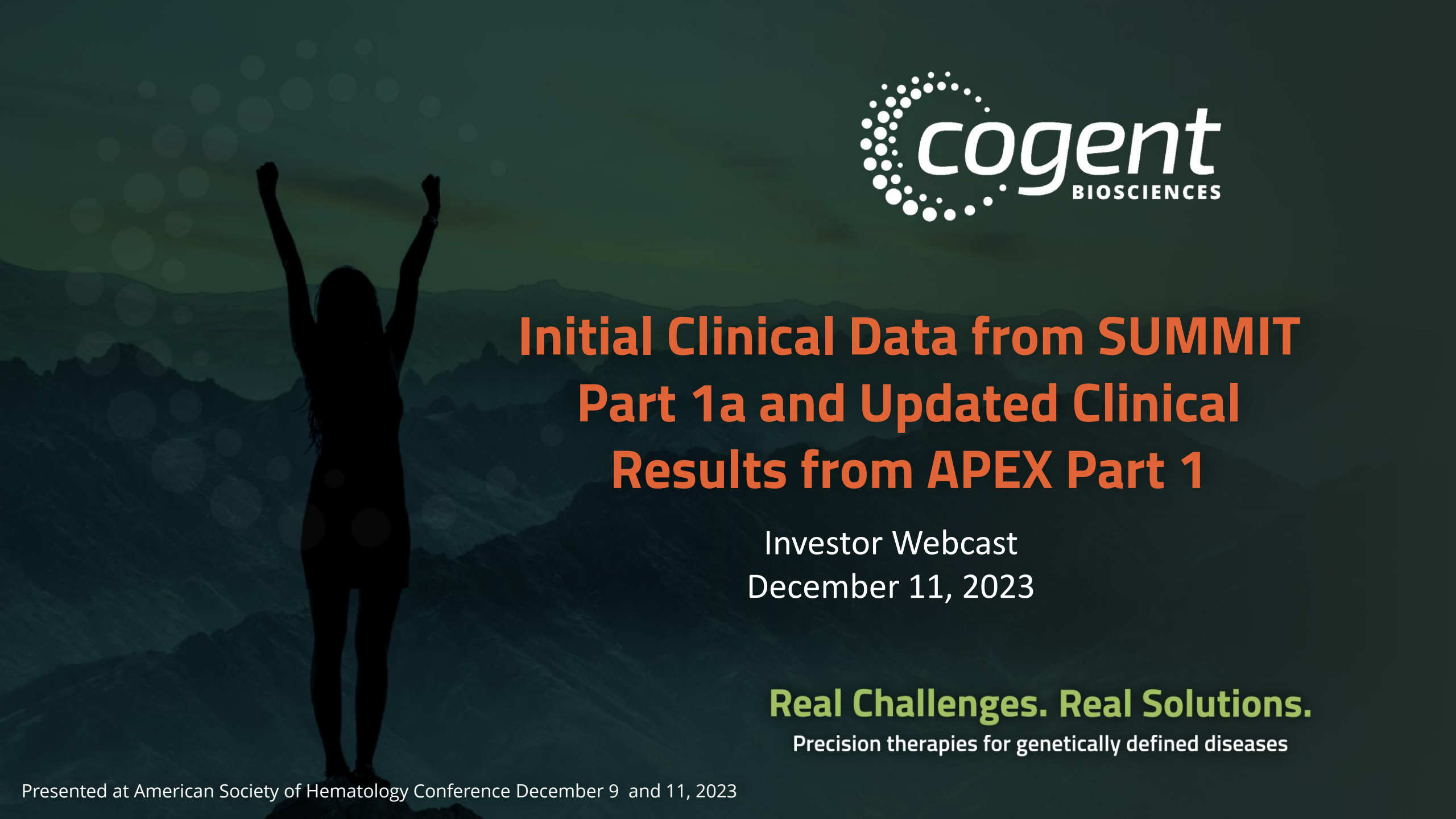


Initial Clinical Data from SUMMIT Part 1a and Updated Clinical Results from APEX Part 1

Investor Webcast
December 11, 2023

Real Challenges. Real Solutions.

Precision therapies for genetically defined diseases

Presented at American Society of Hematology Conference December 9 and 11, 2023

Forward Looking Statements and Risk Factors

This presentation and the accompanying oral commentary contain forward-looking statements that involve risks, uncertainties and assumptions. If the risks or uncertainties ever materialize or the assumptions prove incorrect, our results may differ materially from those expressed or implied by such forward looking statements. All statements other than statements of historical fact could be deemed forward-looking, including, but not limited to, any statements of the plans, strategies, and objectives of management for future operations, including our clinical development and commercialization plans and timelines; any projections of financial information; any statement about historical results that may suggest trends for our business; any statement of expectation or belief regarding future events; potential markets or market size, technology developments, our clinical and research pipelines, clinical and pre-clinical data or the implications thereof, enforceability of our intellectual property rights, competitive strengths or our position within the industry; any statements regarding the anticipated benefits of our collaborations or other strategic transactions; and any statements of assumptions underlying any of the items mentioned.

These statements are based on estimates and information available to us at the time of this presentation and are not guarantees of future performance. Actual results could differ materially from our current expectations as a result of many risks and uncertainties, including but not limited to, risks associated with: the potential impacts of raising additional capital, including dilution to our existing stockholders, restrictions our operations or requirements that we relinquish rights to our technologies or product candidates; business interruptions resulting from the coronavirus disease outbreak or similar public health crises, which could cause a disruption of the development of our product candidates and adversely impact our business; the success, cost, and timing of our product development activities and clinical trials; the timing of our planned regulatory submissions to the FDA for our product candidate bezuclastinib and feedback from the FDA as to our plans; our ability to obtain and maintain regulatory approval for our bezuclastinib product candidate and any other product candidates we may develop, and any related restrictions, limitations, and/or warnings in the label of an approved product candidate; the potential for our identified research priorities to advance our bezuclastinib product candidate; the ability to license additional intellectual property relating to our product candidates from third-parties and to comply with our existing license agreements and collaboration agreements; the ability and willingness of our third-party research institution collaborators to continue research and development activities relating to our product candidates; our ability to commercialize our products in light of the intellectual property rights of others; our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates; the scalability and commercial viability of our manufacturing methods and processes; the commercialization of our product candidates, if approved; our plans to research, develop, and commercialize our product candidates; our ability to attract collaborators with development, regulatory, and commercialization expertise; our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates; among others. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to our business in general, see our periodic filings filed from time to time with the Securities and Exchange Commission. Unless as required by law, we assume no obligation and do not intend to update these forward-looking statements or to conform these statements to actual results or to changes in our expectations.

All of Cogent Biosciences, Inc. (“Cogent”) product candidates are investigational product candidates and their safety and efficacy have not yet been established. Cogent has not obtained marketing approval for any product, and there is no certainty that any marketing approvals will be obtained or as to the timelines on which they will be obtained.

Any data pertaining to Cogent product candidates is interim data and may include investigator-reported interim data for which Cogent has not yet independently reviewed the source data. The interim data may not be representative of the final results that may be obtained in the corresponding trials and results from earlier trials may not be representative of results obtained in later trial or pivotal trials.

Agenda and Speakers

Andrew Robbins
President and
Chief Executive Officer

Frank Siebenhaar, M.D.
PD Dr. Head, University Outpatient Clinic, Institute of Allergology, Charite - Universitätsmedizin Berlin

Pankit Vachhani, M.D.
Associate Professor of Medicine
Division of Hematology and Oncology
University of Alabama at Birmingham

Jessica Sachs, M.D.
Chief Medical Officer

• Introduction and Corporate Overview	Andrew Robbins
• Review of SUMMIT Part 1a Data with Bezuclastinib in Nonadvanced Systemic Mastocytosis	Dr. Frank Siebenhaar
• Review of Updated Phase 1 APEX Data with Bezuclastinib in Advanced Systemic Mastocytosis	Dr. Pankit Vachhani
• Presentation Summary	Andrew Robbins
• Q&A	All

Multiple Clinical and Preclinical Programs with Upcoming Catalysts

Program	Indication	Early Stage Development	Late Stage Development	Regulatory Submission	Approval
Clinical Programs					
Bezuclastinib (KIT inhibitor)	Advanced Systemic Mastocytosis	Apex			
	Nonadvanced Systemic Mastocytosis	Summit			
	Gastrointestinal Stromal Tumors	Peak			

- **Enrolling APEX Part 2 (Registration enabling)**
- **Initial Clinical Data at ASH 2023**
- **Enrolling PEAK Part 2 (Global Phase 3 trial)**

Research Programs

Indication	Hit ID	Lead Generation	Lead Optimization	Candidate Selected	IND Submission
ErbB2 mut					
FGFR2					
PI3Kα					
Target 4					
Target 5					
Target 6					

Expected cash runway into 2026; $312.8 million as of September 30, 2023

Bezuclastinib: Highly Selective and Potent KIT D816V Inhibitor

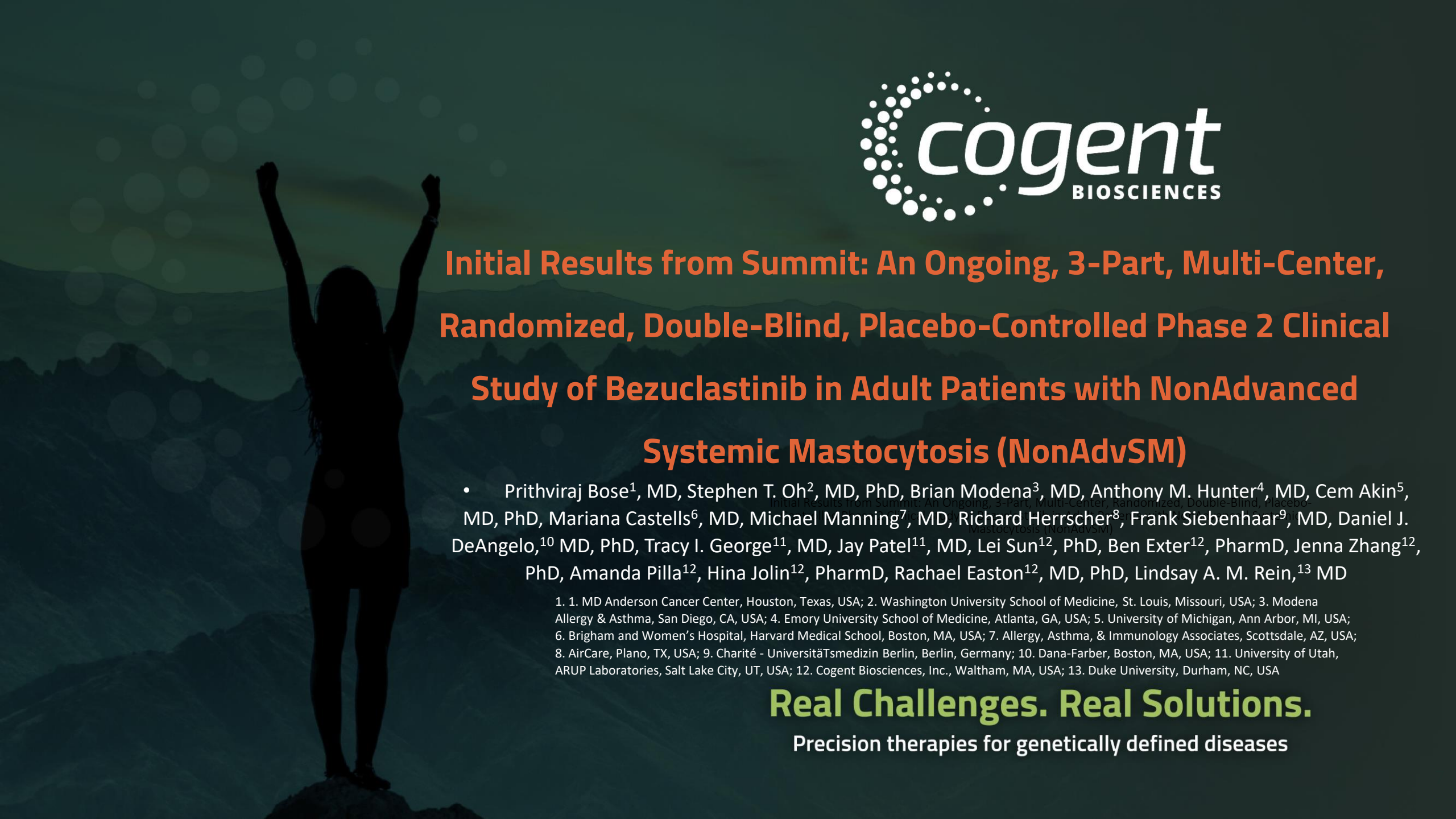
- Oral, selective type I tyrosine kinase inhibitor (TKI) with potent activity against KIT D816V, the driving mutation in 95% of SM
- Preclinically, highly active with specificity for mutations in KIT exons 9, 11, 17, and 18
- Spares closely related kinases and has minimal brain penetration and favorable PK properties[1]
  - Inhibition of closely related kinases have been linked to off-target toxicities, such as bleeding, edema, and pleural effusions[2,3]
- Active clinical trials APEX (NCT04996875) and SUMMIT (NCT05186753) designed to explore the use of bezuclastinib as a therapy for patients diagnosed with all forms of systemic mastocytosis

References: 1. Guarnieri A. et al. Abstract P257 Molecular Cancer Therapeutics, 2021. 20(12_Supplement), P257-P257. 2. Giles FJ et al, Leukemia. 2009;23(10):1698-1707. 3. Liu S, Kurzrock R. Seminars in Oncology. 2015;42(6):863-875

Systemic Mastocytosis: Serious Rare Hematologic Disease with High Unmet Medical Need for New Treatment Options

- Systemic Mastocytosis (SM) is a disease of proliferating and overactive mast cells caused in 95%+[1] of patients by a mutation known as KIT D816V. It is estimated that approximately 25,000 individuals in the U.S. suffer from SM. SM is divided into several sub-types:
- Advanced Systemic Mastocytosis (AdvSM) is a rare, aggressive and life-threatening form the disease that leads to uncontrolled proliferation of mast cells (MC)[1,2]
  - Subtypes: aggressive SM (ASM); SM with associated hematologic neoplasm (SM-AHN); mast cell leukemia (MCL)[1]
  - Based on subtype, the median overall survival ranges from <6 months to 3-4 years[3,4]
- Nonadvanced Systemic Mastocytosis (NonAdvSM) accounts for ~90% of all SM cases[1] and includes:
  - Indolent SM (ISM; ~85%) Characterized by symptoms related to mast cell mediator release[2]
  - Smoldering SM (SSM; ~5%) Characterized by a higher systemic mast cell burden: increased levels of serum tryptase and high degrees of bone marrow involvement[1]
- Unmet need remains for approved therapies which can deliver optimal efficacy without clinically significant toxicities
  - Reported toxicities for marketed tyrosine kinase inhibitor (TKI) therapies include edema, cognitive effects, risks of intracranial bleeding, nausea, vomiting, diarrhea[5-7]

References: 1. Pardanani A. Am J Hematol. 2021;96(4):508-525. 2. DeAngelo DJ et al. Nat Med. 2021;27(12):2183-2191. 3. Ustun C et al. Haematologica. 2016;101(10):1133-1143. 4. Lim K-H et al. Blood. 2009;113(23):5727-5736. 5. AYVAKIT (avapritinib) [package insert]. Blueprint Medicines Corporation; 2021. 6. Magliacane D et al., Transl Med UniSa. 2014;8:65-74. 7. RYDAPT (midostaurin) [package insert]. Novartis Pharmaceuticals; 2021.



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)

- Prithviraj Bose[1], MD, Stephen T. Oh[2], MD, PhD, Brian Modena[3], MD, Anthony M. Hunter[4], MD, Cem Akin[5], MD, PhD, Mariana Castells[6], MD, Michael Manning[7], MD, Richard Herrscher[8], Frank Siebenhaar[9], MD, Daniel J. DeAngelo,[10] MD, PhD, Tracy I. George[11], MD, Jay Patel[11], MD, Lei Sun[12], PhD, Ben Exter[12], PharmD, Jenna Zhang[12], PhD, Amanda Pilla[12], Hina Jolin[12], PharmD, Rachael Easton[12], MD, PhD, Lindsay A. M. Rein,[13] MD

1. 1. MD Anderson Cancer Center, Houston, Texas, USA; 2. Washington University School of Medicine, St. Louis, Missouri, USA; 3. Modena Allergy & Asthma, San Diego, CA, USA; 4. Emory University School of Medicine, Atlanta, GA, USA; 5. University of Michigan, Ann Arbor, MI, USA; 6. Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; 7. Allergy, Asthma, & Immunology Associates, Scottsdale, AZ, USA; 8. AirCare, Plano, TX, USA; 9. Charité - UniversitätTsmedizin Berlin, Berlin, Germany; 10. Dana-Farber, Boston, MA, USA; 11. University of Utah, ARUP Laboratories, Salt Lake City, UT, USA; 12. Cogent Biosciences, Inc., Waltham, MA, USA; 13. Duke University, Durham, NC, USA

Real Challenges. Real Solutions.

Precision therapies for genetically defined diseases

Summit: Phase 2 Clinical Study Evaluating Bezuclastinib in NonAdvSM

PART 1: DOSE OPTIMIZATION (fully enrolled)

Primary Objective: Determine the recommended dose of bezuclastinib

PART 2: EXPANSION

Primary Objective: Determine the efficacy of bezuclastinib

Eligibility

ISM or SSM based on 2016 WHO classification

Moderate – severe symptoms on ≥2 anti-mediator therapies

BSC: Best supportive care

Double-blind Treatment Period (12 weeks)

PART 1a: Formulation A

Screening and Enrollment

N=20

R

1:1:1[a]

- Bezuclastinib 100 mg QD + BSC
- Bezuclastinib 200 mg QD + BSC
- Placebo + BSC

PART 1b: Formulation B[b]

N=34

R

1:1:1

- Bezuclastinib 100 mg QD + BSC
- Bezuclastinib 150 mg QD + BSC
- Placebo + BSC

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

[b] Formulation B is an optimized formulation with improved bioavailability

Selected Dose

Part 1 Endpoints

- Safety
- PK
- Biomarkers
- Symptom improvement based on PRO measures

Double-blind Treatment Period (24 weeks)

N=TBD[c]

R

2:1

- Bezuclastinib (Formulation B) Selected Dose + BSC
- Placebo + BSC

[c] Part 2 will be sized based on Part 1 results and regulatory discussions

OPEN-LABEL EXTENSION (OLE)

Primary Objective: Characterize safety and tolerability of bezuclastinib

Summit Part 1a Enrolled Highly Symptomatic SM Patients with Moderate to Severe Disease

Patient Demographics	All patients (N=20)
Female, n (%)	**15 (75)**
Median Age in years, n (range)	**50.5 (38 – 75)**
ECOG PS, n (%)	
0	**3 (15)**
1	**15 (75)**
2	**2 (10)**
Clinical Characteristics	**All patients (N=20)**
NonAdv Subtype per PI, n (%)	
Indolent SM (ISM)	**18 (90)**
Smoldering SM (SSM)	**2 (10)**
Median (range) MAS Total Score at Eligibility	**45.56 (26.3 – 71.6)**
Mast Cell Burden	**All patients (N=20)**
***KIT* D816V in Whole Blood, Positive, n (%)**	**15 (75)**
Median KIT D816V VAF, % (range)	**0.49 (0 – 32.48)**
Median Bone Marrow MC Burden, % (range)	**22.5 (1 – 80)**
Median Serum Tryptase, ng/mL (range)	**74.35 (10.2- 592.0)**
<20 ng/mL, n (%)	**3 (15)**
≥20 ng/mL, n (%)	**17 (85)**

SM Therapy	All patients (N=20)
Prior avapritinib, n (%)	**1 (5.0)**
Baseline Supportive Care Medications, Median (range)	**3 (2-7)**
H1 blockers, n (%)	**19 (95)**
H2 blockers, n (%)	**18 (90)**
Leukotriene receptor antagonists, n (%)	**8 (40)**
Proton pump inhibitors, n (%)	**7 (35)**
Cromolyn sodium, n (%)	**4 (20)**
Omalizumab, n (%)	**3 (15)**
Corticosteroids, n (%)	**1 (5)**
Patient Disposition	**All patients (N=20)**
Months on Study (Part 1a + OLE), median (range)	**7.03 (2.8 – 16.0)**
Completed Part 1a, n (%)	**20 (100)**
On Study as of Data Cut-off, n (%)	**18 (90)**
Discontinued study, n (%)	**2 (10)**
AE, n (%)	**1 (5)**
Patient Decision, n (%)	**1 (5)**

As of Data Cut-off of 25-Oct-2023

Encouraging Safety at 100-200 mg QD in Patients from Summit Part 1a

All cause TEAEs > 1 patient in bezuclastinib cohorts

	Bezuclastinib 100mg QD n= 7		Bezuclastinib 200mg QD n=5		Placebo n=7	
Preferred Term	**Gr 1 / 2**	**Gr 3**	**Gr 1 / 2**	**Gr 3**	**Gr 1 / 2**	**Gr 3**
Hair color changes	4	-	4	-	1	-
Nausea	3	-	1	-	2	-
Peripheral edema	3	-	-	-	-	-
Diarrhea	2	-	-	-	3	-
GERD	2	-	-	-	-	-
Taste disorder [a]	1	-	2	-	-	-
Neutropenia [a]	1	1	1	-	-	-
Fatigue	1	-	1	1	-	-
Hypophosphatemia	1	-	1	-	-	-
Alopecia	-	-	2	-	-	-
AST / ALT increased	-	1	-	-	-	-

[a] Pooled PTs

As of Data Cut-off of 25-Oct-2023

- The majority of TEAEs were low grade and reversible
- No related SAEs reported
- No bleeding or cognitive impairment events reported
- Dose reductions due to TEAEs included Fatigue (n=2) and 1 patient dose reduced and subsequently discontinued due to ALT increased

Safety in patient assigned to 400 mg QD bezuclastinib

- One patient with SSM was enrolled into 400 mg cohort which was subsequently closed to further enrollment
- Patient experienced Gr 4 neutropenia, dose reduced to 200mg (Cycle 4). Other TRAEs included Gr 3 WBC decreased and Gr 1 anemia

Safety and Tolerability Profile in Open-Label Extension (OLE) Supports Potential for Chronic Dosing

All Cause TEAEs > 1 patient

Open-Label Extension (n=18) *[assigned doses]*								
	Active treatment[α] (n=11)				Placebo → Active treatment (n=7)			
Preferred Term	*100mg* n= 6		*200mg* n= 5		*[Placebo→100mg]* n= 3		*[Placebo→200mg]* n= 4	
	Gr1/2	Gr3+	Gr1/2	Gr3+	Gr1/2	Gr3+	Gr1/2	Gr3+
Hair color changes	1	-	1	-	2	-	1	-
Arthralgia	2	-	-	-	-	-	1	-
URTI	1	-	1	-	-	-	-	-
Weight increased	-	-	1	-	-	-	1	-

[α] Patients on active treatment in Part 1 continued on the same dose in OLE

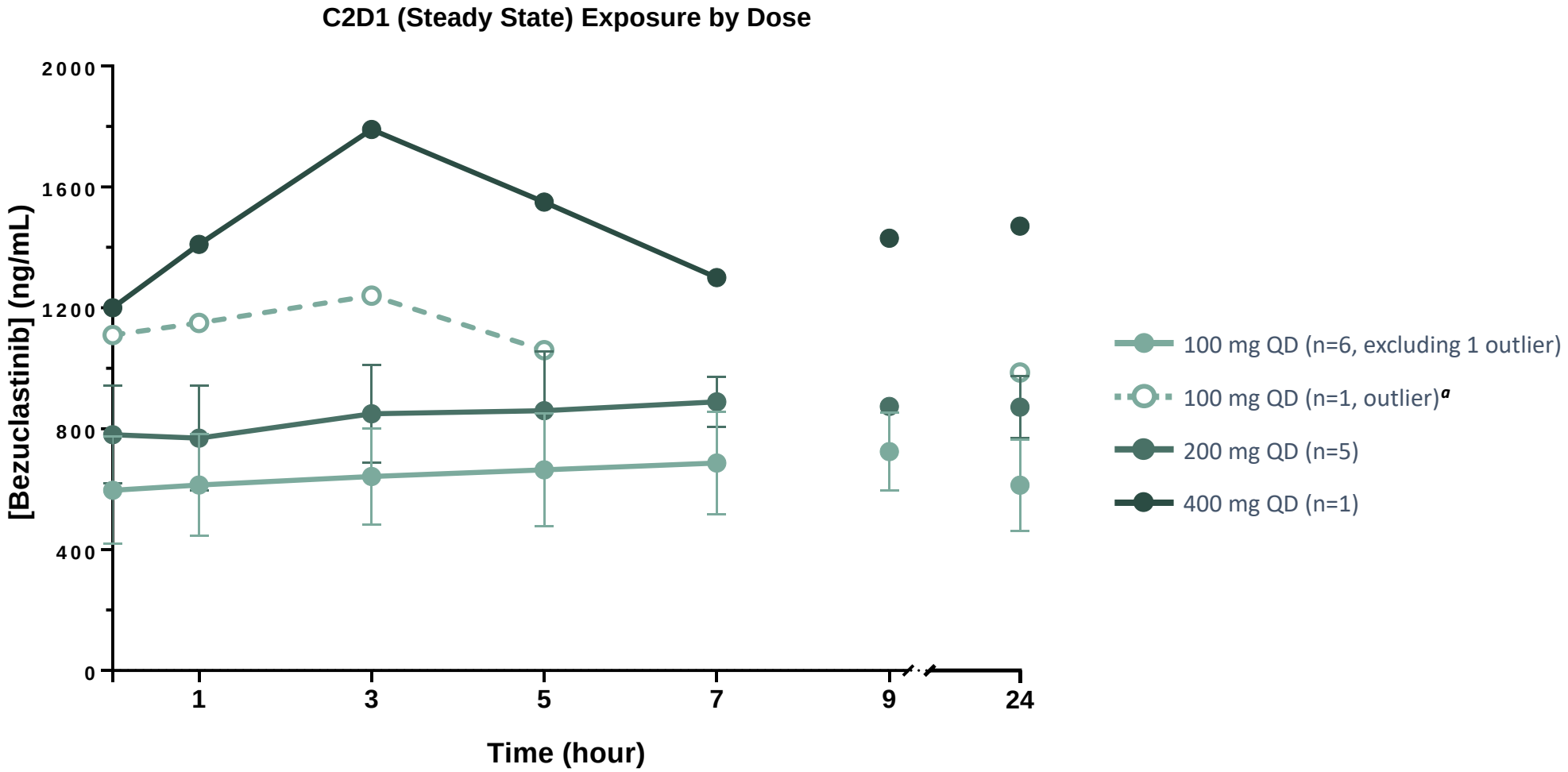
As of Data Cut-off of 25-Oct-2023

- Following completion of Part 1, patients received a median duration of active treatment in OLE of 16 weeks (range: 3.3-53.7)
- Consistent safety profile observed for patients starting bezuclastinib treatment following placebo

Safety in SSM patient reduced from 400 mg → 200 mg QD

- In OLE, TRAEs included: Gr1 taste disorder, Gr1 hair color changes, Gr2 WBC decreased, Gr2 anemia, Gr3 neutropenia and Gr3 fatigue (requiring dose reduction)
- Patient remains on study >400 days

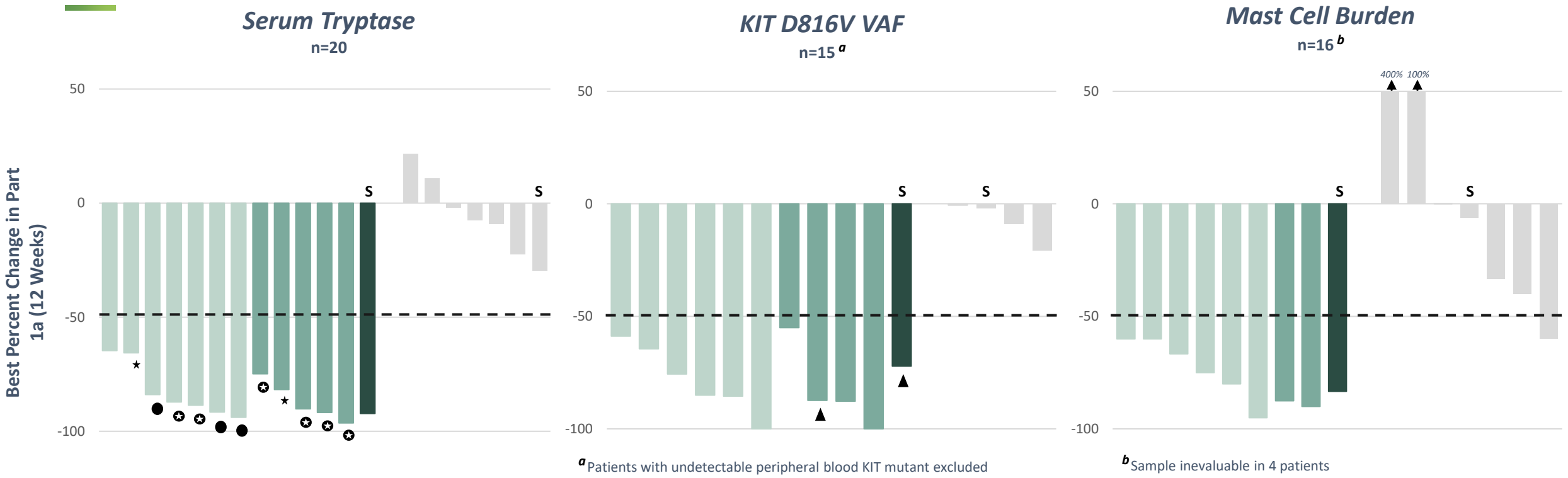
Dose Dependent Increase in Steady State Bezuclastinib Exposure



[a] Patient with outlier PK had a Gr3 ALT elevation leading to dose reduction and subsequent dose discontinuation

As of Data Cut-off of 25-Oct-2023

Within 12 Weeks, 100% of Bezuclastinib Treated Patients Achieved >50% Reduction in Markers of Mast Cell Burden



a Patients with undetectable peripheral blood KIT mutant excluded

b Sample inevaluable in 4 patients

- 90% (9/10) of patients with baseline serum tryptase ≥20ng/mL achieved <20ng/mL after 12 weeks of bezuclastinib
- 67% (8/12) of patients with baseline serum tryptase ≥11.4ng/mL achieved <11.4ng/mL after 12 weeks of bezuclastinib

Dose
- 100 mg QD bezuclastinib
- 200 mg QD bezuclastinib
- 400 mg QD bezuclastinib
- Placebo

Serum Tryptase Outcomes
- ● Achieved <20ng/mL[μ]
- ★ Achieved <11.4ng/mL[μ]
- ✪ Achieved both[μ]

KIT D816V VAF Outcomes
- ▲ Achieved <0.03% (LLD)

S SSM

[μ]In order to achieve, serum tryptase must have been above the threshold at baseline
LLD, lower limit of detection

As of Data Cut-off of 25-Oct-2023

Patient Reported Outcome Measures (PROMs) Used to Assess Severity of Symptoms, HRQoL, and Treatment Benefit[1]

Mastocytosis Quality of Life (MC-QoL)[3]

Disease-specific health-related quality of life measure
PRO Target: Cutaneous & Indolent SM
Range: 0 – 100 total score
Domains: Symptoms, Social life/functioning, Emotions and Skin
Measured in Summit: Baseline and every 4 weeks

Patient Global Impression of Severity (PGIS)

Anchor measure designed to assess patient's impression of symptom severity
PRO Target : NonAdvSM
Range: 5-point scale from 0 (none) to 4 (very severe)
Domains: Overall, dermatological, gastrointestinal, pain, fatigue, cognitive
Measured in Summit: Baseline and every 4 weeks

Mastocytosis Activity Score (MAS)[2]

Disease-specific PROM used to assess symptom severity
PRO Target: Cutaneous & Indolent SM
Range: 0 – 100 total score
Domains: Skin (itching, wheals, flushing); GI (diarrhea, abdominal pain); Other (muscle/joint pain, fatigue, headache, concentration)
Measured in Summit: Baseline and Week 12

Patient Global Impression of Change (PGIC)

Anchor measure designed to assess patient's impression of the change in symptoms since start of treatment
PRO Target : NonAdvSM
Range: 7-point scale from -3 (very much worse) to 3 (very much better)
Domains: Overall, dermatological, gastrointestinal, pain, fatigue, cognitive
Measured in Summit: Every 4 weeks

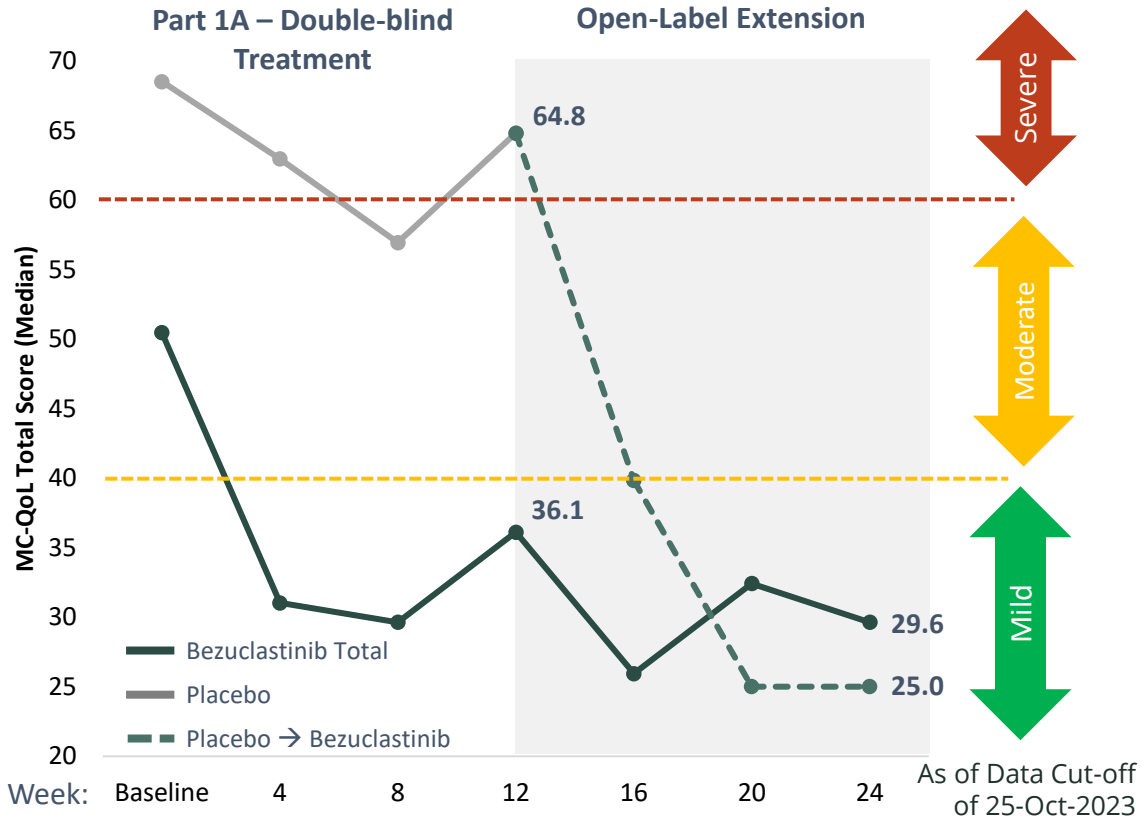
cogent BIOSCIENCES

[1]Trizuljak J, et al. Allergy 2020 Aug;75(8):1927-1938; [2]Siebenhaar F, Sander B, Tram H, Ellrich A, Maurer M, Weller K. Development and validation of the mastocytosis activity score. Allergy. 2018;00:1–8. https://doi.org/10.1111/all.13425; [3]Siebenhaar et al. Allergy 2016 71(6):869-77.

HRQoL – Health-Related Quality of Life

Encouraging Signs of Rapid Improvement in Symptom Severity and Quality of Life

Quality-of-life assessed by MC-QoL



- Median best percent improvement in patients treated with bezuclastinib (n=8) was 37% in Part 1a and 57% in OLE
- After placebo crossover to bezuclastinib in OLE (n=5), the median best percent improvement was 75%

Symptom Severity assessed by MAS

Mastocytosis Activity Score (MAS) % change from baseline at week 12[a]		
	Total Bezuclastinib (N=8)	**Placebo (N=4)**
Median	-35.53	-27.76
Min, Max	-60.1, -5.0	-73.1, 3.3

[a] Not collected in OLE

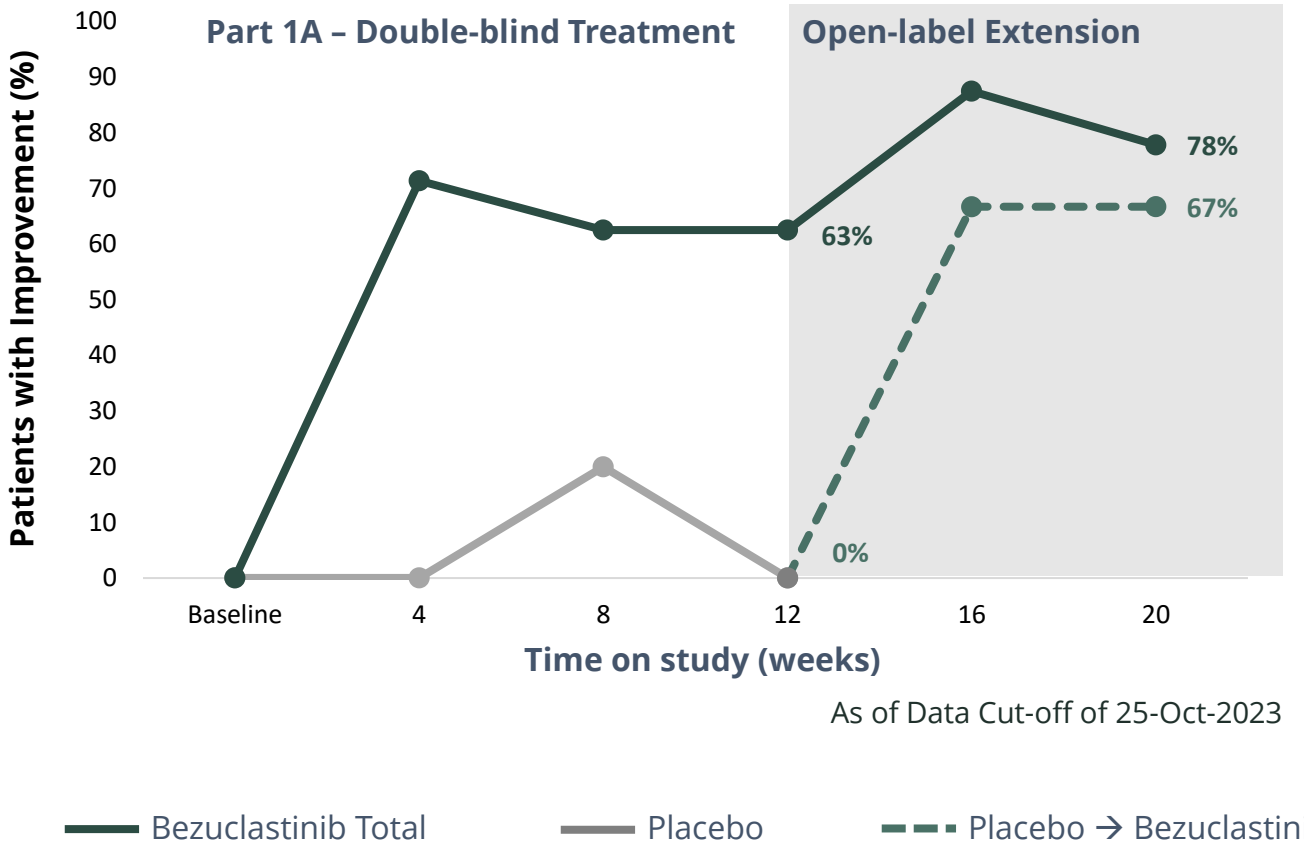
As of Data Cut-off of 25-Oct-2023

- 49% median decrease in MAS for patients treated with 100 mg QD dose level

Bezuclastinib Treatment Provided Rapid and Continued Improvement in Overall Symptom Severity

Patient Global Impression of Severity (PGIS)

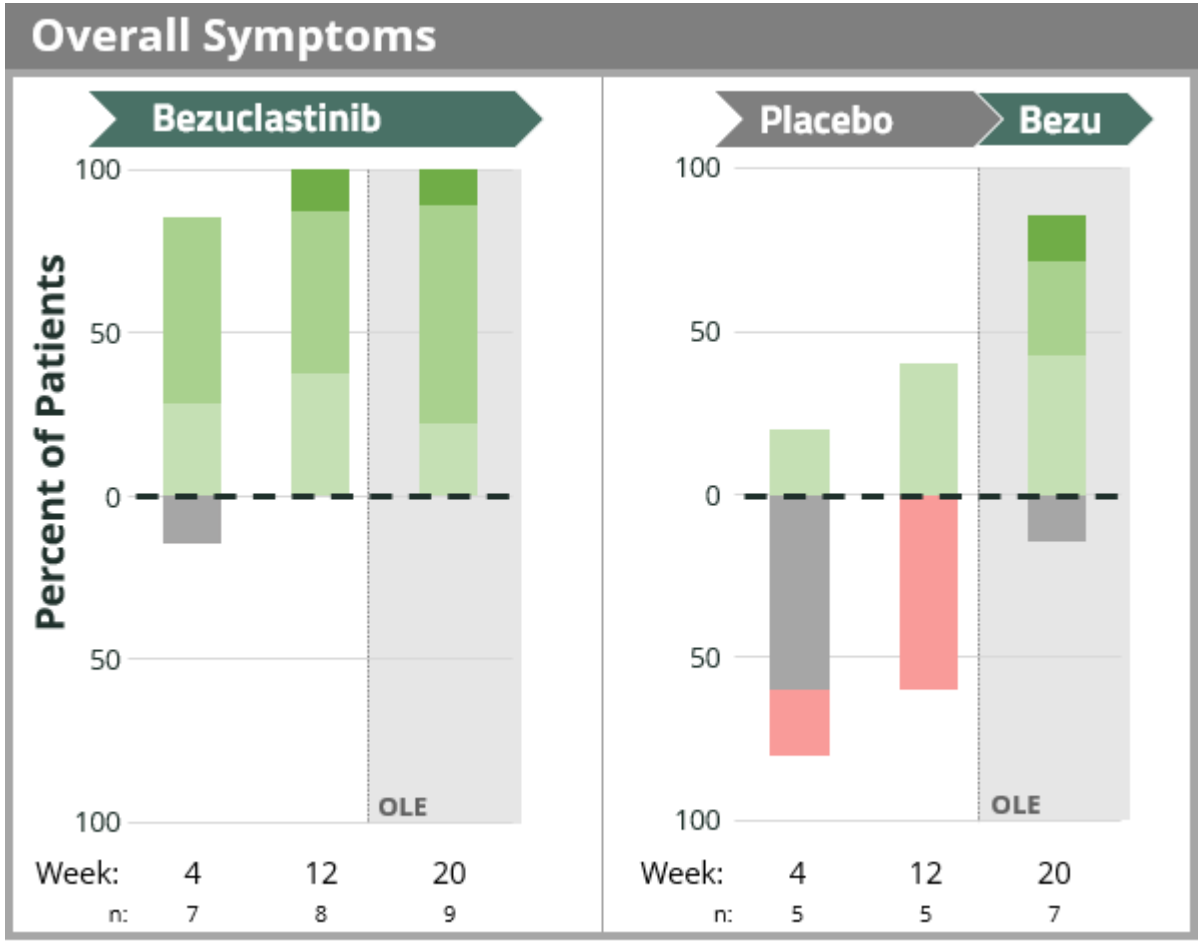
Patients with ≥1 point improvement on PGIS



As of Data Cut-off of 25-Oct-2023

- By the first assessment (4 weeks), 71% (5/7) of patients who received bezuclastinib had ≥1 point improvement in PGIS compared to 0% (0/5) on placebo.
- At 20 weeks, 78% (7/9) of bezuclastinib-treated patients had a ≥1 point improvement.
- During the OLE, 67% (4/6) patients starting bezuclastinib had ≥1 point improvement in overall symptom severity after 4 weeks on active treatment.

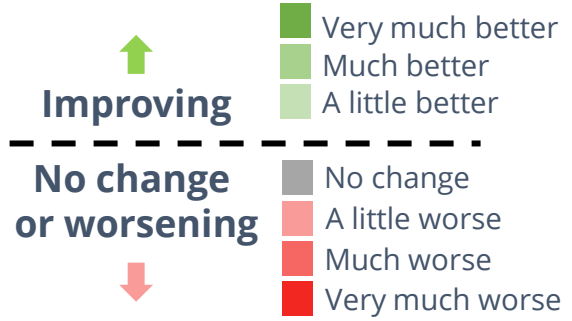
100% Bezuclastinib-Treated Patients Reported Overall Symptom Improvement During Part 1a Which Was Sustained During OLE



As of Data Cut-off of 25-Oct-2023

- At week 12, 63% of patients receiving bezuclastinib reported overall symptoms were much better to very much better. After an additional 8 weeks of bezuclastinib in OLE, this increased to 78%.
- At week 12, no patients receiving placebo reported overall symptoms were much better to very much better; after transitioning to bezuclastinib for 8 weeks in OLE, 43% of these patients reported overall symptoms were much better or very much better.

Patient Global Impression of Change (PGIC)



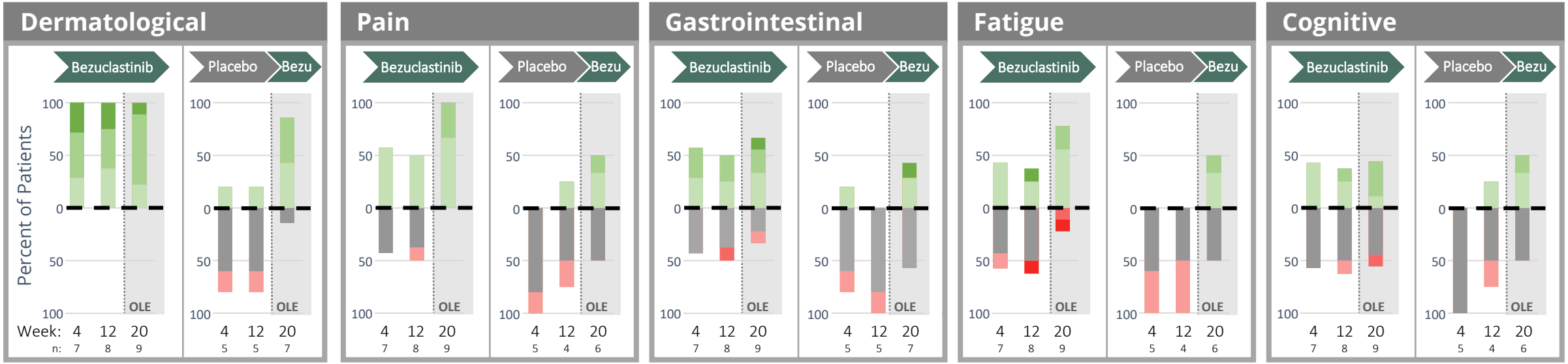
Bezuclastinib-treated Patients Reported Symptomatic Improvement Across Domains During Part 1a Which Deepened During OLE

- With extended treatment (at 20 weeks), 100% of patients reported pain symptoms were better and 78% of patients reported fatigue was improving.
- After 20 weeks of bezuclastinib treatment, more patients compared to week 12 reported dermatological (78%), gastrointestinal (33%), and cognitive symptoms (33%) were much to very much better.

Patient Global Impression of Change (PGIC)

Improving
- Very much better
- Much better
- A little better

No change or worsening
- No change
- A little worse
- Much worse
- Very much worse

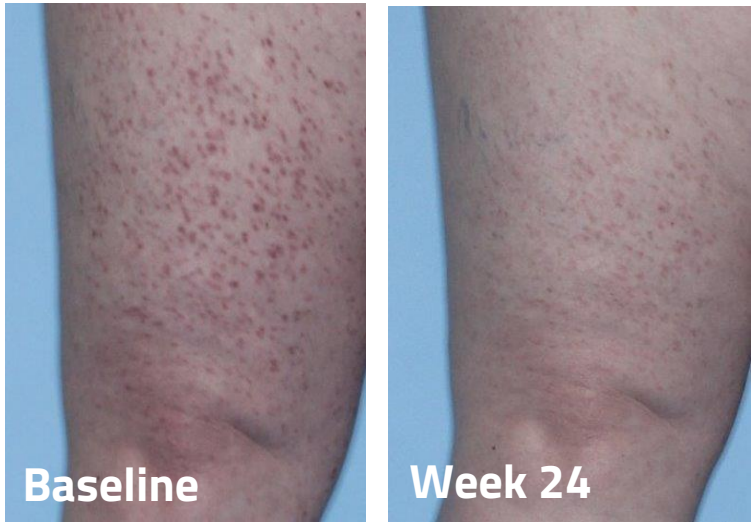


As of Data Cut-off of 25-Oct-2023

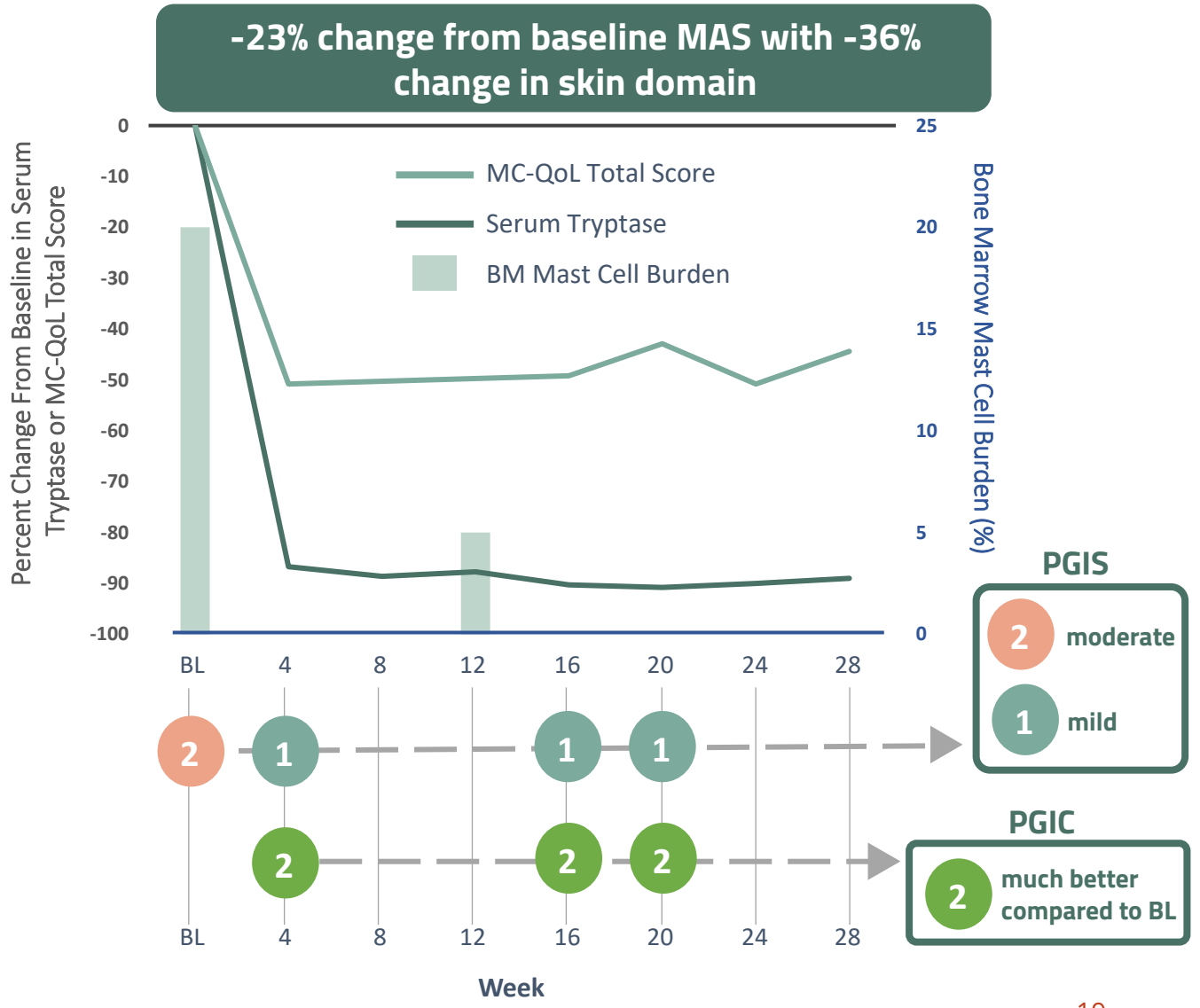
Normalization of Serum Tryptase and Concurrent Improvement in Symptoms After 4 Weeks of Bezuclastinib 100mg QD

46 yo woman diagnosed with ISM

- Moderate symptoms despite use of 2 anti-mediator therapies
  - Baseline MAS 32; MC-QoL 58
  - Baseline BSC: fexofenadine/pseudoephedrine; famotidine
- Randomized to bezuclastinib 100mg QD
- All TRAEs were Grade 1 and included hair color changes, taste disorder, peripheral edema, pruritus, skin exfoliation, dry skin



Patient permission granted for use of photos



Bezuclastinib Treatment Demonstrated Rapid Reduction in Mast Cell Burden, Evidence of Clinical Activity and an Encouraging Safety Profile

- The majority of TEAEs were low grade and reversible with no related SAEs reported
- Safety and tolerability profile in OLE supports potential for chronic dosing
- Within 12 weeks, 100% of patients achieved a ≥50% reduction in markers of mast cell burden (serum tryptase, KIT D816V VAF, and bone marrow MC burden)
- Patients reported rapid symptomatic improvement with bezuclastinib treatment that was sustained and deepened over time
  - MC-QoL best improvement was 37% in 12 weeks of Part 1a and 57% during additional 8 weeks in OLE
  - 63% of patients receiving bezuclastinib had ≥1 point improvement in PGIS during Part 1a vs. 0% of placebo patients. This increased to 78% after an additional 8 weeks of bezuclastinib in OLE. After crossing over to bezuclastinib in the OLE 67% of placebo patients had ≥1 point improvement after 4 weeks on active treatment
  - 63% of patients receiving bezuclastinib reported overall symptoms were much to very much better on PGIC at week 12. This increased to 78% of patients after an additional 8 weeks of bezuclastinib in OLE
- Bezuclastinib shows promise as a potential disease modifying therapy for patients with NonAdvSM
  - Additional clinical data from patients in Part 1b expected early 2024; Part 2 initiation planned for 1H2024

cogent BIOSCIENCES

Safety and Efficacy of Bezuclastinib (CGT9486), a Novel, Highly Selective, Potent KIT D816V Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis (AdvSM): Results From Part 1 of the Phase 2 Apex Trial

Pankit Vachhani[1], MD; Tsewang Tashi[2], MD; Gary Schiller[3], MD; Stephanie Lee[4], MD, MSc; Miguel Piris-Villaespesa[5], MD, PhD; Helena Pomares[6], MD, PhD; Cristina Bulai Livideanu[7]; Jonathan Lambert[8], PhD, BSc, BMBS, FRCP, FRCPath; Anthony M. Hunter[9], MD; Tracy I. George[10], MD; Cristina Papayannidis[11], MD; Khalid Shoumariyeh[12], MD; Lei Sun[13], PhD; Rita Petroro[13], Jenna Zhang[13], PhD; LouAnn Cable[13]; Amanda Pilla[13]; Hina A. Jolin[13], PharmD; Rachael Easton[13], MD; Vinod Pullarkat[2], MD, MRCP

[1]University of Alabama Birmingham, [2]Huntsman Cancer Institute, University of Utah, Division of Hematology & Hematologic Malignancies, Salt Lake City, UT; [3]David Geffen School of Medicine at UCLA, Los Angeles, [4]St. Michael's Hospital, Toronto, [5]Hospital Universitario Ramón y Cajal, Madrid; [6]Institut Catala d'Oncologia, Barcelona; [7]CEREMAST Toulouse, CHU Toulouse; [8]University College London Hospitals NHS Foundation Trust, London; [9]Emory University School of Medicine, Atlanta; [10]ARUP Laboratories, University of Utah School of Medicine, Salt Lake City; [11]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli",Bologna, ITA; [12]University of Freiburg, Freiburg; [13]Cogent Biosciences, Inc., Waltham, MA; [14]City of Hope Medical Center, Duarte, CA

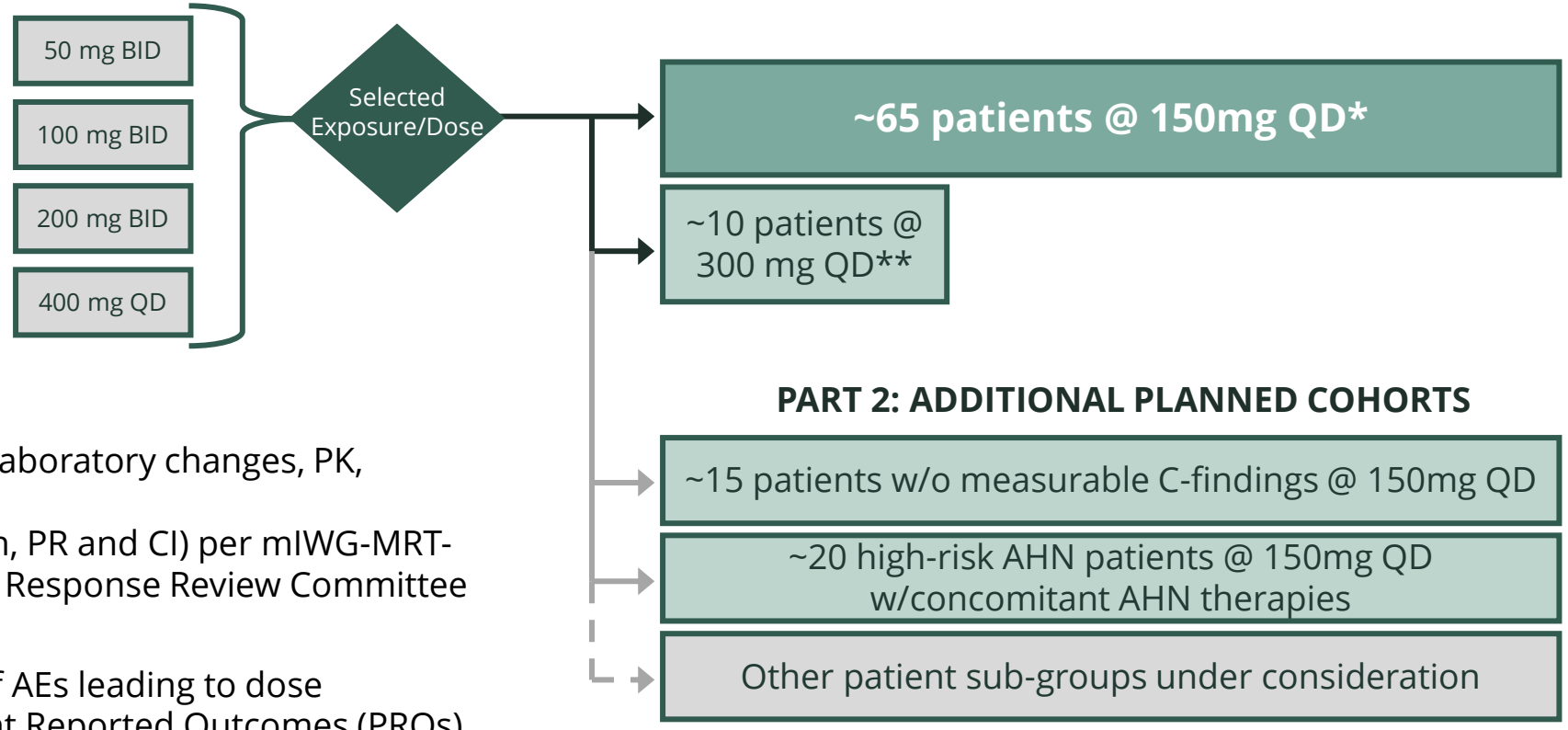
Real Challenges. Real Solutions.

Precision therapies for genetically defined diseases

Apex (NCT04996875): A Phase 2 Open-Label, Multicenter Clinical Study of Bezuclastinib in Patients with Advanced Systemic Mastocytosis

KEY ENTRY CRITERIA

- ASM, SM-AHN, or MCL per WHO 2022 Classification
- Confirmed measurable disease per mIWG-MRT-ECNM (mIWG)
- No restrictions on prior therapy
- Platelet count ≥50 x 10^9/L



Primary Endpoint

- **Part 1:** Incidence of AEs/SAEs, laboratory changes, PK, biomarkers, ORR
- **Part 2:** ORR (confirmed CR, CRh, PR and CI) per mIWG-MRT-ECNM and assessed by Central Response Review Committee

Other Endpoints

- Safety/Tolerability: Incidence of AEs leading to dose modification, changes in Patient Reported Outcomes (PROs)
- Efficacy: DOR, TTR, PFS, OS, pure pathologic response
- PK/PD: plasma concentration of bezuclastinib, serum tryptase, KIT D816V burden, BM mast cells

∫Formulation B is an optimized formulation with improved bioavailability
* Part 2 specifics subject to regulatory authority feedback
** Designed to explore the effect of exceeding IC90 KIT D816V engagement in AdvSM patients.

Vachhani P, et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

Patient Demographics and Characteristics

- 33 patients enrolled[§]; median age: 68 years; range: 33-87

	Total (N=32)	50mg BID (N=8)	100mg BID (N=7)	200mg BID (N=8)	400mg QD (N=9)
Male, n (%)	**21 (65.6)**	6 (75.0)	4 (57.1)	5 (62.5)	6 (66.7)
ECOG PS 0-1, n (%)	**27 (84.4)**	8 (100)	5 (71.4)	7 (87.5)	7 (77.8)
AdvSM Subtype per Central Eligibility Review, n (%)					
ASM	**7 (21.9)**	2 (25)	0	0	5 (55.6)
SM-AHN	**23 (71.9)**	5 (62.5)	6 (85.7)	8 (100)	4 (44.4)
MCL	**2 (6.3)**	1 (12.5)	1 (14.3)	0	0
Prior therapy for AdvSM, n (%)[∫]					
TKI Naïve*	**22 (69)**	7 (88)	4 (57)	6 (75)	5 (56)
Avapritinib	**5 (16)**	0	2 (29)	2 (25)	1 (11)
Midostaurin	**10 (31)**	1 (13)	3 (43)	2 (25)	4 (44)
SRSF2/ASXL1/RUNX1 Mutation in Peripheral Blood	**19 (59.4)**	5 (62.5)	5 (71.4)	5 (62.5)	4 (44.4)
***KIT* D816V in Whole Blood, Positive, n (%)**	**29 (90.6)**	8 (100)	6 (85.7)	7 (87.5)	8 (88.9)
Median KIT D816V VAF, % (range)	**6.1 (0-47.2)**	3.4 (0-39.0)	29.2 (0-38.9)	2.9 (0-47.2)	1.9 (0-42.2)
Median Bone Marrow MC Burden, % (range)	**30 (5-90)**	50 (20-70)	70 (5-90)	10 (5-30)	40 (10-80)
Median Serum Tryptase, ng/mL (range)	**153.5 (35.0-1578.0)**	178.0 (130.0-605.0)	233.0 (53.6-1578.0)	97.1 (35.0-131.0)	182.0 (50.2-370.0)

[§]One patient never dosed was excluded
[∫] Additional therapies included cytoreductives and biologics
*Patients who have received no prior SM-directed therapy with midostaurin and/or avapritinib

Data as of: 25Sep2023
Vachhani P,. et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

Bezuclastinib Continues to Demonstrate a Differentiated Safety Profile

- The majority of adverse events were of low grade and reversible.
- No related cognitive impairment or bleeding events reported.
- The majority of hematological adverse events were of low grade, reversible and did not require dose reduction.
- Related SAEs reported in 4 patients including Gr4 Thrombocytopenia, Gr3 Hypersensitivity (mediator flare), Gr3 Leishmaniasis, and Gr3 DILI (presented with late onset [day 488] and mixed cholestatic pattern of injury and subject was subsequently found to have biliary outflow tract obstruction).
- 9/32 patients required dose reduction due to adverse events, 6 of whom were at 400 mg; 3/32 patients discontinued due to adverse events.

Treatment Related Adverse Events in > 10% Patients

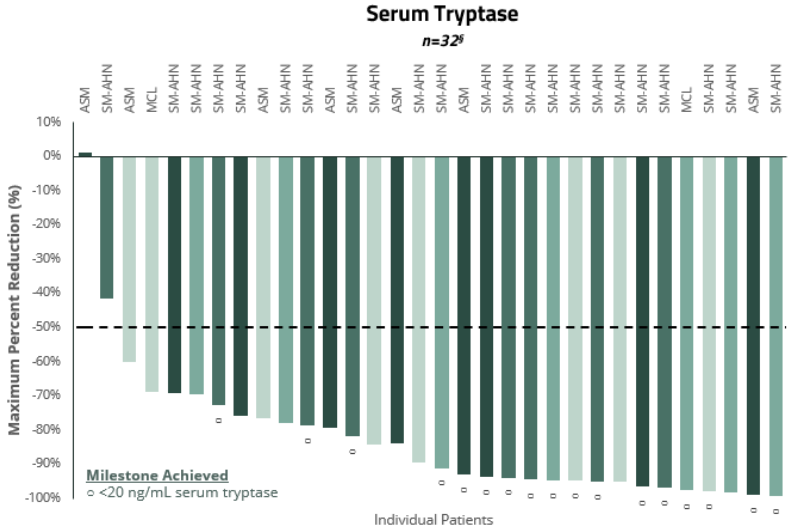
	Total (n=32) n (%)		50 mg BID (n=8) n (%)	100 mg BID (n=7) n (%)	200 mg BID (n=8) n (%)	400 mg QD (n=9) n (%)
Preferred Term	All grade	Grade ≥3	All grade	All grade	All grade	All grade
Hair color changes	**11 (34)**	**0**	0	4 (57)	3 (38)	4 (44)
Thrombocytopenia*	**7 (22)**	**2 (6)**	0	4 (57)	1 (13)	2 (22)
Transaminase increased*	**7 (22)**	**1 (3)**	3 (38)	2 (29)	1 (13)	1 (11)
Neutropenia*	**6 (19)**	**3 (9)**	1 (13)	2 (29)	1 (13)	2 (22)
Taste disorder*	**6 (19)**	**0**	1 (13)	1 (14)	1 (13)	3 (33)
Peripheral edema	**4 (13)**	**0**	0	1 (14)	1 (13)	2 (22)
Periorbital edema	**4 (13)**	**1 (3)**	0	0	3 (38)	1 (11)

Includes pooled preferred terms

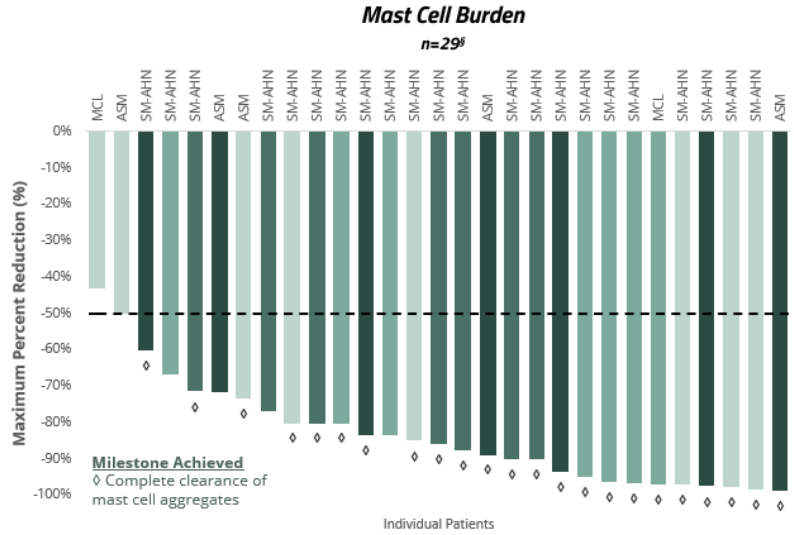
DILI – Drug Induced Liver Injury
Data as of: 25Sep2023
Vachhani P,. et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

Bezuclastinib Demonstrates Rapid and Deep Clinical Activity

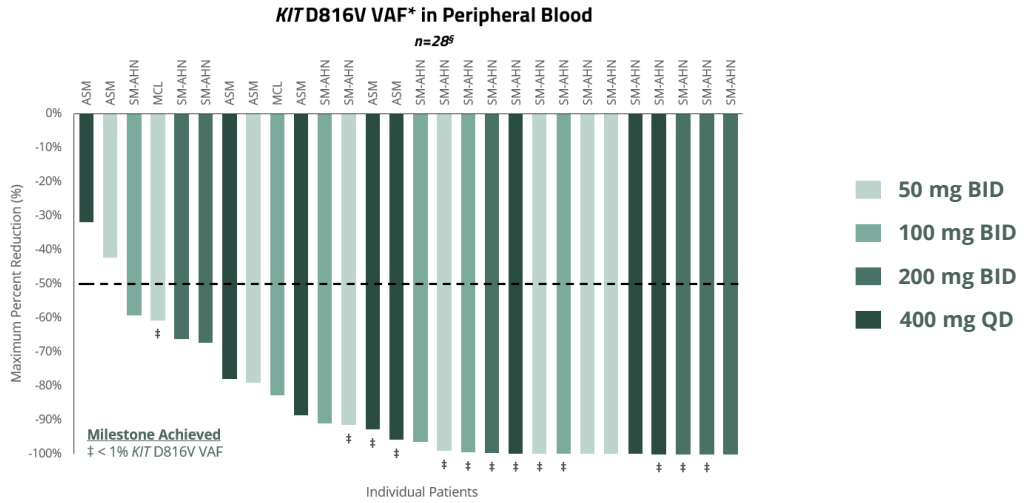
- Serum Tryptase
  - 94% (30/32) of patients achieved a ≥ 50% reduction
  - 100% (29/29) of patients with at least 2 cycles of treatment achieved a ≥ 50% reduction
  - 53% (17/32) achieved below 20 ng/mL
  - Median time to first serum tryptase <20 ng/mL was 4.0 weeks (range: 1.1-66.9)
- Bone Marrow MC Burden
  - 97% (28/29) of patients with baseline and at least 1 post-baseline assessment achieved a ≥ 50% reduction
  - 79% (23/29) achieved complete clearance of mast cell aggregates by central review
  - Median time to first clearance of mast cell aggregates was 9.0 weeks (range: 7.3-34.3)
- KIT D816V VAF in Peripheral Blood
  - 93% (26/28) of patients achieved a ≥ 50% reduction
  - Median time to first VAF below 1% was 9.0 weeks (range: 6.0-85.3)



§One patient without post-baseline data was excluded



§Four patients without post-baseline data were excluded



§Five patients excluded: Three (3) were KIT D816V negative at baseline and two (2) had no post-baseline data

*Central lab lower limit of detection of KIT D816V VAF by ddPCR is 0.03% mutated alleles

Data as of: 25Sep2023

Vachhani , et al. ..... Hematology (ASH) 2023; San Diego, CA, . Dec 2023: Publication Number: 4567

Apex Part 1: Responses Observed by mIWG-MRT-ECNM and PPR Criteria

Best Response, n (%) [Ω]	Total* Confirmed and unconfirmed mIWG-MRT-ECNM Responses per CRRC Assessment (n=27)	Confirmed mIWG-MRT-ECNM Responses per CRRC Assessment (n=27)	mIWG-MRT-ECNM per CRRC Assessment* (TKI[‡] Therapy Naïve) (n=18)	mIWG-MRT-ECNM per CRRC Assessment* (Prior TKI[‡] Exposure) (n=9)
Overall response rate				
CR + CRh + PR + CI[†]	**15 (56)**	**12 (44)**	**11 (61)**	**4 (44)**
CR + CRh + PR	**14 (52)**	**10 (37)**	**10 (56)**	**4 (44)**
Complete Response (CR + CRh)	**6 (22)**	**6 (22)**	**6 (33)**	**0 (0)**
Partial Response (PR)	**8 (30)**	**4 (15)**	**4 (22)**	**4 (44)**
Clinical Improvement (CI)	**1 (4)**	**2 (7)**	**1 (6)**	**0 (0)**
Stable Disease (SD)	**9 (33)**	**12 (44)**	**6 (33)**	**3 (33)**
Not evaluable	**3 (11)**	**3 (11)**	**1 (6)**	**2 (22)**

[Ω]5 patients without measurable C-finding at baseline were not mIWG-MRT-ECNM evaluable (inevaluable, IE) and therefore are excluded; one additional patient was excluded due to discontinuation prior to first dose (not dosed [ND]).

*4 patients who remain on therapy but have not yet reached the 12-week confirmation duration for partial response (PR) are included

[‡] SM-directed therapy with midostaurin and/or avapritinib
[†] Primary endpoint of Apex study

Best Response, n (%) [α]	Total (n=32)	PPR per Investigator Assessment (TKI[‡] Therapy Naïve) (n=22)	PPR per Investigator Assessment (Prior TKI[‡] Therapy) (n=10)
Overall response rate (CR + PR)	**24 (75)**	19 (86)	5 (50)
Complete Response (CR)	**14 (44)**	12 (55)	2 (20)
Partial Response (PR)	**10 (31)**	7 (32)	3 (33)
Stable Disease (SD)	**5 (16)**	2 (9)	3 (33)
Not Evaluable	**3 (9)**	1 (5)	2 (20)

[α]One patient was excluded due to discontinuation prior to first dose (Not Dosed [ND]).

[‡] SM-directed therapy with midostaurin and/or avapritinib

Data as of: 25Sep2023
Vachhani P, et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

Conclusions

- **Bezuclastinib continues to demonstrate a differentiated safety profile**
  - The majority of adverse events reported were low grade and reversible
  - No related cognitive impairment or bleeding events reported
  - 28% of patients required dose reduction due to adverse events; 9% of patients discontinued due to adverse events
- **Treatment with bezuclastinib resulted in encouraging signs of clinical activity**
  - 56% overall response rate (CR + CRh + PR + CI; confirmed and unconfirmed) per mIWG-MRT-ECNM and 75% ORR (CR +PR) per PPR criteria
  - Deep reductions demonstrated across commonly used biomarkers of mast cell activity:

≥50% Serum Tryptase	≥50% KIT D816V VAF	≥50% Bone Marrow MC Burden
94% of patients	93% of patients	97% of patients

- **Exposure achieved with 100 mg BID (200 mg per day) dose resulted in optimal efficacy and safety outcomes**
  - All patients receiving 100mg BID achieved PR or better and remain on trial with 3 patients at ≥20 cycles
  - Dose of 100mg BID was well tolerated; majority of dose reductions occurred in patients receiving 400mg total daily dose (200 mg BID or 400 mg QD)
- **Enrollment to Part 2 is ongoing**
  - 150 mg QD of the optimized formulation expected to deliver optimal exposures consistent with 100 mg BID of original formulation
  - A cohort evaluating bezuclastinib with concomitant AHN therapy, which is supported by nonclinical data, is open for enrollment

cogent BIOSCIENCES

Data as of: 25Sep2023

Vachhani P, et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

Multiple Clinical and Preclinical Programs with Upcoming Catalysts

Program	Indication	Early Stage Development	Late Stage Development	Regulatory Submission	Approval
Clinical Programs					
Bezuclastinib (KIT inhibitor)	Advanced Systemic Mastocytosis	Apex			
	Nonadvanced Systemic Mastocytosis	Summit			
	Gastrointestinal Stromal Tumors	Peak			

- Enrolling APEX Part 2 (Registration enabling)
- Initial Clinical Data at ASH 2023
- Enrolling PEAK Part 2 (Global Phase 3 trial)

Research Programs

Indication	Hit ID	Lead Generation	Lead Optimization	Candidate Selected	IND Submission
ErbB2 mut					
FGFR2					
PI3Kα					
Target 4					
Target 5					
Target 6					

Expected cash runway into 2026; $312.8 million as of September 30, 2023


cogent
BIOSCIENCES
Q&A
Real Challenges. Real Solutions.
Precision therapies for genetically defined diseases