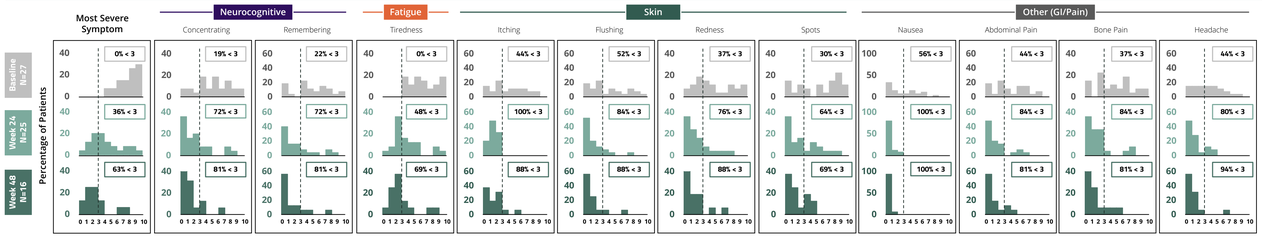
Figure 7 | Mean Most Severe Symptom Score



- MS2D2 most severe symptom reduced from baseline by a mean of 3.7 points and 48.3% at 24 weeks
- MS2D2 most severe symptom reduced from baseline by a mean of 4.5 points and 62.6% at 48 weeks

Improvement Observed Across All MS2D2 Symptoms Including the Most Severe Symptom

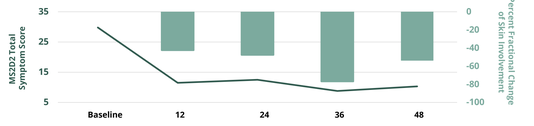
Figure 8 | Distribution of Symptom Scores and Percentage of Patients with < 3 Symptom Severity by MS2D2 Symptom

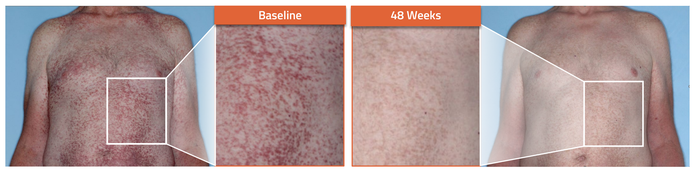


[a]Each bar represents the percentage of patients with symptom severity score between the numbers bracketing it. Far left bar reports percentage of patients with symptom severity score of at least 0 (least severe) but less than 1. Far right bar represents percentage of patients with symptom severity score of 9 to 10 (most severe).

Patient Case | 65-Year-Old Man With NonAdvSM Randomized to Bezuclastinib 100mg QD

- No related AEs reported
- Began trial with 3 BSC medications and discontinued 2 of 3 by week 48
- Most severe symptom reported by patient was spots (7/10 at baseline)





CONCLUSIONS

Summit Part 1+OLE Continues to Demonstrate Encouraging Safety and Efficacy with 100mg Bezuclastinib in Patients with NonAdvSM

Favorable safety and tolerability profile with bezuclastinib treatment:
- The majority of TEAEs were low grade and reversible
- No treatment-related bleeding or cognitive impairment AEs reported

Sustained improvement in patient symptom severity and reduced requirement for BSC meds at 48 weeks:
- MS2D2 Total Symptom Score (TSS) was reduced from baseline by a mean of 64.6% and 28.8 points
- 88% of patients reached at least 50% reduction in MS2D2 TSS
- 63% reduction in severity in the most severe symptom
- Significant improvement in percent of patients reporting < 3 severity score for each symptom of MS2D2 with many achieving near resolution of each symptom (< 1 severity score)
- 47% of patients had reductions or discontinuations of BSC medications

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; 75(8):1927-1938. 4. Mesa RA et al. Cancer 2022; 128(20):3691-3699. 5. Pyatilova P, Siebenhaar F. Immunol Allergy Clin North Am 2023; 43(4):751-762. 6. DeAngelo DJ, et al. Nat Med 2021; 27(12):2183-2191. 7. Ayvakit (avapritinib) [product information]. Cambridge, MA: Blueprint Medicines Corporation; May 2023. 8. DeAngelo DJ, et al. [abstract] In: Blood (ASH) 2022; 140 (Supplement 1): 1512-13. 9. Modena B, et al. Poster 694 presented at: 2024 AAAAI annual meeting; February 23-26, 2024; Washington, DC. 10. Rein L, et al. Abstract P1055 presented at: 2024 EHA annual meeting; June 13-16, 2024; Madrid, Spain. 11. Rein L, et al. Poster 4556 presented at: 2024 ASH annual meeting; December 7-10, 2024; San Diego, CA.

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