The Phase 2/3 Study of Elenestinib, a Highly Potent and Selective Tyrosine Kinase Inhibitor, in Patients With Indolent Systemic Mastocytosis

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Introduction

- Indolent systemic mastocytosis (ISM) is a clonal mast-cell (MC) disease primarily driven by D816V-mutant *KIT* in ~95% of cases[1–3]
- The prevalence of systemic mastocytosis (SM) has been estimated at up to 1 in 5000 people[4–7]
- ISM is characterized by the accumulation and hyperactivation of aberrant MCs in bone marrow, skin, the gastrointestinal tract, and other organs[8]
- Patients with ISM often experience long-term debilitating symptoms related to release of MC mediators that impact quality of life[9–12]
- Consequences for patients with ISM include:
  - Anaphylaxis, which may occur in 20–50% of patients[13–15]
  - Musculoskeletal complications, including osteoporosis (~25% of patients), osteopenia (~30% of patients), and fragility fractures (~30% lifetime risk), are also common in these patients[16–18]
  - Mastocytosis-typical skin lesions that may be experienced as disfiguring[10,19]
- Elenestinib is a next-generation, potent, and highly selective KIT D816V inhibitor with limited central nervous system penetration[20]
- The Phase 2/3 HARBOR trial (NCT04910685) is an ongoing, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of elenestinib plus symptom-directed therapy (SDT) in patients with ISM and smoldering SM (SSM)
- The safety, tolerability, and efficacy in Part 1 of HARBOR demonstrated a benefit/risk profile that supports the Part 2 and Part 3 design[20]
- This study will further evaluate the impact of KIT D816V inhibition on symptom improvement, anaphylaxis rates, bone density loss, and disease burden markers such as *KIT* D816V variant allele frequency, serum tryptase, and bone marrow MCs in patients with ISM and SSM

Key eligibility criteria for enrolling cohorts

Inclusion criteria

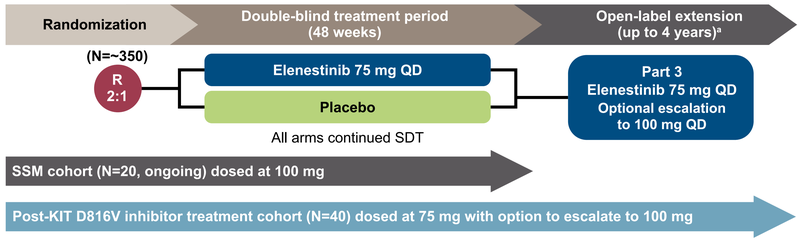
- ≥18 years of age
- Eastern Cooperative Oncology Group performance status is 0–2
- Moderate to severe symptoms based on the ISM-SAF mean TSS (Part 2, Post–KIT D816V inhibitor cohort)
- Centrally confirmed diagnosis of ISM (Part 2, Post–KIT D816V inhibitor cohort) or SSM (SSM cohort) confirmed by central review of B- and C-findings according to WHO diagnostic criteria[a,21] and failure to achieve adequate symptom control for ≥1 baseline symptoms (Part 2 only)[b]
- SDT for ISM symptom management[c] must be stable for ≥14 days prior to starting screening procedures (Part 2)

Exclusion criteria

- Patient has been diagnosed with another SM subclassification, including an associated hematologic neoplasm, or C-findings attributable to SM
- Patient has previously received treatment with any selective KIT inhibitors (excluding post-KIT D816V inhibitor cohort)
- Patient is currently receiving an investigational agent in another interventional study
- Patient has a history of a primary malignancy that has been diagnosed or required therapy within 3 years prior to the study
- TEAEs from previous KIT inhibitors must be resolved to Grade ≤1 prior to the first dose of elenestinib (Post–KIT D816V inhibitor cohort)

[a]An archival biopsy may be used if completed within the past 12 months. [b]Using ≥2 of the following symptomatic therapies: H1 blockers, H2 blockers, proton-pump inhibitors, leukotriene inhibitors, cromolyn sodium, corticosteroids, omalizumab.
ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form (©2018 Blueprint Medicines Corporation); SDT, symptom-directed therapy; SM, systemic mastocytosis; SSM, smoldering systemic mastocytosis; TEAE, treatment-emergent adverse event; TSS, total symptom score; WHO, World Health Organization.

Figure 1. Study design



[a]Up to a total of 5 years treatment between Parts 2 and 3.
QD, once daily; R, randomized.

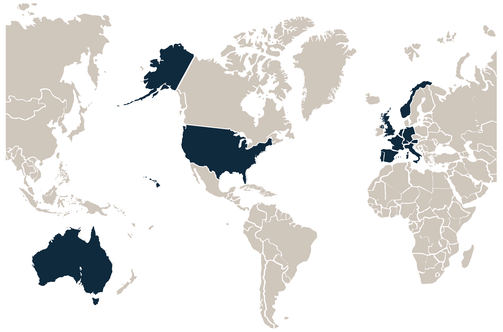
Figure 2. Study site locations

Study sites located in

Europe
- Austria
- Belgium
- France
- Germany
- Italy
- Netherlands
- Norway
- Portugal
- Spain
- Switzerland
- United Kingdom

United States

Australia



Study endpoints

Primary

Randomized Part 2
- Mean change in ISM-SAF TSS from baseline[a]

Open-label Part 3
- Long-term safety and tolerability by determining AEs, SAEs, and lab parameters
- Mean change in ISM-SAF TSS

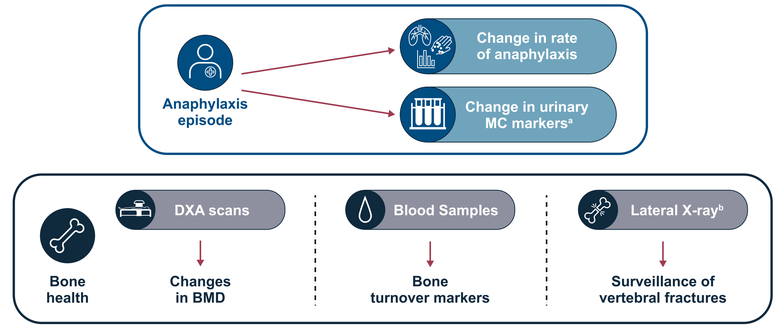
Secondary and exploratory[a]

- Proportion of patients achieving:
  - Normalization of tryptase
  - Undetectable or ≥50% reduction in *KIT* D816V VAF
  - Controlled disease
  - Symptom control as measured by TSS
- Change in quality of life measures
- Change in bone mineral density and bone health
- Change in annualized rate of anaphylaxis

Post–KIT D816V inhibitor and SSM cohorts
- Change in ISM-SAF TSS
- Safety and tolerability determined by AEs, SAEs, and lab parameters
- Change in measures of disease burden including serum tryptase and *KIT* D816V VAF
- Proportion of patients achieving PPR (SSM cohort only)

[a]Part 2 is compared to placebo. Measured after 48 weeks of treatment. Part 3 is open label.
AE, adverse event; PPR, pure pathologic response; SAE, serious adverse event; VAF, variant allele frequency.

Measuring anaphylaxis and bone health



[a]During a possible acute event in US patients only. [b]In patients with a history of fractures, or who have been identified during screening as having osteopenia or osteoporosis.
BMD, bone mass density; DXA, dual-energy X-ray absorptiometry; MC, mast cell.

Summary

- HARBOR Part 2 has been optimized to include:
  - Endpoints that evaluate disease modification, including anaphylaxis frequency and bone density, as these will address issues that critically impact the overall health of the patients
  - Timing of endpoints that reflect the chronic nature of disease
- HARBOR Part 3 will prospectively evaluate multiple doses, providing dosing flexibility
- HARBOR Part 2 has initiated and there are active sites in the USA, Australia, and 11 countries throughout Europe

To learn more about this clinical trial, scan the QR code:

Scan the QR code to view our **Interactive Poster**

Conflicts of interest/ disclosures

Dr Akin has received consulting fees and research support from Blueprint Medicines Corporation and Cogent Biosciences, and consulting fees from Novartis.

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