UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of The Securities Exchange Act of 1934

Date of Report (Date of Earliest Event Reported): December 11, 2022

COGENT BIOSCIENCES, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-38443**	**46-5308248**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

275 Wyman Street, 3rd Floor **Waltham, Massachusetts** **(Address of principal executive offices)**	**02451** **(Zip Code)**

Registrant's telephone number, including area code (617) 945-5576

200 Cambridge Park Drive, Suite 2500
Cambridge, Massachusetts 02140
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common stock, $0.001 Par Value	COGT	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 or Rule 12b-2 of the Securities Exchange Act of 1934.

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 7.01 Regulation FD Disclosure.

On December 11, 2022, Cogent Biosciences, Inc., a Delaware corporation (the "Company"), issued a press release announcing positive updated clinical data from its ongoing Phase 2 APEX trial evaluating bezuclastinib in patients with advanced systemic mastocytosis. The Company will present the updated clinical data on a webcast on December 12, 2022 at 8:00 am ET. Copies of the press release and corporate presentation are attached as Exhibits 99.1 and 99.2, respectively, to this Current Report on Form 8-K and are incorporated herein by reference.

The information in this Current Report on Form 8-K, including Exhibits 99.1 and 99.2 attached hereto, is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press release issued by Cogent Biosciences, Inc. on December 11, 2022, furnished herewith.
99.2	Cogent Biosciences, Inc. corporate presentation, furnished herewith.
104	The cover page from the Company's Current Report on Form 8-K formatted in Inline XBRL.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: December 12, 2022

COGENT BIOSCIENCES, INC.

By: /s/ Evan D. Kearns
Evan D. Kearns
Chief Legal Officer

Cogent Biosciences Announces Positive Updated Clinical Data from Ongoing Phase 2 APEX Trial Evaluating Bezuclastinib in Patients with Advanced Systemic Mastocytosis (AdvSM)

• 89% ORR in TKI-therapy naïve patients; 73% ORR in all evaluable patients with 27-week median follow-up

• Rapid and deep responses seen including first confirmed CR at 20 weeks; 77% of patients with at least 2 cycles of treatment had complete clearance of bone marrow mast cell aggregates

• Favorable safety and tolerability profile with no related cognitive effects or reported intracranial bleeding events

• Cogent to host investor webcast Monday, December 12 at 8:00 a.m. ET

WALTHAM, Mass. and BOULDER, Colo., December 11, 2022 — Cogent Biosciences, Inc. (Nasdaq: COGT), a biotechnology company focused on developing precision therapies for genetically defined diseases, today announced positive updated clinical data from its ongoing Phase 2 APEX clinical trial evaluating the selective KIT D816V inhibitor bezuclastinib in patients with advanced systemic mastocytosis (AdvSM). The data are being presented in an oral presentation at the 64th American Society of Hematology (ASH) Annual Meeting in New Orleans, LA.

“Advanced systemic mastocytosis is a rare and life-threatening disease,” said Daniel J. DeAngelo, M.D., Ph.D., Chief of the Division of Leukemia at the Dana-Farber Cancer Institute and APEX clinical trial investigator. “Updated results from the APEX trial demonstrate rapid and deep responses with bezuclastinib while maintaining an impressive safety and tolerability profile.”

“We are very encouraged by the clinical profile that bezuclastinib has shown to date,” said Andrew Robbins, President and Chief Executive Officer at Cogent Biosciences. “We are especially excited that a growing body of data supports bezuclastinib’s differentiated safety and tolerability profile enabling therapeutic exposures that could support key differentiation for both AdvSM patients and non-advanced systemic mastocytosis patients.”

Updated Data from Ongoing Phase 2 APEX Clinical Trial

APEX is a global, open-label, multi-center, two-part Phase 2 clinical trial in patients with AdvSM evaluating the safety, efficacy, pharmacokinetic, and pharmacodynamic profiles of bezuclastinib. As of the data cutoff date of October 26, 2022, 16 patients had been treated in Part 1 at one of four dose levels (50 mg BID, 100 mg BID, 200 mg BID or 400 mg QD). The median age of patients at study entry was 69 years (ranging from 33-87 years). Patients were enrolled with the following sub-types: three patients with aggressive systemic mastocytosis (ASM), 12 patients with systemic mastocytosis with associated hematologic neo-plasm (SM-AHN), and one patient with mast cell leukemia (MCL). Three patients had received prior avapritinib and midostaurin treatment.

Updated Safety Data

As of the cutoff date October 26, 2022, bezuclastinib was generally well-tolerated at all doses. The majority of adverse events were Grade 1/2 and occurred in no more than one patient. Grade 3 events reported as at least possibly related to bezuclastinib were neutropenia (2 patients), thrombocytopenia (1 patient), anemia (1 patient) and hypersensitivity/mediator flare (1 patient). Importantly, there were no related cases of cognitive impairment and no reported intracranial bleeding events, which have been associated with other KIT inhibitors. Limited low-grade edema was observed, and analysis of platelet counts in bezuclastinib-treated patients showed no trend in platelet reduction at any dose.

Updated Clinical Activity Data

As of the cutoff date of October 26, 2022, 11 patients were evaluable for response per the modified IWG-MRT-ECNM criteria, and 12 patients were evaluable for response using pure pathological response (PPR) criteria. Reported ORR per mIWG-MRT-ECNM criteria includes centrally adjudicated confirmed and unconfirmed CR, CRh, PR, and CI.

- 89% ORR in TKI therapy naïve patients, including 67% of patients achieving CR, CRh or PR, and 22% of patients achieving CR or CRh
    - 73% ORR in all patients, regardless of prior treatment
- 75% ORR in all patients by PPR criteria, regardless of prior treatment

Additionally, results of key markers of clinical activity were reported from 16 patients.

- 14/16 patients achieved ≥ 50% reduction in serum tryptase levels by central assessment
    - 85% median reduction in serum tryptase
    - Eight of these patients achieved reduction to <20 ng/mL
- 13/13 patients with ≥2 cycles of treatment achieved ≥50% reduction in bone marrow mast cells by central review
    - 10 of these patients achieved complete clearance of bone marrow mast cell aggregates
- 11/12 patients with baseline D816V mutation and ≥2 cycles of treatment achieved ≥50% reduction in KIT D816V variant allele fraction (VAF) by droplet digital polymerase chain reaction (ddPCR)

Bezuclastinib Clinical Development

Based on the continued favorable safety and tolerability profile and clinical activity observed to date in the Phase 2 APEX clinical trial with bezuclastinib for patients with AdvSM, Cogent will continue enrolling patients in Part 1 of APEX to determine a recommended dose for use in Part 2 of the trial.

In addition, Cogent continues to actively enroll patients in SUMMIT, a Phase 2 clinical trial with bezuclastinib for patients with non-advanced systemic mastocytosis (NonAdvSM), and PEAK, a registrational randomized, open-label, global, Phase 3 clinical trial in patients with imatinib-resistant Gastrointestinal Stromal Tumors (GIST). Cogent plans to present initial clinical efficacy results from the PEAK lead-in study during the first half of 2023 and present initial clinical data from SUMMIT in the second half of 2023.

Webcast Information & ASH Poster

Cogent will host a webcast on December 12, 2022 at 8:00 a.m.ET (7:00 a.m. CT) to discuss today's updated clinical data from the ongoing APEX trial. The live event can be accessed on the Investor page of Cogent's website at investors.cogentbio.com. A replay of the webcast will be available approximately two hours after the completion of the event and will be archived for up to 30 days.

The ASH poster is available to registered conference attendees as well as on the Posters and Publications section of Cogent's website at www.cogentbio.com/research.

About Cogent Biosciences, Inc.

Cogent Biosciences is a biotechnology company focused on developing precision therapies for genetically defined diseases. The most advanced clinical program, bezuclastinib, is a selective tyrosine kinase inhibitor that is designed to potently inhibit the KIT D816V mutation as well as other mutations in KIT exon 17. KIT D816V is responsible for driving systemic mastocytosis, a serious disease caused by unchecked proliferation of mast cells. Exon 17 mutations are also found in patients with advanced gastrointestinal stromal tumors (GIST), a type of cancer with strong dependence on oncogenic KIT signaling. In addition to bezuclastinib, the Cogent Research Team is developing a portfolio of novel targeted therapies to help patients fighting serious, genetically driven diseases initially targeting FGFR2 and ErbB2. Cogent Biosciences is based in Waltham, MA and Boulder, CO. Visit our website for more information at www.cogentbio.com. Follow Cogent Biosciences on social media: Twitter and LinkedIn. Information that may be important to investors will be routinely posted on our website and Twitter.

Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including, but not limited to, statements regarding the potential for bezuclastinib to become a best-in-class treatment option for patients with AdvSM, the potential for bezuclastinib to achieve therapeutic exposures that could support key differentiation for patients with both AdvSM and NonAdvSM, Cogent's plans to continue enrolling patients in Part 1 of APEX to determine a recommended dose for use in Part 2 of the trial, Cogent's plan to present initial clinical efficacy results from the PEAK lead-in study during the first half of 2023, and Cogent's plan to present initial clinical data from SUMMIT in the second half of 2023. The use of words such as, but not limited to, "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "will," or "would" and similar words expressions are intended to identify forward-looking statements. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our clinical results, the rate of enrollment in our clinical trials and other future conditions. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements. We may not actually achieve the forecasts or milestones disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Such forward-looking statements are subject to a number of material risks and uncertainties including but not limited to those set forth under the caption "Risk Factors" in Cogent's most recent Quarterly Report on Form 10-Q filed with the SEC. Any forward-looking statement speaks only as of the date on which it was made. Neither we, nor our affiliates, advisors or representatives, undertake any obligation to publicly update or revise any forward-looking statement, whether as result of new information, future events or otherwise, except as required by law. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date hereof.

Contact:

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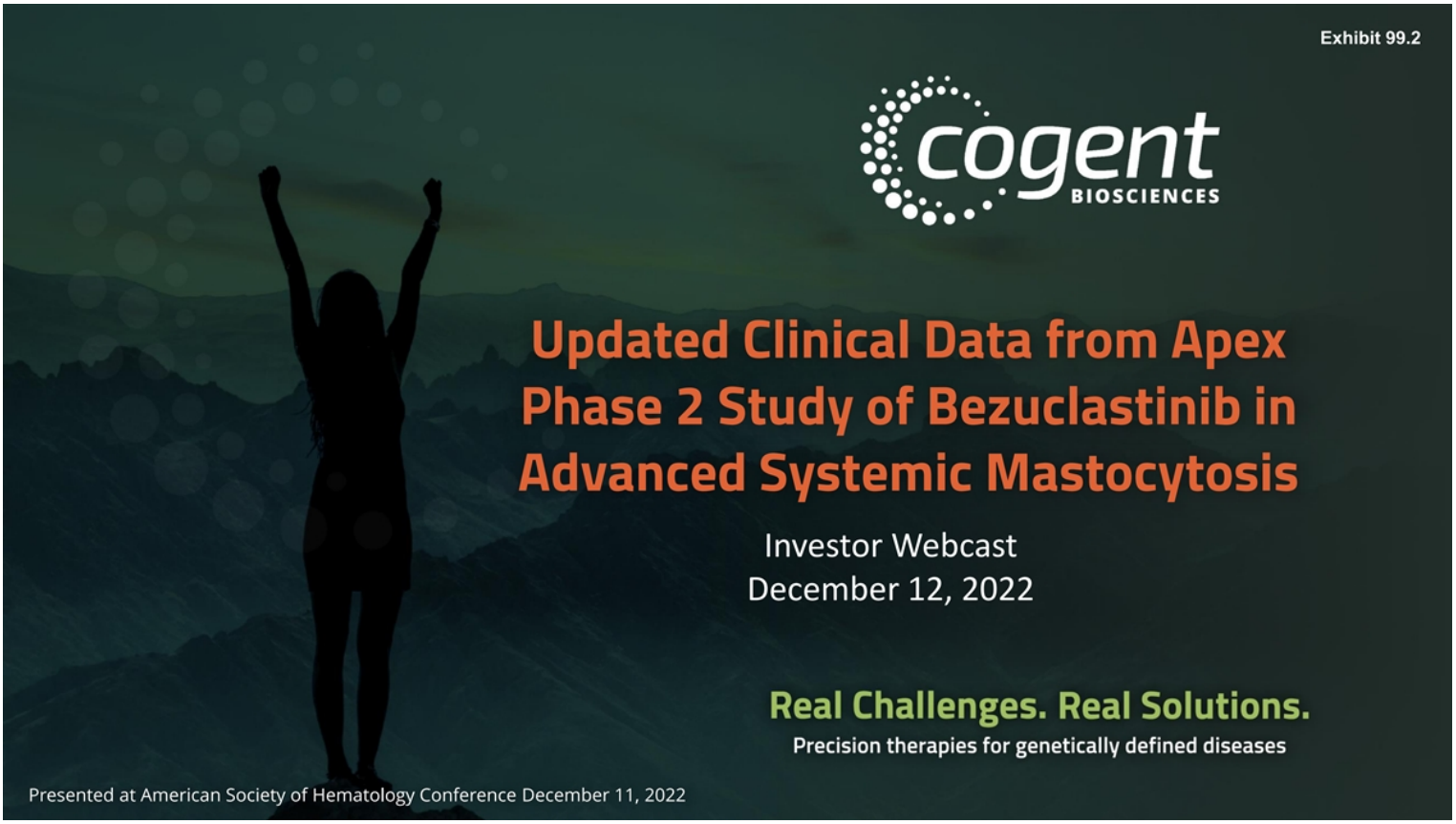
617-830-1653

Exhibit 99.2



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Updated Clinical Data from Apex Phase 2 Study of Bezuclastinib in Advanced Systemic Mastocytosis

Investor Webcast
December 12, 2022

Real Challenges. Real Solutions.
Precision therapies for genetically defined diseases

Presented at American Society of Hematology Conference December 11, 2022

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

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 Updated 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

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			

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

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Cash runway into 2025; $289.1 million as of September 30, 2022

Unmet Need Remains for Advanced Systemic Mastocytosis Patients

Disease Overview: Aggressive and life-threatening form of systemic mastocytosis (SM) that is primarily driven by KIT D816V mutation and 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]

Unmet Need Remains: Approved therapies with associated dose-limiting toxicities

- Reported toxicities for marketed therapies: nausea, vomiting, diarrhea, edema, intracranial bleeding, cognitive effects[5-7]

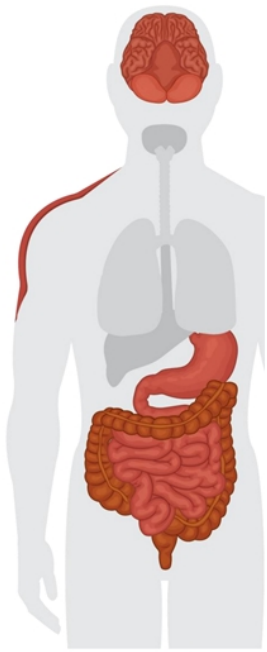
Neurological
Headache, brain fog, cognitive dysfunction, anxiety, depression

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)

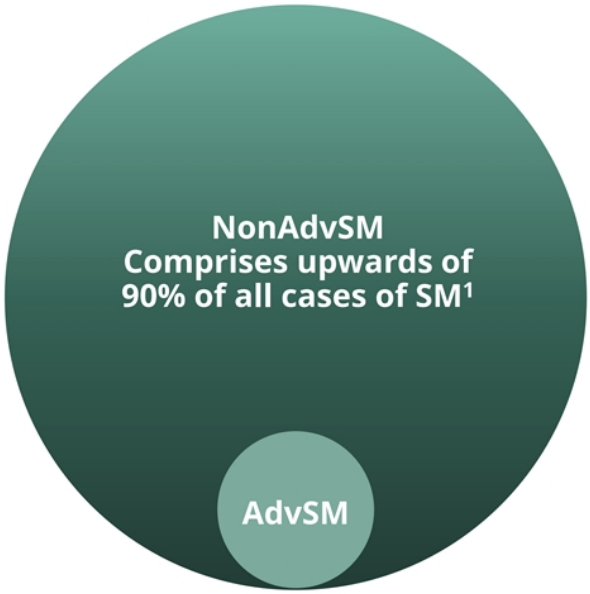
Other
Cardiovascular
Ear/Nose/Throat/Respiratory
Skeletal
Gynecological
Urinary



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

Large, Yet Not Well Understood Population of SM Patients

Systemic Mastocytosis: Estimated prevalence in the U.S. is **20,000–30,000**[1] patients



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

[1]Coltoff A, Mascarenhas J., 2019.

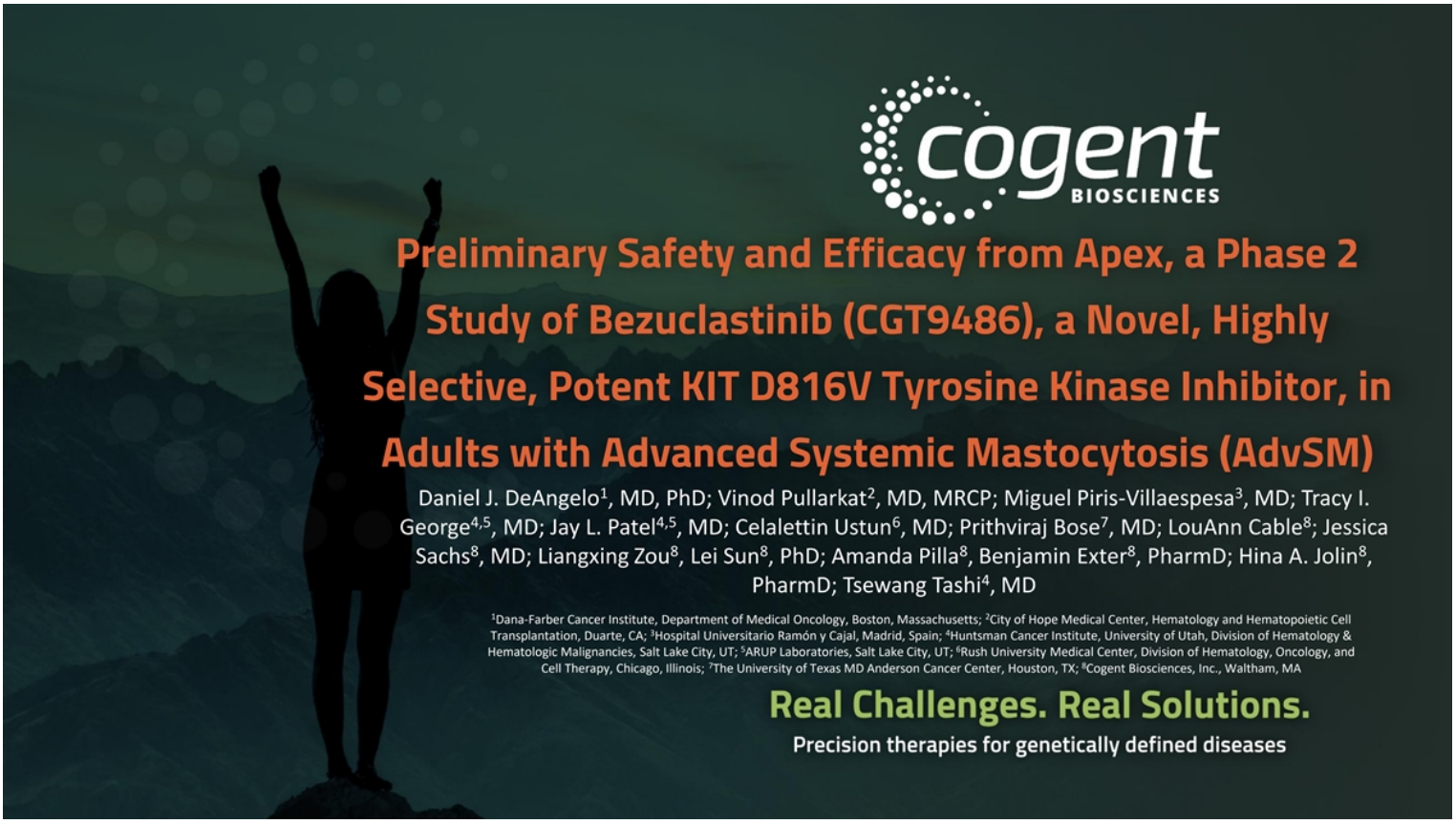
Bezuclastinib: Highly Selective and Potent KIT D816V Inhibitor

- Oral, selective, and 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
- Spares closely related kinases, 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]

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

Compound	KIT V560G/D816V (HMC 1.2)	WT KIT	PDGFRα	PDGFRβ	CSF1R	FLT3	KDR
Bezuclastinib	14	121	> 10,000	> 10,000	> 10,000	> 1000	> 1000
Avapritinib	13	114	53	10	249	305	> 1000
BLU-263	6	355	21	6	161	345	> 1000

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



Preliminary Safety and Efficacy from Apex, a Phase 2 Study of Bezuclastinib (CGT9486), a Novel, Highly Selective, Potent KIT D816V Tyrosine Kinase Inhibitor, in Adults with Advanced Systemic Mastocytosis (AdvSM)

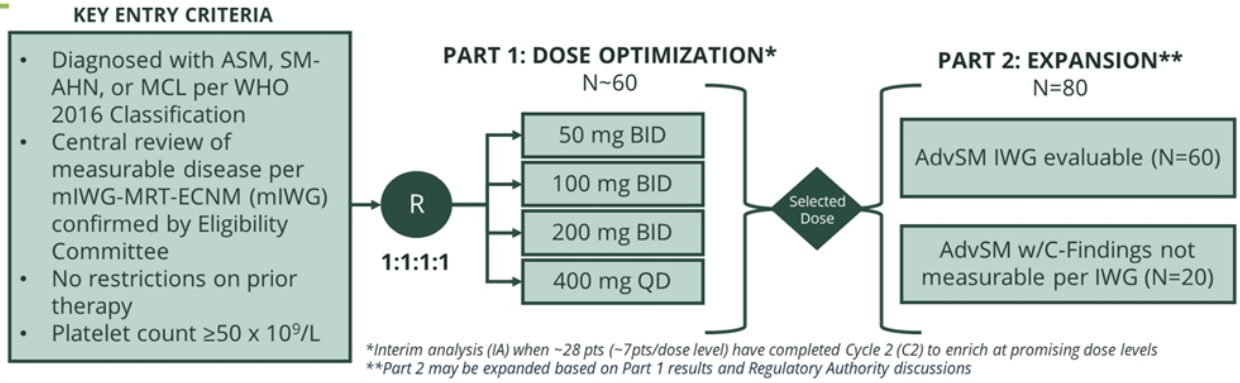
Daniel J. DeAngelo[1], MD, PhD; Vinod Pullarkat[2], MD, MRCP; Miguel Piris-Villaespesa[3], MD; Tracy I. George[4,5], MD; Jay L. Patel[4,5], MD; Celalettin Ustun[6], MD; Prithviraj Bose[7], MD; LouAnn Cable[8]; Jessica Sachs[8], MD; Liangxing Zou[8], Lei Sun[8], PhD; Amanda Pilla[8], Benjamin Exter[8], PharmD; Hina A. Jolin[8], PharmD; Tsewang Tashi[4], MD

[1]Dana-Farber Cancer Institute, Department of Medical Oncology, Boston, Massachusetts; [2]City of Hope Medical Center, Hematology and Hematopoietic Cell Transplantation, Duarte, CA; [3]Hospital Universitario Ramón y Cajal, Madrid, Spain; [4]Huntsman Cancer Institute, University of Utah, Division of Hematology & Hematologic Malignancies, Salt Lake City, UT; [5]ARUP Laboratories, Salt Lake City, UT; [6]Rush University Medical Center, Division of Hematology, Oncology, and Cell Therapy, Chicago, Illinois; [7]The University of Texas MD Anderson Cancer Center, Houston, TX; [8]Cogent Biosciences, Inc., Waltham, MA

Real Challenges. Real Solutions.

Precision therapies for genetically defined diseases

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



*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

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

Patient Demographics and Characteristics

- 16 patients enrolled; median age: 69 years; Range: 33-87

	Total (N=16)	50mg BID (N=4)	100mg BID (N=3)	200mg BID (N=4)	400mg QD (N=5)
Male, n (%)	**13 (81)**	3 (75)	3 (100)	3 (75)	4 (80)
ECOG PS 0-1, n (%)	**14 (88)**	4 (100)	3 (100)	4 (100)	3 (60)
AdvSM Subtype per Central Eligibility Review, n (%)					
ASM	**3 (19)**	1 (25)	0 (0)	0 (0)	2 (40)
SM-AHN	**12 (75)**	3 (75)	2 (67)	4 (100)	3 (60)
MCL	**1 (6)**	0 (0)	1 (33)	0 (0)	0 (0)
Prior therapy for AdvSM, n (%)[∫]					
Treatment Naïve*	**11 (69)**	3 (75)	2 (67)	3 (75)	3 (60)
Avapritinib	**3 (19)**	0 (0)	1 (33)	1 (25)	1 (20)
Midostaurin	**3 (19)**	0 (0)	1 (33)	1 (25)	1 (20)
***KIT* D816V in Whole Blood, Positive, n (%)**	**14 (88)**	4 (100)	3 (100)	3 (75)	4 (80)
Median KIT D816V VAF, % (range)[‡]	**10.6 (0.02-47.18)**	14.3 (0.02 – 37.4)	7.98 (7.04 – 32.28)	27.85 (8.7 – 47.18)	7.18 (0.93 – 13.48)
Median Bone Marrow MC Burden, % (range)	**30 (7-80)**	45 (20-70)	70 (30-80)	20 (7-30)	30 (10-80)
Median Serum Tryptase, ng/mL (range)	**178 (50-1578)**	334 (169-605)	253 (144-1578)	97 (67.9-121)	232 (50-370)

**Patients who have received no prior SM directed therapies*
[∫] Additional therapies included PEG interferon-α, cladribine, hydroxyurea, azacytidine, decitabine, brentuximab vedotin, and other
[‡] Includes patients with positive KIT D816V

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Data as of: 26Oct2022
DeAngelo D,. et al. American Society of Hematology (ASH) 2022 Annual Meeting; New Orleans, LA, 11 Oct 2022: Publication Number: 626

Safety and Tolerability of Bezuclastinib

Treatment Related Adverse Events in > 10% Patients and all Related SAEs

	Total (n=16)		TKI‡ Therapy Naïve (n=13)	Prior TKI‡ Exposure (n=3)	50 mg BID (n=4)	100 mg BID (n=3)	200 mg BID (n=4)	400 mg QD (n=5)
Preferred Term	All grade	Grade ≥3	All grade	All grade	All grade	All grade	All grade	All grade
Hair color changes	**4 (25)**	**0**	2	2	0	2	1	1
Taste disorder^	**4 (25)**	**0**	3	1	1	0	1	2
Neutropenia∫	**4 (25)**	**2 (13)**	4	0	1	1	1	1
Edema peripheral	**3 (19)**	**0**	1	2	0	0	1	2
Thrombocytopenia	**3 (19)**	**1 (6)**	3	0	0	1	0	2
Nausea	**2 (13)**	**0**	1	1	0	1	0	1
Fatigue	**2 (13)**	**0**	1	1	1	0	1	0
Vomiting	**2 (13)**	**0**	1	1	0	1	0	1
Anemia	**2 (13)**	**1(6)**	0	2	0	1	1	0
Hypersensitivity (mediator flare)#	**1 (6)**	**1(6)**	1	0	0	0	0	1

‡SM-directed therapy with midostaurin and avapritinib
^ Includes pooled preferred terms of terms of Taste disorder and Dysgeusia
∫Includes pooled preferred terms of Neutropenia, Neutrophil count decreased, and WBC decreased
#Serious adverse event

- The majority of TEAEs were of low grade with one related SAE and no related Grade 4 events
- No related cognitive effects or bleeding events reported
- The majority of hematological TEAEs were of low grade, reversible and did not require dose modification
- No discontinuations with 3 patients dose reduced due to TEAEs; one re-escalated to randomized dose

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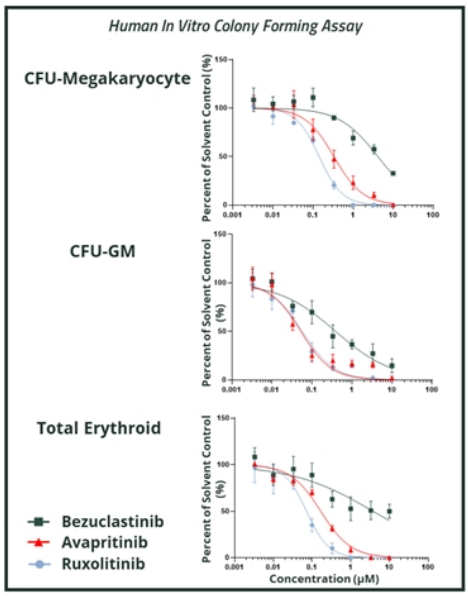
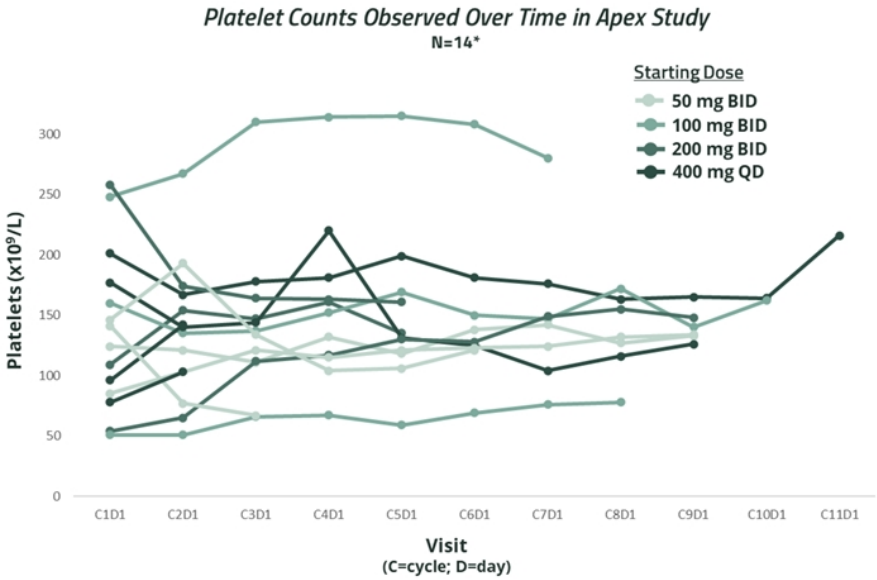
Data as of: 26Oct2022
DeAngelo D,. et al. American Society of Hematology (ASH) 2022 Annual Meeting; New Orleans, LA, 11 Oct 2022: Publication Number: 626

Limited Effect of Bezuclastinib on Platelet Counts in Apex Study, Supported by Preclinical Data





All patients in Apex were required to have platelet count ≥50 x 10^9/L for 2 weeks prior to the first dose of study drug
**Two patients excluded: (1) due to presence of essential thrombocythemia at baseline; (1) no post-baseline assessment*

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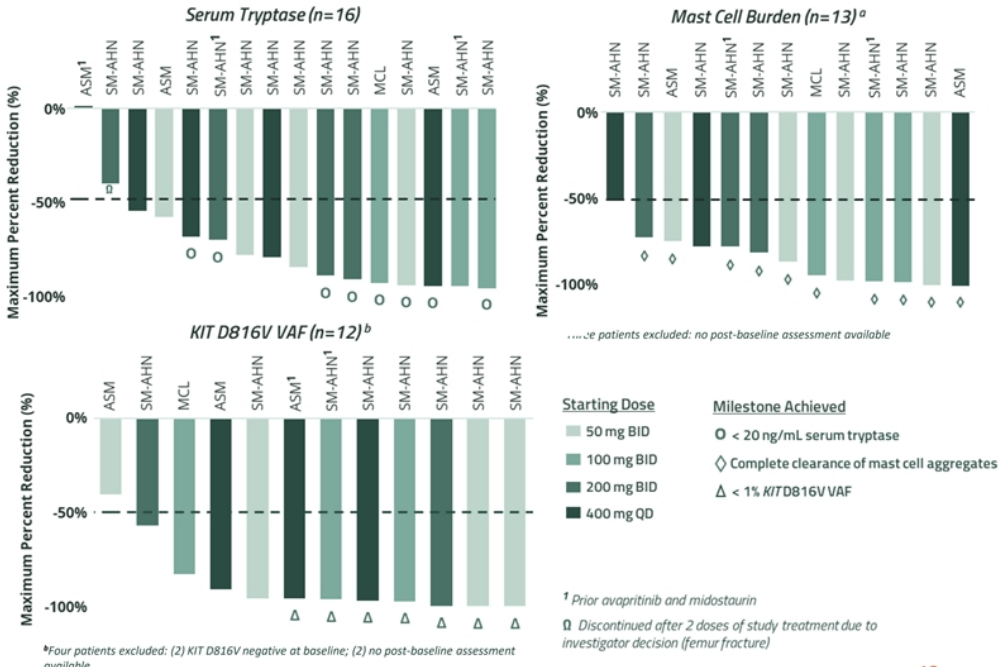
Bezuclastinib Demonstrates Reductions in Markers of Mast Cell Burden

– Serum Tryptase
  - 88% of patients achieved a ≥ 50% reduction
  - 85% median reduction
  - 50% achieved levels <20 ng/mL

– Bone Marrow MC Burden
  - 100% of patients with at least 2 cycles of treatment achieved a ≥ 50% reduction
  - 77% achieved complete clearance of mast cell aggregates by central review

– *KIT* D816V VAF
  - 92% of patients with at least 2 cycles of treatment achieved a ≥ 50% reduction



[a] ...e patients excluded: no post-baseline assessment available

[b] Four patients excluded: (2) KIT D816V negative at baseline; (2) no post-baseline assessment available

[1] Prior avapritinib and midostaurin

Ω Discontinued after 2 doses of study treatment due to investigator decision (femur fracture)

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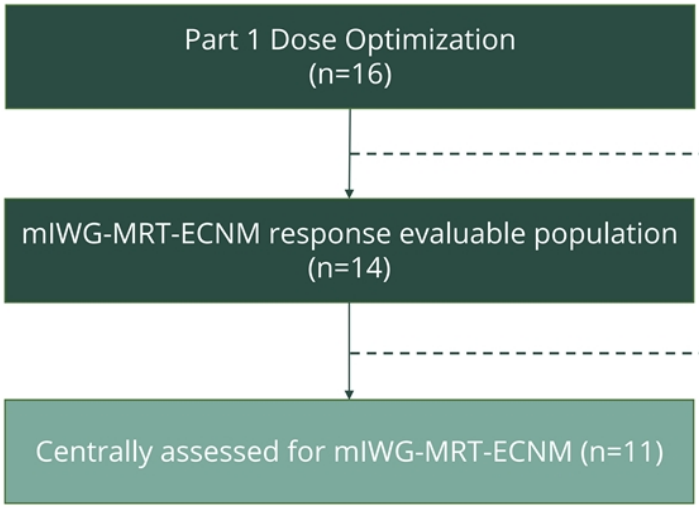
Patients included in mIWG-MRT-ECNM Response Evaluable Population



- **Patients inevaluable (n=2)**
  - n=1 no measurable C-finding at baseline
  - n=1 received confounding concomitant medication
- **Patients excluded (n=3)**
  - n=2 off study prior to first response timepoint
  - n=1 ongoing; has not reached first response timepoint

Response Assessment per mIWG-MRT-ECNM and PPR Criteria

Response Assessment	mIWG-MRT-ECNM Response Criteria*	Pure Pathological Response Criteria
Complete Remission (CR)	✓ Absence of neoplastic MC aggregates in bone marrow ✓ Serum tryptase ≤ 20 ng/mL ✓ Remission of peripheral blood counts ✓ Complete resolution of all mIWG C-findings	✓ Absence of neoplastic MC aggregates in bone marrow ✓ Serum tryptase < 20 ng/mL ✓ Remission of peripheral blood counts
Partial Remission (PR)	✓ Reduction of neoplastic MC in bone marrow by ≥ 50% ✓ Reduction of serum tryptase by ≥ 50% ✓ Resolution of ≥ 1 mIWG C-finding	✓ Reduction of neoplastic MC in bone marrow by ≥ 50% ✓ Reduction of serum tryptase by ≥ 50%
Clinical Improvement (CI)	✓ Resolution of ≥1 mIWG C-finding in the absence of CR, CRh, PR, or PD	Not a part of PPR Criteria

*confirmed response duration must be ≥ 12 weeks

Early Responses Observed by mIWG-MRT-ECNM and PPR Criteria

Best Response, n (%) * [β] (confirmed and unconfirmed)	Total (n=11)	mIWG-MRT-ECNM per CRRC Assessment (TKI[‡] Therapy Naïve) (n=9)	mIWG-MRT-ECNM per CRRC Assessment (Prior TKI[‡] Exposure) (n=2)
Overall response rate			
CR + CRh + PR + CI[†]	**8 (73)**	8 (89)	0 (0)
CR + CRh + PR	**6 (55)**	6 (67)	0 (0)
Complete Response (CR + CRh)	**2 (18)**	2 (22)	0 (0)
Partial Response (PR)	**4 (36)**	4 (44)	0 (0)
Clinical Improvement (CI)	**2 (18)**	2 (22)	0 (0)
Stable Disease (SD)	**3 (27)**	1 (11)	2 (100)

**3 patients pending confirmation of response are included: (2) PR; (1) CR in patients diagnosed with SM-AHN*
[β] mIWG-evaluable patients who have at least one post-baseline assessment are included
[‡] SM-directed therapy with midostaurin and avapritinib
[†] Primary endpoint of Apex study

Best Response, n (%) [α]	Total (n=12)	PPR per Investigator Assessment (TKI[‡] Therapy Naïve) (n=10)	PPR per Investigator Assessment (Prior TKI[‡] Therapy) (n=2)
Overall response rate (CR + PR)	**9 (75)**	7 (70)	2 (100)
Complete Response (CR)	**3 (25)**	3 (30)	0 (0)
Partial Response (PR)	**6 (50)**	4 (40)	2 (100)
Stable Disease (SD)	**3 (25)**	3 (30)	0 (0)

[α] PPR-evaluable patients who have at least one post-baseline assessment are included.
[‡] SM-directed therapy with midostaurin and avapritinib

- Median duration on treatment = 27 weeks (range: 0.3-40)
- First confirmed CRh by mIWG documented as early as 8 weeks and first confirmed CR as early as 20 weeks

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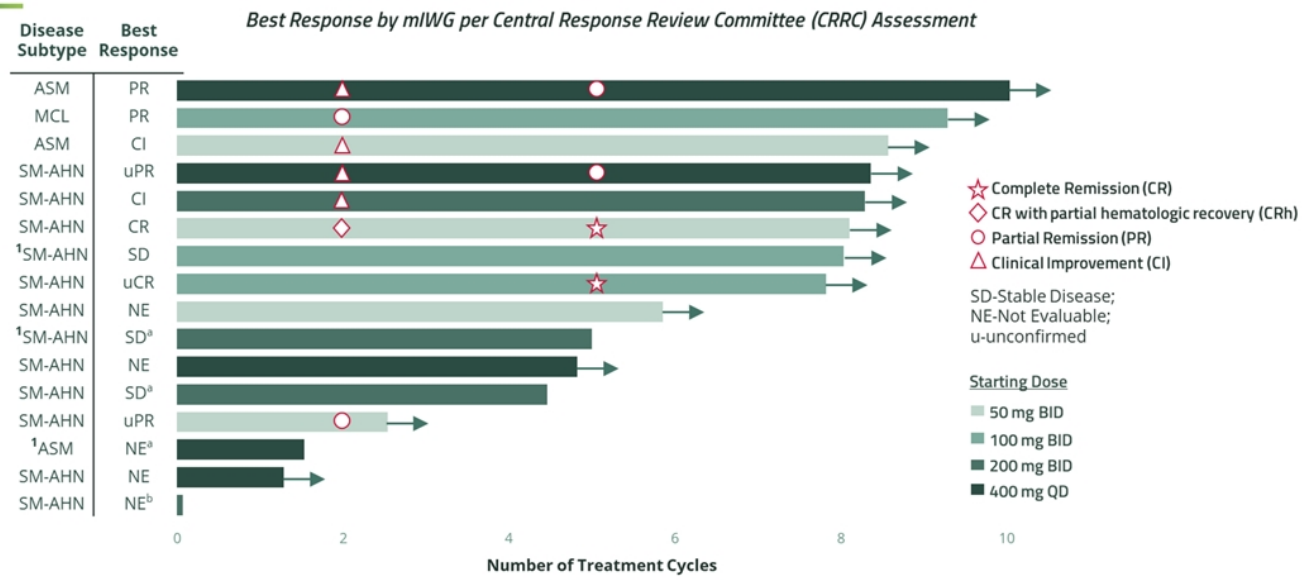
Early Responses Observed by mIWG-MRT-ECNM Criteria



[1] *Prior avapritinib and midostaurin.*

[a] *Discontinued due to disease progression*

[b] *Discontinued after 2 doses of study treatment due to investigator decision (femur fracture)*

Includes confirmed and unconfirmed responses

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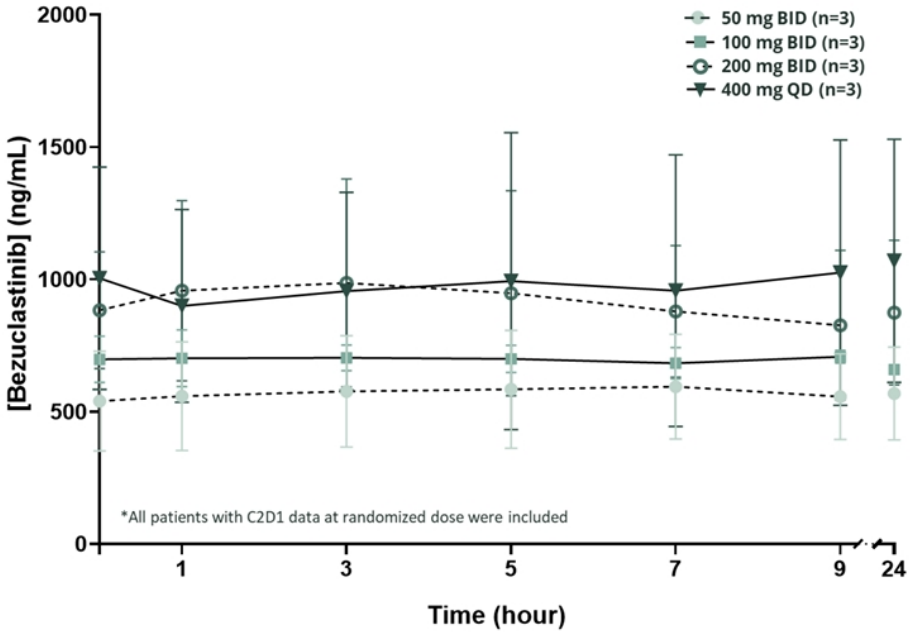
Dose Dependent Increase in Steady State (Cycle 2 Day 1) Bezuclastinib Exposure Regardless of BID or QD Dosing



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Bezuclastinib Clinical Data Summary

- **The highly potent and selective TKI bezuclastinib was generally well-tolerated across all dose levels and continues to demonstrate a differentiated safety profile**
  - No related cognitive effects or bleeding events reported
  - Limited effect of bezuclastinib on platelet counts in patients, supported by preclinical data
- **Treatment with bezuclastinib resulted in encouraging early signs of clinical activity demonstrated across all dose levels**
  - mIWG-MRT-ECNM: 89% overall response rate (CR + CRh + PR + CI) in TKI therapy-naïve patients and 73% in all patients at median follow up of 27 weeks
    - First confirmed CRh by mIWG as early as 8 weeks and first confirmed CR as early as 20 weeks
  - 88%, 92%, and 100% of patients with available data achieved a 50% reduction in serum tryptase, *KIT* D816V VAF, and bone marrow MC burden, respectively
- **Enrollment to Part 1 is ongoing**

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			

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

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Cash runway into 2025; $289.1 million as of September 30, 2022

Q&A

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THANK YOU
Real Challenges. Real Solutions.
Precision therapies for genetically defined diseases