Summit: A 3-Part, Phase 2 Study of Bezuclastinib (CGT9486), an Oral, Selective, and Potent KIT D816V Inhibitor, in Adult Patients with Nonadvanced Systemic Mastocytosis (NonAdvSM)

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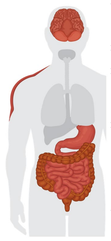
Introduction

Nonadvanced Systemic Mastocytosis (NonAdvSM)

- Systemic mastocytosis (SM) is primarily driven by mutations in the *KIT* gene (D816V) resulting in the clonal proliferation of abnormal neoplastic mast cells[1,2,3,4]
- NonAdvSM accounts for ~90% of all SM cases[1]
  - **Indolent SM** (ISM; ~85%)
    Characterized by symptoms related to mast cell degranulation/mediator release[5]
    - **Bone Marrow Mastocytosis**
      Characterized by mast cell infiltration in the bone marrow with no skin or multiorgan visceral lesions
  - **Smoldering SM** (SSM; ~5%)
    Characterized by a higher systemic mast cell burden, evidenced by increased levels of serum tryptase and high degrees of bone marrow involvement[1]

Fig. 1: Potential Signs + Symptoms



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

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

- Patients with ISM or SSM experience a variety of disabling and potentially serious symptoms caused by mast cell release/degranulation (**Fig. 1**)
  - Most severe manifestation is anaphylaxis which can be recurrent and life-threatening[7, 8, 9]
  - Patients experience debilitating impairment to their health-related quality of life[6]
- Patient reported outcome (PRO) tools are used in this population to measure severity of symptoms and treatment benefit[5]
- Currently there are no approved therapies for the treatment of NonAdvSM

Bezuclastinib (CGT9486)

- An oral, highly selective type I tyrosine kinase inhibitor (TKI) with potent activity against *KIT* D816V
  - Highly active against other *KIT* mutations in exons 9, 11, 17 and 18
  - In preclinical studies, in contrast to other KIT inhibitors, bezuclastinib demonstrated no significant activity against closely related kinases that have been linked to toxicity, including PDGFRα, PDGFRβ, VEGFR2 (KDR), and CSF1R (FMS)[8-11] **(Table 1)**
  - Minimal brain exposure with no evidence of CNS-related effects in nonclinical safety pharmacology and toxicology studies[8, 9]

Table 1. Kinase Inhibition Profile of Clinical Stage and Approved KIT D816V Agents

Compound	Cell IC_{50} (nM)*						
	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

- Preliminary Ph2 data suggest that bezuclastinib is well-tolerated and is associated with encouraging early signs of clinical activity in patients with advanced SM
  - Meaningful reductions in serum tryptase, mast cell burden, and KIT D816V VAF[8]
- Formulation B was created in order to increase the proportion of active ingredient in the tablet; patients completing Part 1A who elect to continue in Part 3 may be transitioned to formulation B

Summit: Phase 2 Study of Bezuclastinib in Patients with NonAdvSM

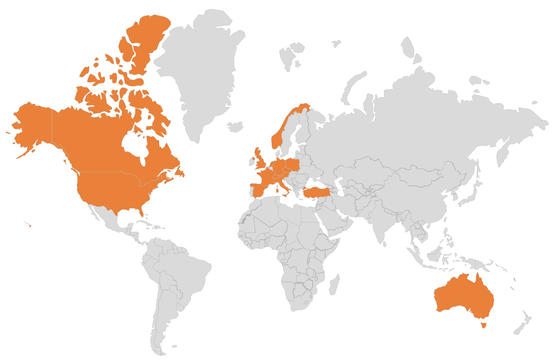
Overview

- Multi-center, phase 2, double blind, placebo-controlled, 3-part clinical study evaluating the safety and efficacy of bezuclastinib in patients with NonAdvSM with inadequate control of SM symptoms despite treatment on a stable best supportive care (BSC) regimen of ≥2 antimediator therapies (NCT05186753)
  - Bezuclastinib or placebo: administered orally, once daily, for 28 days of each 4-week cycle
  - Severity of adverse events (AE) graded using the NCI-CTCAE v5.0
- Primary endpoint assessed by a disease-specific PRO tool that evaluates the most relevant NonAdvSM symptoms
- Impact on measures of mast cell burden will be explored including *KIT* D816V mutational burden, bone marrow mast cell burden, and serum tryptase

Study Design: 3-Part, Phase 2 Study (Fig. 2, Table 2-3)

- Part 1: Dose Selection (n~48)
  - Part 1A: Patients will be randomized to BSC + either 1 of 2 doses of bezuclastinib (formulation A) or placebo
  - Part 1B: Patients will be randomized to BSC + either 1 of 2 doses of bezuclastinib (formulation B) or placebo
- Part 2: Dose Expansion (n~90)
  - Patients will be randomized to the Part 1 selected dose of bezuclastinib or placebo + BSC
- Part 3: Long-term Extension
  - Patients will receive open-label bezuclastinib + BSC
  - Includes all patients who complete treatment in Part 1 or Part 2
  - Intrapatient dose modification to the selected dose of bezuclastinib is permitted for patients initially enrolled in Part 1

Selected Countries for Summit Study



*Visit **clinicaltrials.gov/ct2/show/NCT05186753** or contact **trialinfo@cogentbio.com** for up-to-date site information

Fig. 2: Summit: Phase 2, Multi-center, Double blind, Placebo-controlled, 3-Part Clinical Study Design

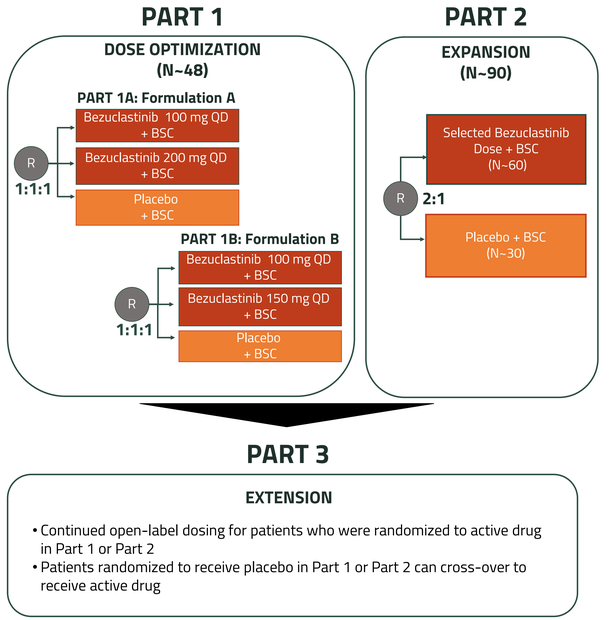


Table 2: Summit Study Objectives, Endpoints, and Study Design

	Part 1A	Part 1B	Part 2
Primary Objective	Determine the recommended dose of bezuclastinib		Determine the efficacy of bezuclastinib at the selected dose vs placebo
Primary Endpoint	• Safety assessments • PK and PD markers • Improvement in symptoms of disease based on PRO measures		Change in disease-specific PRO from baseline to week 24
Secondary Endpoints	• Changes in measures of mast cell burden • Changes in signs and symptoms • Quality of Life • Safety and Tolerability • PK		• Changes in measures of mast cell burden • Changes in signs/symptoms • Quality of Life • Safety and Tolerability
Study Design	Randomized (all QD + BSC): •Bezuclastinib (A) 100 mg •Bezuclastinib (A) 200 mg •Placebo	Randomized (all QD + BSC): •Bezuclastinib (B) 100 mg •Bezuclastinib (B) 150 mg •Placebo QD + BSC	Randomized (all QD +BSC): •Bezuclastinib (B) selected dose •Placebo
Enrollment	~48 patients		~90 patients
Rollover (Part 3)	•Continued open-label dosing in Part 3 for patients who were randomized to active drug in Part 1 or Part 2 •Patients randomized to receive placebo in Part 1 or Part 2 can cross-over to receive active drug in Part 3		

(A)Bezuclastinib formulation A
(B)Bezuclastinib formulation B

Objectives and Endpoints

Summit aims to evaluate the safety, efficacy, and measures of mast cell burden (e.g., bone marrow mast cell burden, serum tryptase level and *KIT* D816V mutation burden) of the *KIT* inhibitor bezuclastinib in patients with NonAdvSM (**Table 2**)

Table 3: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Diagnosed with 1 of the following World Health Organization (WHO) classifications for SM (ISM, including BMM, or SSM)[12] • Inadequate control of symptoms despite a stable regimen of at least 2 antimediator therapies • Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 2	• Diagnosed with mastocytosis of the skin without systemic involvement • Received prior treatment with any targeted KIT inhibitor with the exception of approved agents for the treatment of SM • Received prior cytoreductive therapy or investigational agent for <14 days or 5 half-lives of the drug and for cladribine, interferon alpha, pegylated interferon, or antibody therapy <28 days or 5 half-lives of the drug (whichever is longer), before starting screening assessments • Active, uncontrolled, systemic bacterial, fungal, or viral infections at screening • Need for treatment with systemic corticosteroids (i.e., >10 mg/day prednisone or equivalent) • Patient on stable dose of prednisone ≤10 mg/day (or equivalent) are eligible

Summary

- NonAdvSM is primarily driven by mutations in *KIT* D816V leading to varying degrees of mast cell burden and characterized by disabling symptoms related to mediator release.
- Summit is a multi-center, phase 2, double blind, placebo-controlled, 3-part clinical study evaluating the safety, efficacy, PK, and PD in patients with SSM and moderate to severe ISM.
  - Disease specific PRO endpoints capture change in disease, symptoms and quality of life improvements.
  - Bone marrow mast cell percentage, serum tryptase level, and KIT D816V mutation burden will aid in the evaluation of disease improvement, target engagement and pharmacodynamic activity.
- Data from Summit will inform the clinical development pathway of bezuclastinib as a potential disease modifying treatment for patients with NonAdvSM.
- The Summit trial is actively recruiting.

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