

# Apex Part 2 Trial in Progress: A Phase 2 Open-Label Clinical Study of Bezuclastinib in Adult Patients with Advanced Systemic Mastocytosis

Isaac Goncalves<sup>1</sup>, Stephen J. Fuller<sup>2</sup>, Jason Gotlib<sup>3</sup>, Pankit Vachhani<sup>4</sup>, Vinod Pullarkat<sup>5</sup>, Daniel J. DeAngelo<sup>6</sup>, Saskia K. Klein<sup>7</sup>, Wolfgang Sperr<sup>8</sup>, Karin Hartmann<sup>9</sup>, Khalid Shoumariyeh<sup>10</sup>, Jens Panse<sup>11</sup>, Teng Fong Ng<sup>12</sup>, Miguel Piris-Vallaespesa<sup>13</sup>, Tsewang Tashi<sup>14</sup>, Anthony Hunter<sup>15</sup>, Prithviraj Bose<sup>16</sup>, Cecilia Arana Yi<sup>17</sup>, Manish Jain<sup>18</sup>, Helena Pomares-Marin<sup>19</sup>, Tracy I. George<sup>20</sup>, Jay Patel<sup>20</sup>, Cristina Papayannidis<sup>21</sup>, Minakshi Taparia<sup>22</sup>, Cristina Bulai Livideanu<sup>23</sup>, Andreas Reiter<sup>24</sup>, Juliana Schwaab<sup>24</sup>, Ingunn Dybedal<sup>25</sup>, Jonathan Lambert<sup>26</sup>, Tania Jain<sup>27</sup>, Ewa Wierzbicka-Hainaut<sup>28</sup>, Olivier Hermine<sup>29</sup>, Massimiliano Bonifacio<sup>30</sup>, Gabriella Hobbs<sup>31</sup>, Michael Deininger<sup>32</sup>, Amanda Pilla<sup>33</sup>, Marcus A. Carden<sup>33</sup>, Deepti H. Radia<sup>34</sup>

1. Peter MacCallum Cancer Centre, Victoria, Australia; 2. University of Sydney Nepean Hospital, Kingswood, Australia; 3. Stanford Cancer Institute, Stanford, CA; 4. University of Alabama at Birmingham, Birmingham, Alabama; 5. City of Hope, Duarte, CA; 6. Dana-Farber Cancer Institute, Boston, MA, USA; 7. University Medical Center Groningen, Netherlands; 8. Medical University of Vienna, Austria; 9. University Hospital Basel and University of Basel, Basel, Switzerland; 10. University Hospital Freiburg, Freiburg, Germany; 11. Uniklinik RWTH Aachen, Center for Integrated Oncology Aachen, Bonn, Cologne, Düsseldorf, CIO-ABCD; 12. Gold Coast University Hospital, Queensland, Australia; 13. Hospital Universitario Ramón y Cajal, Madrid; 14. Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; 15. Emory University School of Medicine, Atlanta, GA, USA; 16. MD Anderson Cancer Center, Houston, Texas, USA; 17. Mayo Clinic Arizona, Phoenix, AZ, USA; 18. The Leeds Teaching Hospital NHS Foundation Trust, Leeds, United Kingdom; 19. Institut Català d'Oncologia Hospitalet – Hospital Duran I Reynals, Barcelona, Spain; 20. University of Utah, ARUP Laboratories, Salt Lake City, UT, USA; 21. IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia “Seràgnoli”, Bologna, ITA; 22. University of Alberta, Canada; 23. CEREMAST Toulouse, Dermatology Department, Toulouse University Hospital, Toulouse, France; 24. University Hospital Mannheim, Heidelberg University, Mannheim, Germany; 25. Oslo University Hospital, Oslo, Norway; 26. University College London Hospitals NHS Foundation Trust, London; 27. Johns Hopkins University, Baltimore, MD; 28. CHU de Poitiers, Poitiers, France; 29. CEREMAST Necker Hospital, Paris, France; 30. Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; 31. Massachusetts General Hospital, Boston, MA, USA; 32. Versiti, Milwaukee, WI; 33. Cogent Biosciences, Waltham, MA, USA; 34. Guy's and St. Thomas' NHS Foundation Trust, London

## INTRODUCTION

### Unmet Need Remains for Advanced Systemic Mastocytosis Patients

- Systemic mastocytosis (SM) is a rare heterogeneous disease characterized by the aberrant accumulation of neoplastic mast cells (MC)<sup>1,2</sup>
- In about 95% of adult patients, SM is driven by a gain-of-function mutation (D816V) in exon 17 of *KIT*<sup>1,2</sup>
- Advanced SM (AdvSM) is a life-threatening form of SM and includes three subtypes: aggressive SM (ASM), mast cell leukemia (MCL), and SM with an associated hematologic neoplasm (SM-AHN), which is the most common form of AdvSM; the AHN component is typically of myeloid lineage<sup>1</sup>
- C-findings indicate organ damage by neoplastic mast cell infiltration; presence of C-findings helps determine AdvSM subtype
- Response to treatment can be assessed using mIWG-MRT-ECNM Criteria or Pure Pathological Response Criteria

#### C-findings Per WHO, C-findings Per mIWG-MRT-ECNM, and Response Criteria

| C-findings per WHO (diagnosis)                                                                | C-findings per mIWG-MRT-ECNM (response)    | mIWG-MRT-ECNM Response Criteria                                                                                                                                                                                                                                                         | Pure Pathological Response Criteria                                                                                                                                                     |
|-----------------------------------------------------------------------------------------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bone Marrow dysfunction caused by neoplastic mast cell infiltration evidence by ≥ 1 cytopenia | <b>Non-hematologic Organ Damage</b>        | <b>Complete Remission (CR)<sup>a</sup></b> <ul style="list-style-type: none"><li>✓ Absence of neoplastic MC aggregates in bone marrow</li><li>✓ Serum tryptase ≤ 20 ng/mL</li><li>✓ Remission of peripheral blood counts</li><li>✓ Complete resolution of all mIWG C-findings</li></ul> | <b>Absence of neoplastic MC aggregates in bone marrow</b> <ul style="list-style-type: none"><li>✓ Serum tryptase &lt; 20 ng/mL</li><li>✓ Remission of peripheral blood counts</li></ul> |
|                                                                                               | Symptomatic ascites or pleural effusions   |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                         |
|                                                                                               | Liver function abnormalities               |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                         |
| Palpable splenomegaly with hypersplenism ± weight loss ± hypalbuminemia                       | Hypoalbuminemia                            | <b>Partial Remission (PR)</b> <ul style="list-style-type: none"><li>✓ Reduction of neoplastic MC in bone marrow by ≥ 50%</li><li>✓ Reduction of serum tryptase by ≥ 50%</li><li>✓ Resolution of ≥ 1 mIWG C-finding</li></ul>                                                            | <b>Absence of neoplastic MC in bone marrow by ≥ 50%</b> <ul style="list-style-type: none"><li>✓ Reduction of serum tryptase by ≥ 50%</li></ul>                                          |
|                                                                                               | Marked symptomatic splenomegaly            |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                         |
| Large-sized osteolysis (≥2 cm) with pathologic fracture ± bone pain                           | Weight loss                                |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                         |
| Ascites and elevated liver enzymes ± hepatomegaly or cirrhotic liver ± portal hypertension    | <b>Hematologic Organ Damage</b>            | <b>Clinical Improvement (CI)</b> <ul style="list-style-type: none"><li>✓ Resolution of ≥ 1 mIWG C-finding in the absence of CR, CRh, PR, or PD</li></ul>                                                                                                                                | <b>Not a part of PPR Criteria</b>                                                                                                                                                       |
|                                                                                               | Absolute neutrophil count (ANC)            |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                         |
|                                                                                               | Anemia (transfusion-independent)           |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                         |
| Malabsorption with hypoalbuminemia ± weight loss                                              | Anemia (transfusion-dependent)             |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                         |
|                                                                                               | Thrombocytopenia (transfusion-independent) |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                         |
|                                                                                               | Thrombocytopenia (transfusion-dependent)   |                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                         |

<sup>a</sup>CR for PPR includes molecular CR, which is undetectable *KIT*

- Despite improvement in disease control with the approval of tyrosine kinase inhibitors (TKIs), there is still unmet need for improved tolerability and efficacy in AdvSM treatments, as well as therapies for patients with SM-AHN who have progression of myeloid neoplasms.
  - Reported inferior response rate, lack of durability, and poor tolerability with midostaurin<sup>3-4</sup>
  - Reported toxicities for marketed D816V-targeted tyrosine kinase inhibitor (TKI) therapies also include nausea, vomiting, diarrhea, edema, intracranial bleeding, and cognitive effects<sup>5-6</sup>

### Bezuclastinib: Highly Selective and Potent *KIT* D816V Inhibitor

- Oral, selective type I tyrosine kinase inhibitor (TKI) that potently inhibits *KIT* D816V
- Minimal brain penetration and favorable PK properties. Spares closely related kinases, including PDGFR, CSF1R, FLT3, and KDR<sup>7</sup>
- Inhibition of closely related kinases have been linked to off-target toxicities: bleeding, edema, pleural effusions<sup>8,9</sup>

#### Kinase Inhibition Profile of Clinical Stage and Approved KIT D816V Agents; Cell IC<sub>50</sub> (nM)

| Compound      | <i>KIT</i> 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 |
| Elenestinib   | 6                                | 21      | 6       | 161     | 345   | >1000 |

Adapted from Guarnieri et al. 2022.

### Dose selection for Apex Part 2

***In Part 1, bezuclastinib demonstrates an encouraging safety profile and durable responses, with optimal efficacy and safety outcomes at 100mg BID dose of original formulation<sup>10</sup>***

- Efficacy at 100mg: 83% overall response rate per mIWG-MRT-ECNM and deep reductions across biomarkers of mast cell activity
- Safety at 100mg: The majority of hematological adverse events were low grade, reversible, and did not require dose reduction; no reported intracranial bleeding events or treatment-related deaths
- 150 mg QD of the optimized formulation delivers similar exposures to 100 mg BID of original formulation<sup>10</sup>

#### Mean (CV%) Steady-State (Cycle 2 Day 1) Exposures

| Study Part (Formulation)            | Part 1 (Original Formulation) | Part 2 Stage 1 (Optimized Formulation <sup>a</sup> ) |
|-------------------------------------|-------------------------------|------------------------------------------------------|
| Bezuclastinib Dose                  | 100 mg BID (N=7)              | 150 mg QD (N=10)                                     |
| C <sub>max,ss</sub> (ng/mL)         | 861 (26.8)                    | 850 (29.9)                                           |
| AUC <sub>0-24hr,ss</sub> (ng*hr/mL) | 18,900 (30.8)                 | 17,600 (31.3)                                        |

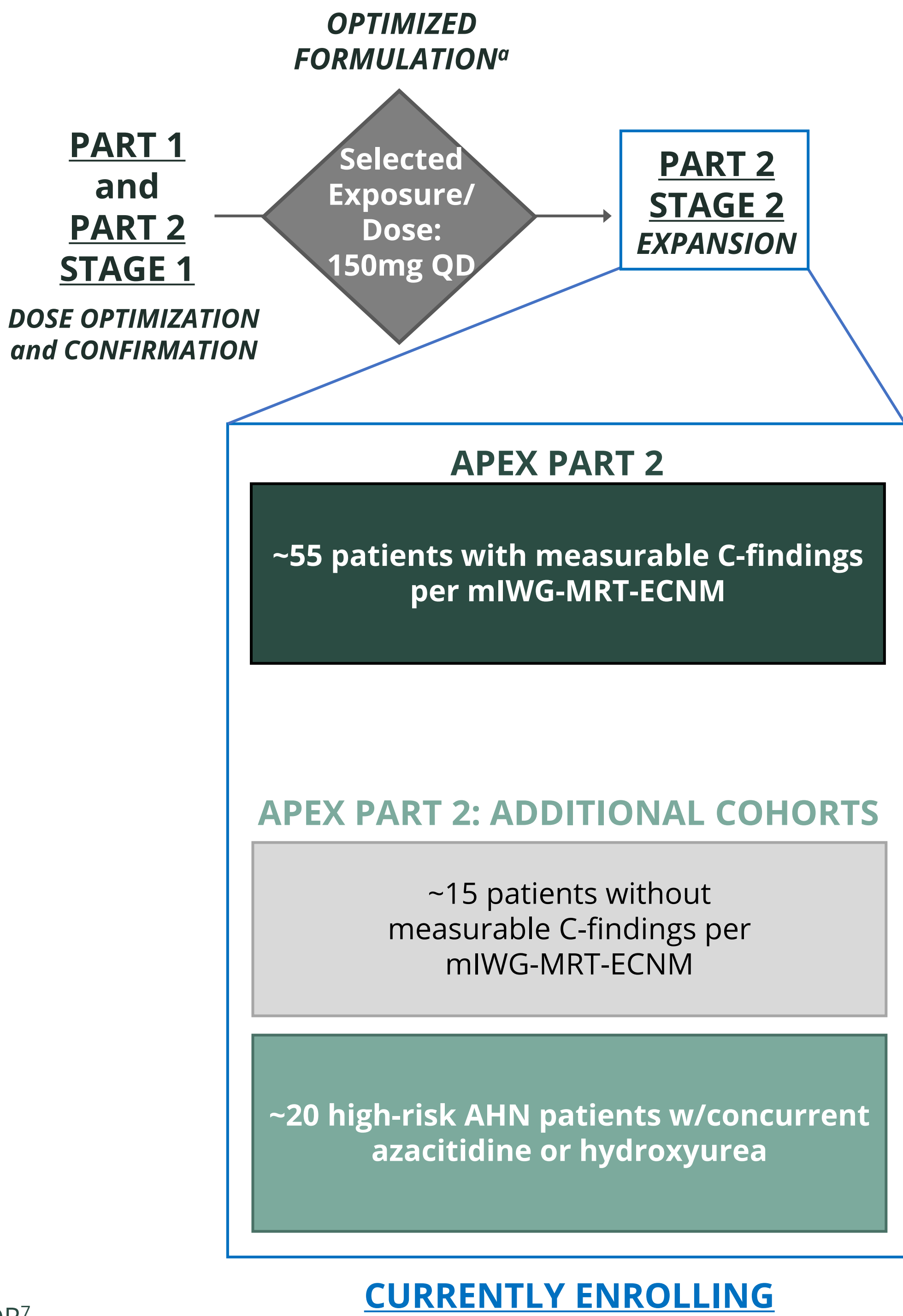
<sup>a</sup>The original formulation was modified to improve bioavailability.

### Enrollment to Part 2 is ongoing

- Enrollment continues in an additional cohort evaluating bezuclastinib with concomitant AHN therapy

## APEX CLINICAL TRIAL

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



<sup>a</sup>The original formulation was modified to improve bioavailability.

### Apex Part 2

| Key Inclusion Criteria                                                                                                                                                                                                                     | Study Objectives and Endpoints: Apex Part 2 Stage 2 Expansion                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>ASM, SM-AHN, or MCL per WHO Classification</li><li>Confirmed measurable disease per mIWG-MRT-ECNM (mIWG)</li><li>Prior therapies are allowed</li><li>Platelet count ≥50 x 10<sup>9</sup>/L</li></ul> | <b>Primary Objective</b> <ul style="list-style-type: none"><li>Determine the efficacy of bezuclastinib at the selected optimal dose in patients with AdvSM who are evaluable based on the modified IWG-MRT-ECNM response criteria</li></ul>                                                                                                                                                                                        |
|                                                                                                                                                                                                                                            | <b>Primary Endpoint</b> <ul style="list-style-type: none"><li>ORR defined as the percentage of subjects classified as confirmed responders (complete response [CR], CR with incomplete hematologic recovery [CRh], partial response [PR], and clinical improvement [CI]) according to modified IWG-MRT-ECNM response criteria as assessed by Central Response Review Committee (CRRCC)</li></ul>                                   |
|                                                                                                                                                                                                                                            | <b>Secondary Endpoints</b> <ul style="list-style-type: none"><li>ORR according to PPR, including complete remission, complete remission with partial hematologic recovery, molecular complete remission, and partial remission</li></ul>                                                                                                                                                                                           |
|                                                                                                                                                                                                                                            | <b>Exploratory Endpoints</b> <ul style="list-style-type: none"><li>Incidence of AEs, SAEs, AEs leading to dose modifications, and changes from baseline in laboratory results</li><li>Changes in skin lesions and skin tissue mast cell burden</li><li>Changes in usage of concomitant medications as rescue therapy</li><li>Changes in spleen and liver size</li><li>Changes in bone density and bone formation markers</li></ul> |

### Apex Part 2 (SM-AHN Substudy)

| Rollover Cohort                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | High-Risk Cohort                                                                                                                                                                                                                                                                                                                                                           | Study Objectives and Endpoints: Apex Part 2 Stage 2 SM-AHN Substudy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Key Inclusion Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                            | <b>Exploratory Objectives</b> <ul style="list-style-type: none"><li>Evaluate the safety and tolerability of bezuclastinib administered concomitantly with azacitidine or hydroxyurea in subjects with SM-AHN</li><li>Assess the pharmacokinetics (PK) and Pharmacodynamic (PD) of bezuclastinib administered concomitantly with azacitidine or hydroxyurea in subjects with SM-AHN</li><li>Evaluate the preliminary efficacy of bezuclastinib administered concomitantly with azacitidine or hydroxyurea in subjects with SM-AHN</li><li>Evaluate AHN histopathologic response</li><li>Evaluate effect of concomitant therapy regimen on ability to undergo HSCT</li></ul> |
| <ul style="list-style-type: none"><li>Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 3</li><li>Demonstrate centrally confirmed AHN progression and require immediate AHN-directed therapy while receiving bezuclastinib during either Part 1 or Part 2 of the study.</li><li>Have received bezuclastinib for at least 5 cycles during Part 1 or Part 2</li><li>Have demonstrated beneficial reductions in mast cell markers from previous bezuclastinib therapy</li><li>Have clinically acceptable laboratory screening results</li></ul> | <ul style="list-style-type: none"><li>ECOG Performance Status 0 to 3</li><li>Currently receiving or indicated for azacitidine as AHN-directed therapy</li><li>Pathologic diagnoses of SM-AHN via bone marrow assessment</li><li>Have clinically acceptable laboratory screening results</li></ul>                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Key Exclusion Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                            | <b>Exploratory Endpoints</b> <ul style="list-style-type: none"><li>Incidence of AEs, SAEs, AEs leading to dose modifications, and changes from baseline in laboratory results</li><li>Plasma concentration and PK parameters</li><li>Change from baseline in serum tryptase and <i>KIT</i> D816V</li><li>Pure pathologic response.</li><li>Overall response rate</li><li>Duration of response</li><li>Progression-free survival (PFS)</li><li>Overall survival</li><li>Change in pathologic findings related to AHN</li><li>Cytogenetic response, as data permit</li><li>Proportion of patients receiving HSCT, time to HSCT</li></ul>                                     |
| <ul style="list-style-type: none"><li>Have not demonstrated acceptable tolerability of previous bezuclastinib therapy, as defined by the following:<ul style="list-style-type: none"><li>Ongoing ≥Grade 3 adverse event at least possibly related to bezuclastinib</li><li>Bezuclastinib dose reduced by 2 or more dose levels due to treatment-related adverse events</li></ul></li><li>Patients with acute myeloid leukemia or who are appropriate for hematopoietic stem cell transplantation are excluded.</li></ul>                                     | <ul style="list-style-type: none"><li>Previously treated with investigational therapy for AdvSM</li><li>Persistent toxicity from previous approved therapy for AdvSM</li><li>Previously treated with azacitidine and discontinued due to TRAE</li><li>Received any cytoreductive therapy</li><li>Patients with AML or who are appropriate for HSCT are excluded.</li></ul> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

### Sites<sup>a</sup> Participating in the Apex Study

| Europe                                                       |                                                                               |
|--------------------------------------------------------------|-------------------------------------------------------------------------------|
| Medical University of Vienna AKH Wien, Austria               | AOU Careggi, Italy                                                            |
| CHU Liege, Belgium                                           | University Medical Center Groningen, Netherlands                              |
| CEREMAST Toulouse, Toulouse University Hospital, France      | Oslo University Hospital, Norway                                              |
| CHU de Poitiers, France                                      | Medical University of Lublin, Poland                                          |
| CEREMAST Necker Hospital, France                             | Hospital Universitario Ramón y Cajal, Spain                                   |
| Uniklinik RWTH Aachen, Germany                               | Institut Català d'Oncologia de L'Hospitalet – Hospital Duran I Reynals, Spain |
| University Hospital Mannheim, Germany                        | University Hospital Vall d'Hebron, Spain                                      |
| University Hospital Freiburg, Germany                        | University Hospital Basel, Switzerland                                        |
| University Hospital Schelswig-Holstein, Germany              | The Leeds Teaching Hospital, NHS Foundation Trust, UK                         |
| IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy    | Guy's and St. Thomas' NHS Foundation Trust, UK                                |
| AOU San Giovanni di Dio e Ruggi d'Aragona, Italy             | University College London Hospitals, NHS Foundation Trust, UK                 |
| Azienda Ospedaliera Universitaria Integrata di Verona, Italy |                                                                               |

<sup>a</sup>Visit <https://clinicaltrials.gov/study/NCT04996875> or contact [trialinfo@cogentbio.com](mailto:trialinfo@cogentbio.com) for up-to-date site information.

| North America                                      |  |
|----------------------------------------------------|--|
| Stanford Cancer Institute, USA                     |  |
| Dana-Farber Cancer Institute, USA                  |  |
| Huntsman Cancer Institute, University of Utah, USA |  |
| Cleveland Clinic Taussig Cancer Center, USA        |  |
| UCLA Health, USA                                   |  |
| Emory University School of Medicine, USA           |  |
| MD Anderson Cancer Center, USA                     |  |
| City of Hope, USA                                  |  |
| Mayo Clinic Arizona, USA                           |  |
| University of Alabama at Birmingham, USA           |  |
| MUSC Health University Medical Center, USA         |  |
| University of Alberta, Canada                      |  |
| St. Michael's Hospital, Canada                     |  |

| Australia                                       |  |
|-------------------------------------------------|--|
| Peter MacCallum Cancer Centre, Australia        |  |
| University of Sydney Nepean Hospital, Australia |  |
| Gold Coast University Hospital, Australia       |  |

#### ACKNOWLEDGEMENTS:

We would like to thank our patients and those who support them, including family, caregivers, patient advocates, Investigators, and site staff. The authors and sponsor would also like to acknowledge the contribution of additional sites and investigators: Aurélie Jaspers, CHU Liege; Nikolas von Bubnoff, University Hospital Schleswig-Holstein; Massimo Triggiani, AOU San Giovanni di Dio e Ruggi d'Aragona; Francesco Mannelli, AOU Careggi; Marek Hus, Medical University of Lublin; Olga Salameró, University Hospital Vall d'Hebron; Sudipto Mukherjee, Cleveland Clinic Taussig Cancer Center; Gary Schiller, UCLA Health; Kelli Williams, MUSC Health University Medical Center; Stephanie Lee, St. Michael's Hospital