Initial Data from APEX Phase 2 Study of Bezuclastinib in Advanced Systemic Mastocytosis

Investor Webcast

Presented at the European Hematology Association Congress
June 10, 2022

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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 regarding the potential for bezuclastinib to provide meaningful clinical activity to systemic mastocytosis patients without the tolerability challenges seen with other available treatment options, the expectation to accelerate timelines and investment and provide another APEX clinical update by the end of 2022, the expectation to present SUMMIT clinical data in NonAdvSM patients in 2023, and the plan to continue enrolling patients in Part 1 of APEX to determine a recommended dose for use in Part 2 of the trial; any statements of the plans, strategies, and objectives of management for future operations, including our clinical development and commercialization plans; 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 product pipeline, 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 on 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 to the development of our product candidates and adversely impact our business; our expected use of our existing cash and the net proceeds from this offering; the success, cost, and duration of our product development activities and clinical trials; the timing of our planned regulatory submissions to the FDA for our bezuclastinib product candidate, also known as CGT9486; 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 or for our teams to discover and develop additional product candidates; the ability to license additional intellectual property rights relating to our bezuclastinib product candidate or future product candidates from third-parties and to comply with our existing or future license agreements and/or collaboration agreements; our ability to commercialize our bezuclastinib product candidate and future product candidates in light of the intellectual property rights of others; our ability to obtain funding for our operations, including funding necessary to complete further discovery, development and commercialization of our existing and future product candidates; the scalability and commercial viability of our manufacturing methods and processes; the commercialization of our product candidates, if approved; our ability to attract collaborators with development, regulatory, and commercialization expertise; future agreements with third parties in connection with the commercialization of our product candidates and any other approved product; the size and growth potential of the markets for our product candidates, and our ability to serve those markets; the rate and degree of market acceptance of our product candidates; the pricing and reimbursement of our product candidates, if approved; regulatory developments in the United States and foreign countries; our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately; the development and success of competing therapies that are or may be under development in clinical trials or become available commercially; our ability to attract and retain key scientific and management personnel; the accuracy of our estimates regarding expenses, future revenue, capital requirements, and needs for additional financing; our use of the proceeds from the private placements, sales of our preferred stock and other public offerings of our common stock from time to time; and our expectations regarding our ability to obtain and maintain intellectual property protection for our bezuclastinib product candidate and future 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 most recent Annual Report on Form 10-K and our subsequent periodic reports 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.

Webcast Agenda and Speakers

Andrew Robbins
President and Chief Executive Officer

Daniel J. DeAngelo, M.D., Ph.D.
Chief of the Division of Leukemia
Dana-Farber Cancer Institute

Jessica Sachs, M.D.
Chief Medical Officer

Introduction & Corporate Overview	**Andrew Robbins**
Review of Initial APEX Data with Bezuclastinib in Advanced Systemic Mastocytosis (ASM) patients	**Dr. Daniel DeAngelo**
Presentation Summary	**Andrew Robbins**
Q&A	**Andrew Robbins** **Dr. Jessica Sachs** **Dr. Daniel DeAngelo**

Cogent Biosciences: Emerging Leader in Precision Medicines for Genetically Defined Diseases

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			

Demonstrating differentiated profile as potential best-in-class selective KIT mutant inhibitor

Research Programs

Indication	Hit ID	Lead Generation	Lead Optimization	GLP	IND Submission
FGFR2					
ErbB2 mut					
Target 3					
Target 4					
Target 5					
Target 6					

Building exciting portfolio of next-generation potent, selective kinase inhibitors

Cash runway into 2024; $191.0 million as of March 31, 2022

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Significant Unmet Need Remains for Advanced Systemic Mastocytosis Patients

Disease Overview: Aggressive and life-threatening form of systemic mastocytosis (SM) that is primarily driven by mutations in *KIT* D816V and leads to uncontrolled proliferation of mast cells (MC)[1-5]

- Subtypes: aggressive SM (ASM); SM with associated hematologic neoplasm (SM-AHN); mast cell leukemia (MCL)[6]
- Based on subtype, the median overall survival ranges from <6 months to 3-4 years[4-7]

Significant Unmet Need Remains: Few approved therapies, which have associated dose-limiting toxicities

- Reported toxicities for marketed therapies: nausea, vomiting, diarrhea, edema, intracranial bleeding, cognitive effects[10-12]

Neurological
Headache, brain fog, cognitive dysfunction, anxiety, depression

Systemic
Anaphylaxis

Cutaneous (skin)
Flushing of the face/neck/chest, hives, skin rashes, itching with or without rash

Gastrointestinal
Diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease (GERD)

Other

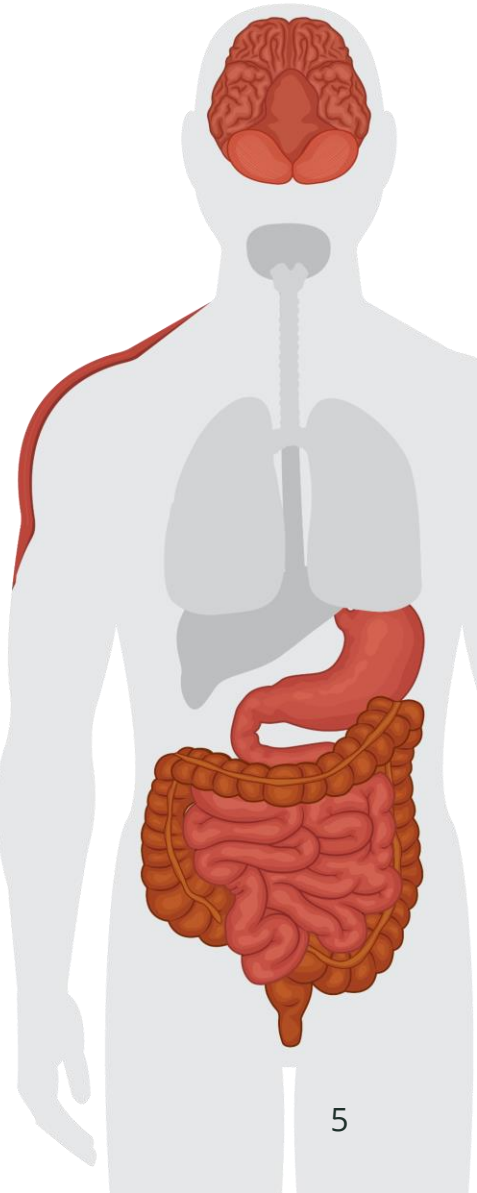
Cardiovascular
Light-headedness, syncope (fainting), rapid heart rate, chest pain, low blood pressure, high blood pressure at reaction start, blood pressure instability

Ear/Nose/Throat/Respiratory
Nasal itching and congestion, throat itching and swelling, wheezing, shortness of breath

Skeletal
Bone/muscle pain, osteopenia, osteoporosis

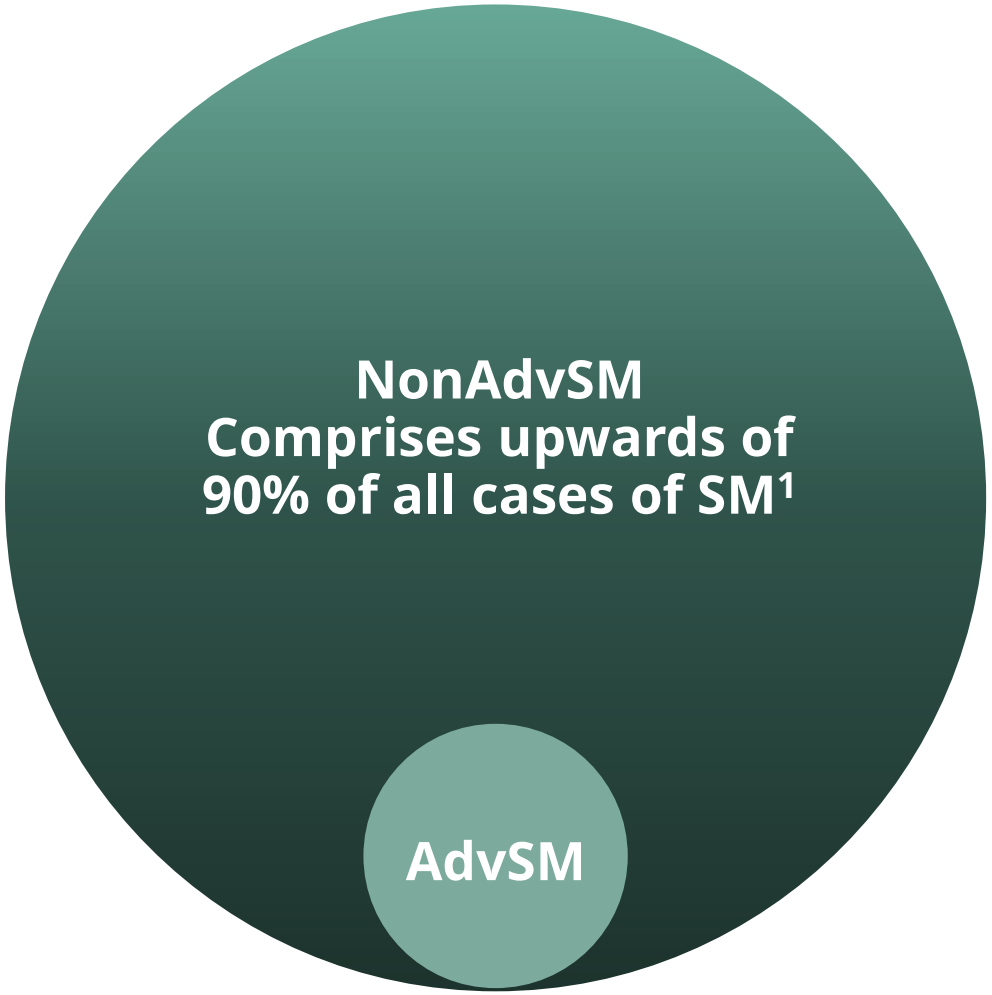
Gynecological
Uterine cramps, bleeding

Urinary
Bladder irritability, frequent voiding



Large, Yet Not Well Understood Population of SM Patients

Systemic Mastocytosis: Estimated prevalence in the U.S. is **20,000–30,000**[16] patients



Significant unmet medical need for clinically active, well-tolerated treatment options for this patient population

Bezuclastinib: Highly Selective and Potent KIT D816V Inhibitor

- Oral, selective, and potent type I tyrosine kinase inhibitor (TKI) with potent activity against *KIT* D816V, an activation loop mutation
- Preclinically, highly active with specificity for mutations in *KIT* exons 9, 11, 17, and 18, including D816V
- Spares closely related kinases, has minimal brain penetration, and favorable PK properties[13]
  - Inhibition of closely related kinases have been linked to off-target toxicities, such as bleeding, edema and pleural effusions[14,15]

Kinase Inhibition Profile of Clinical Stage and Approved *KIT* D816V Agents; Cell IC_{50} (nM)

Compound	*KIT* V560G/ D816V (HMC 1.2)	PDGFRα	PDGFRβ	CSF1R	FLT3	KDR
Bezuclastinib	14	>10,000	>10,000	>10,000	>1000	>1000
Avapritinib	13	53	10	249	305	>1000
BLU-263	6	21	6	161	345	>1000

Summary of mIWG-MRT-ECNM Response Thresholds

Response duration must be ≥12 weeks	Serum Tryptase Improvement	Mast Cell Improvement*	C-Findings	Peripheral Blood Counts
CR *(complete remission)*	**<20 ng/mL**	**No presence of mast cell aggregates**	**Resolution of palpable hepatosplenomegaly and all C-findings**	• **ANC ≥1×10⁹/L with normal differential** • **Platelet count ≥100×10⁹/L** • **Hgb level ≥11 g/dL**
CRh *(CR with partial recovery of peripheral blood counts)*	**<20 ng/mL**	**No presence of mast cell aggregates**	**Resolution of palpable hepatosplenomegaly and all C-findings**	• **ANC ≥0.5×10⁹/L with normal differential** • **Platelet count ≥50×10⁹/L** • **Hgb level ≥8 g/dL**
PR *(partial remission)*	**≥50% reduction**	**≥ 50% reduction**	**Resolution of at least one C-finding**	**n/a**

* Improvement in mast cells in bone marrow and/or other biopsied extracutaneous tissue

A Phase 2 Study of Bezuclastinib (CGT9486), A Novel, Highly Selective, Potent *KIT* D816V Inhibitor, in Adults with Advanced Systemic Mastocytosis (Apex): Methods, Baseline Data, and Early Insights

ABSTRACT CODE: P1049
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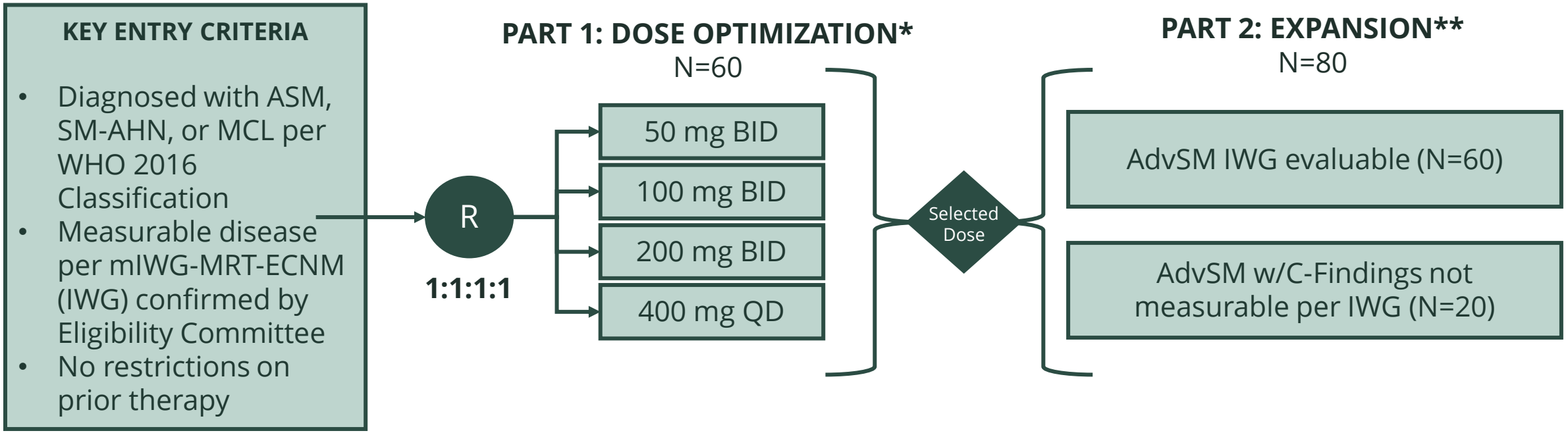
10 JUNE 2022

APEX: A Phase 2 Open-Label, Multicenter Clinical Study of Bezuclastinib in Patients with Advanced Systemic Mastocytosis



Primary Endpoint

- **Dose Optimization:** Incidence of AEs/SAEs, laboratory changes, PK, biomarkers, ORR
- **Expansion:** 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

**Interim analysis (IA) when ~28 pts (~7pts/dose level) have completed Cycle 2 (C2) to enrich at promising dose levels*
***Part 2 may be expanded based on Part 1 results and Regulatory Authority discussions*

Demography and Baseline Characteristics

Baseline Characteristics: 11 mIWG-evaluable patients enrolled as of 24-May-2022; median age 70 years (range: 48-87)

Baseline Characteristics	50mg BID (N=3)	100mg BID (N=3)	200mg BID (N=3)	400mg QD (N=2)	Total (N=11)
Male, n (%)	2 (67)	3 (100)	2 (67)	2 (100)	**9 (82)**
ECOG PS 0-1	2 (67)	3 (100)	3 (100)	1 (50)	**9 (82)**
AdvSM Subtype per Central Eligibility Review, n (%)					
ASM	1 (33)	0 (0)	0 (0)	1 (50)	**2 (18)**
SM-AHN	2 (67)	2 (67)	3 (100)	1 (50)	**8 (73)**
MCL	0 (0)	1 (33)	0 (0)	0 (0)	**1 (9)**
***KIT* D816V in Whole Blood, Positive, n (%)**	3 (100)	3 (100)	2 (67)	2 (100)	**10 (91)**
Treatment Naive, n (%)	3 (100)	2 (67)	2 (67)	2 (100)	**9 (82)**
Prior Avapritinib, n (%)	0 (0)	1 (33)	1 (33)	0 (0)	**2 (18)**
Prior Midostaurin, n (%)	0 (0)	1 (33)	1 (33)	0 (0)	**2 (18)**
Median Bone Marrow MC Burden, % (range)	60 (30-70)	70 (30-80)	10 (7-30)	55 (30-80)	**30 (7-80)**
Median Serum Tryptase, ng/mL (range)	187 (169-605)	253 (144-1578)	83 (67.9-111)	301 (232-370)	**182 (67.9-1578)**

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Summary of Safety and Tolerability

- Majority of treatment emergent adverse events (TEAE) were of low-grade with one serious adverse event (SAE) and no Grade 4 events
  - No periorbital/peripheral edema, cognitive effects or intracranial bleeding reported
- No treatment discontinuations; all patients remained on study*
- Two patients dose reduced due to AEs; one re-escalated to randomized dose

TEAE Occurring in >1 Patient and All Grade 3 Events

Preferred Term, n (%) (N=11)	TEAE		
	Grade 1/2	Grade 3	Grade 4
Anemia	2 (18)	1 (9)	0 (0)
Neutropenia	1 (9)	1 (9)	0 (0)
Thrombocytopenia	2 (18)	0 (0)	0 (0)
Diarrhea‡	0 (0)	1 (9)	0 (0)
Hypersensitivity†	0 (0)	1 (9)	0 (0)

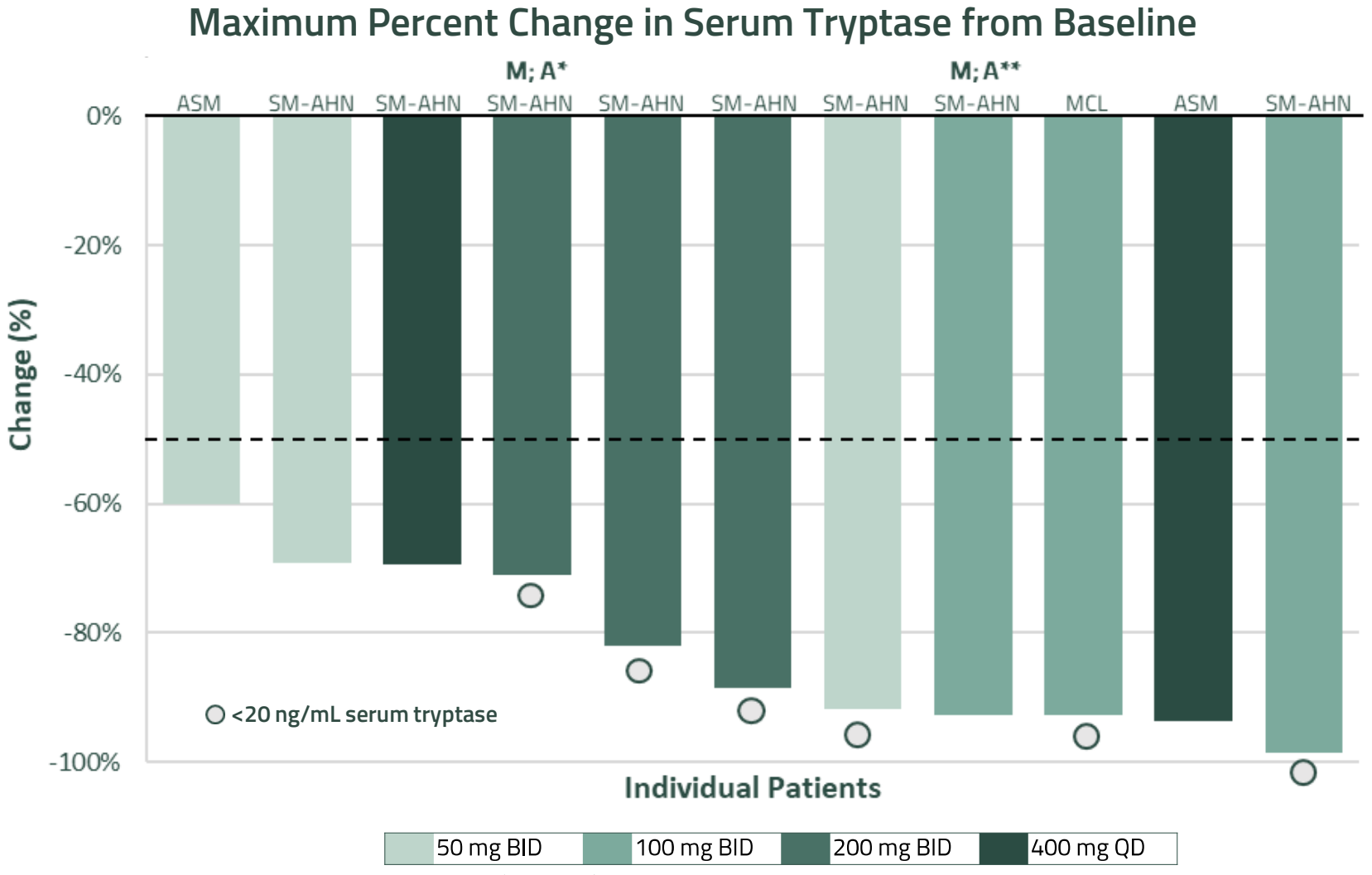
‡ Investigator assessed as not related to treatment
† SAE of hypersensitivity (mediator flare); patient continued treatment and remains on study (See: Patient Summary; Case 2)

** Subsequent to data cut-off, one SM-AHN patient with chronic myelomonocytic leukemia (CMML) transformed to acute myeloid leukemia (AML) and discontinued participation in the trial*

Bezuclastinib Demonstrated Substantial Serum Tryptase Reductions

Summary of Clinical Activity

- 11/11 patients experienced a ≥50% reduction in serum tryptase
- 89% median reduction in serum tryptase
- 6/11 patients achieved a serum tryptase level <20 ng/mL
- Prior avapritinib patients achieved similar magnitude improvement as treatment naïve population



A, prior avapritinib; M, prior midostaurin

*Patient discontinued ava due to intracranial hemorrhage, **Patient discontinued ava due to thrombocytopenia

Data as of: 24May2022

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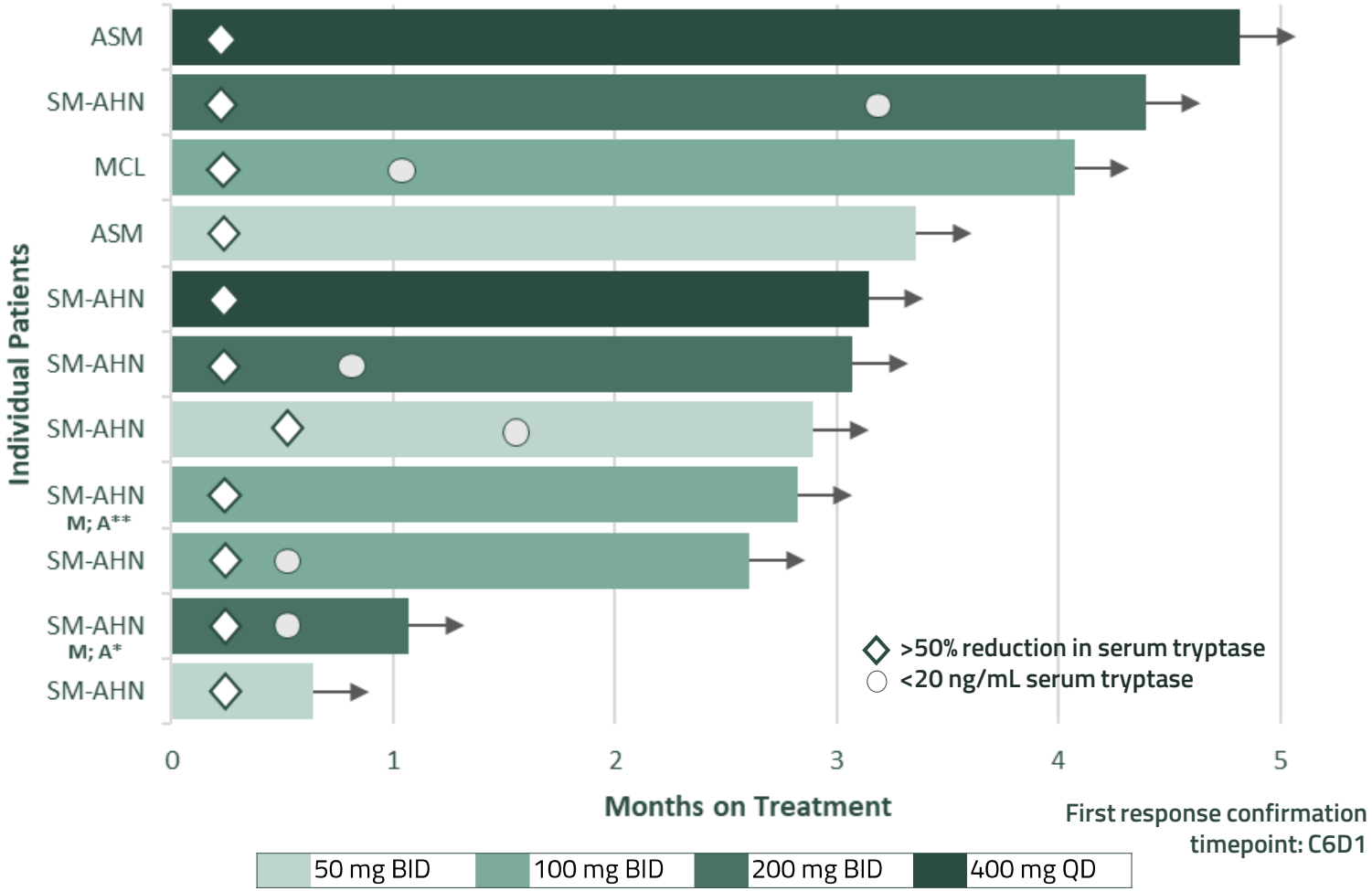
Bezuclastinib Demonstrated Rapid Serum Tryptase Reductions

Summary of Clinical Activity

- 10/11 patients achieved ≥50% serum tryptase reduction within first week of treatment
- 4 patients achieved <20 ng/mL serum tryptase level during first month of treatment
- Serum tryptase reductions seen across all three patient sub-types

Time to Serum Tryptase Reduction and Duration on Treatment



First response confirmation timepoint: C6D1

A, prior avapritinib; M, prior midostaurin
*Patient discontinued ava due to intracranial hemorrhage, **Patient discontinued ava due to thrombocytopenia

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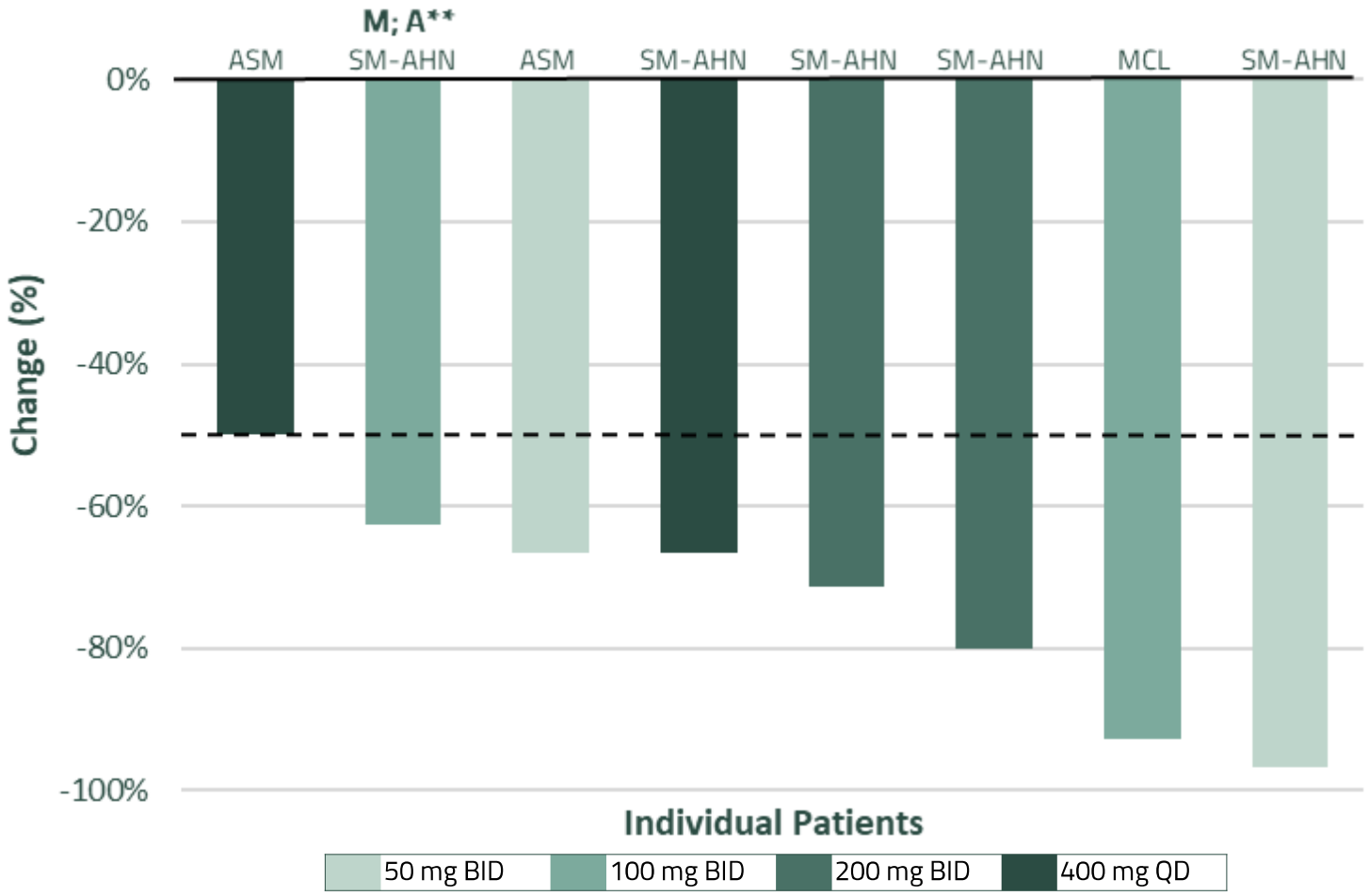
Bezuclastinib Demonstrated Impressive Bone Marrow MC Reductions

Summary of Clinical Activity

- 8/8 patients with ≥2 cycles of treatment and available Cycle 3, Day 1 (C3D1) data achieved ≥50% reduction in bone marrow mast cells
- 6/8 patients (C3D1) achieved complete clearance of mast cell aggregates by central review

Percent Change in Bone Marrow Mast Cell at C3D1



A, prior avapritinib; M, prior midostaurin
****Patient discontinued avapritinib due to thrombocytopenia**

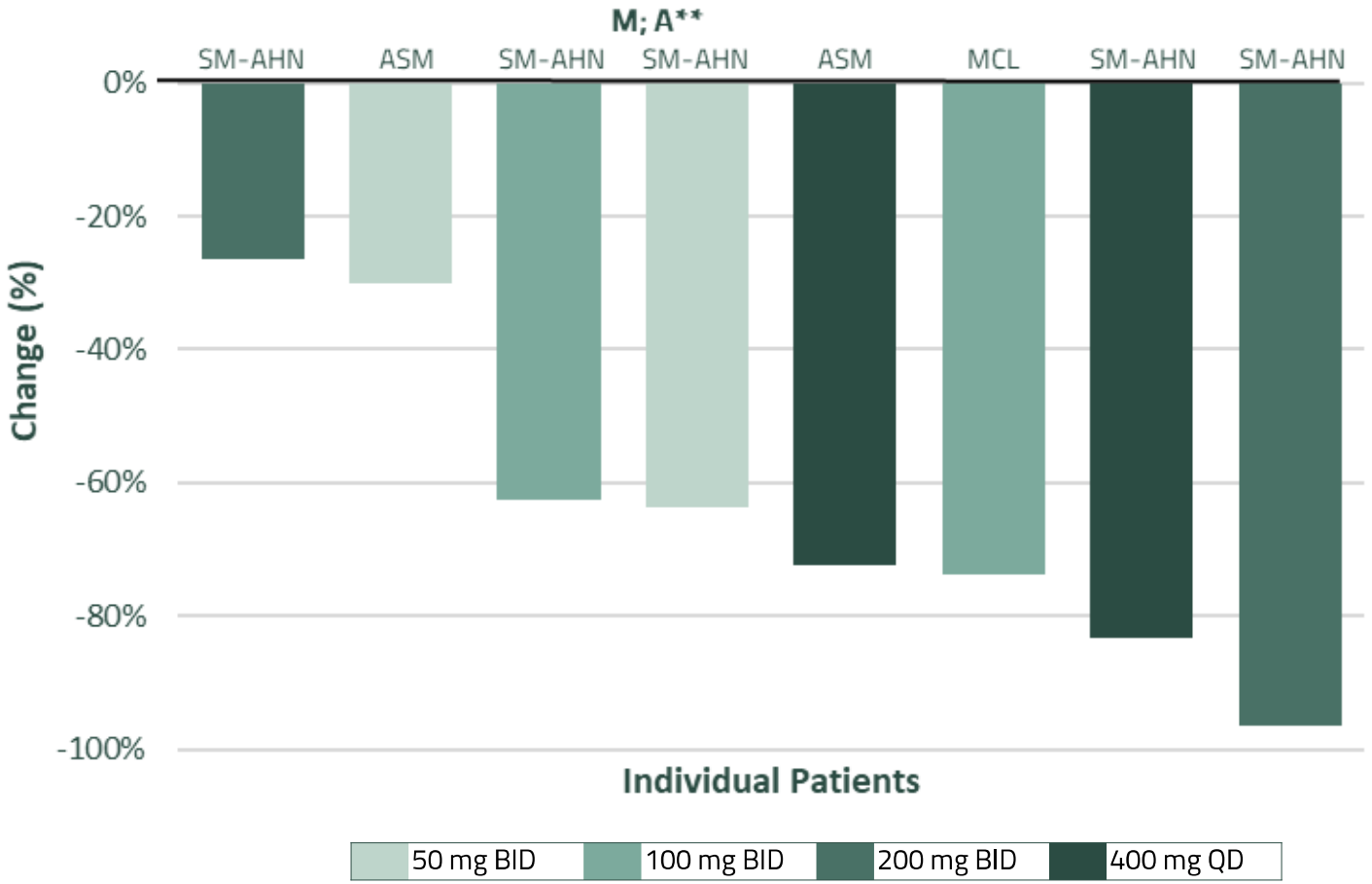
Data as of: 24May2022
DeAngelo D,. et al. European Hematology Association (EHA) 2022 Hybrid Congress; Vienna, Austria, 10 June 2022: Abstract Code: P1049

Bezuclastinib Demonstrated Impressive KIT D816V VAF Reductions

Summary of Clinical Activity

- 8/8 patients (C3D1) demonstrated decreases in KIT D816V variant allele fraction (VAF) by ddPCR

Percent Change in KIT D816V VAF at C3D1



A, prior Avapritinib; M, prior midostaurin
****Patient discontinued Avapritinib due to thrombocytopenia**

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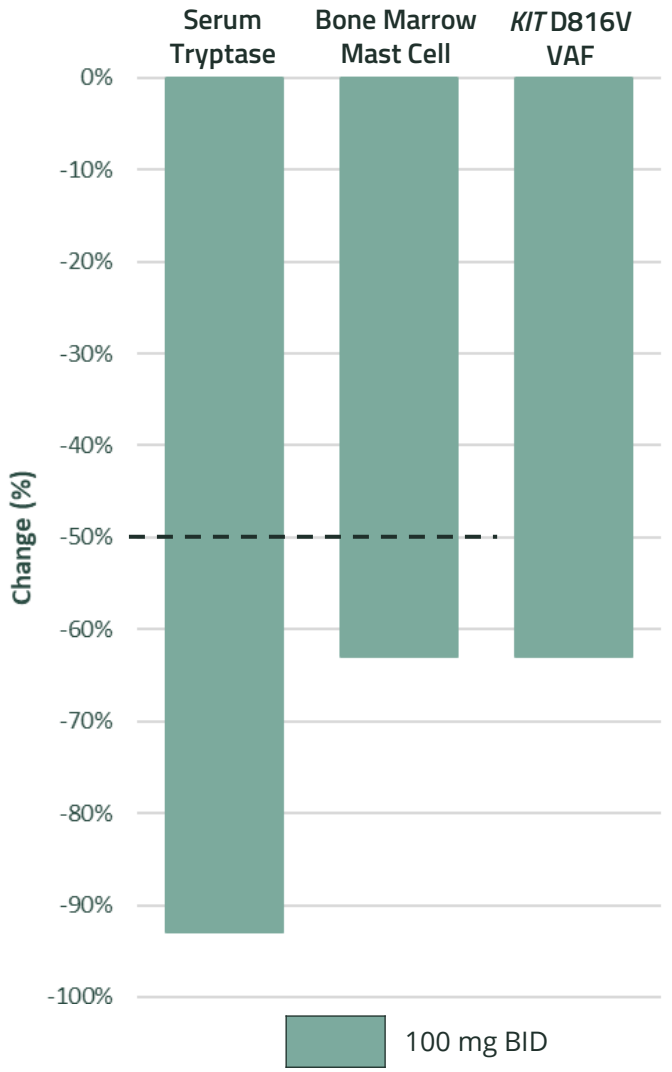
Case 1: Robust Clinical Activity in Avapritinib-Intolerant Patient

- **Background:** Patient with SM-AHN, prior treatment with midostaurin (progression) and avapritinib (toxicity: Grade 3 thrombocytopenia and anemia)
  - Baseline labs: serum tryptase 1578 ng/mL, MC burden 80%, C-finding: platelets <75K/µL
  - Randomized to bezuclastinib 100 mg BID

- **Safety:** Grade 3 anemia; patient remains on study treatment >2 months without treatment interruption or dose reduction

- **Clinical Activity:** 93% reduction in serum tryptase (>50% by C1D8), 63% reduction in bone marrow MC, and a 63% reduction in *KIT* D816V VAF



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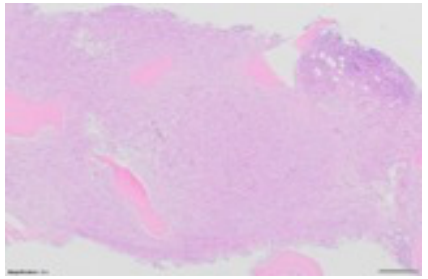
Case 2: Rapid and Durable Clinical Activity for ASM Patient >4 months

- **Background:** Patient with ASM, no prior TKI exposure
  - Baseline tryptase 370 ng/mL, baseline MC burden 80%, C-finding: spleen >5 cm below left coastal margin
  - Randomized to 400 mg QD

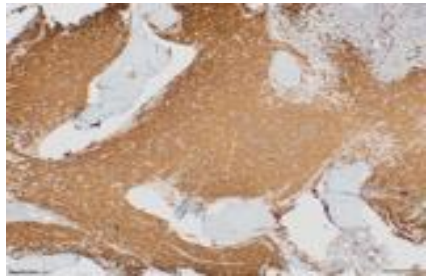
- **Safety:** Hypersensitivity (mediator flare) on C1D2, dose reduced from 400 mg QD to 200 mg QD without interruption; symptoms resolved within 24 hours; patient remains on study treatment >4 months

- **Clinical Activity:** 94% reduction in serum tryptase (>50% by C1D8), 50% reduction in bone marrow MC, and 72% reduction in *KIT* D816V VAF

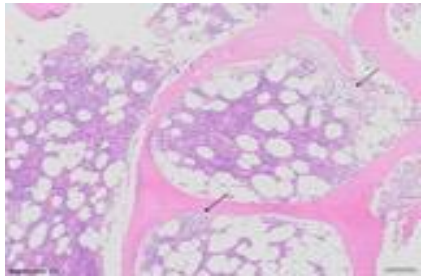
Patient Summary, Case 2 - (a, b) Prior to and (c, d) After 2 Cycles of Bezuclastinib Treatment



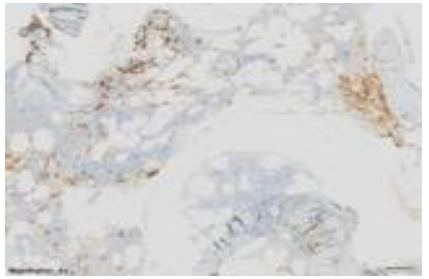
(a) Diffuse marrow infiltration by MC with minimal residual trilineage hematopoiesis



(b) IHC staining: CD117 (cKIT)



(c) MC infiltration decreased, arranged in paratrabecular aggregates (arrows)



(d) IHC staining: CD117 (cKIT)

Courtesy of Guys' and St. Thomas' NHS Foundation Trust;
Investigator: Dr. Deepti Radia, BSC, MBBS, MRCPI, FRC Path, MSc Med Ed; Pathologist: Dr Yurina Miki, MBBS BSc FRCPath.

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Bezuclastinib has Potential to Provide Meaningful Clinical Benefit

- **Bezuclastinib is a highly potent and selective tyrosine kinase inhibitor that targets the *KIT* D816V mutation, the primary driver of systemic mastocytosis**

- **Bezuclastinib was generally well-tolerated across all dose levels**
  - Majority of adverse events were Gr 1/2 and seen in no more than one patient, with one serious adverse event and no Grade 4 events reported
    - No reported periorbital/peripheral edema, cognitive effects or intracranial bleeding events
  - Hematological events are expected in this patient population with advanced hematologic disease, frequently presenting with baseline cytopenias related to underlying disease and/or prior therapy

- **Encouraging early signs of clinical activity demonstrated across all dose levels**
  - Clinically meaningful reduction in serum tryptase levels, reductions in MC burden, and KIT D816V VAF in all evaluable patients across doses tested
    - With median 89%, all patients achieved ≥50% serum tryptase reduction; all C3D1 patients achieved ≥50% bone marrow MC reductions
  - Patients treated with prior KIT inhibitors, including avapritinib, demonstrated similar magnitude reductions across serum tryptase, MC burden, and *KIT* D816V VAF

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Investor Webcast Summary

CogentBio.com

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Cogent Biosciences: Emerging Leader in Precision Medicines for Genetically Defined Diseases

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			

Demonstrating differentiated profile as potential best-in-class selective KIT mutant inhibitor

Research Programs

Indication	Hit ID	Lead Generation	Lead Optimization	GLP	IND Submission
FGFR2					
ErbB2 mut					
Target 3					
Target 4					
Target 5					
Target 6					

Building exciting portfolio of next-generation potent, selective kinase inhibitors

Cash runway into 2024; $191.0 million as of March 31, 2022
Additional APEX data by the end of 2022
Initial SUMMIT and PEAK lead-in data during 1H 2023

Questions & Answers

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Appendix

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References + Disclosures

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