Evaluating the Disease-Modifying Potential of Elenestinib, a Highly Potent and Selective Tyrosine Kinase Inhibitor, in Patients With Indolent Systemic Mastocytosis: An Update on the Pivotal HARBOR Study

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Introduction

- Systemic mastocytosis (SM), of which indolent systemic mastocytosis (ISM) is the most common form, is a clonal mast cell (MC) disease primarily driven by the *KIT* D816V mutation in ~95% of cases[1–3]
- ISM is characterized by MC accumulation and aberrant activation, resulting in chronic and debilitating manifestations such as anaphylaxis,[4–6] skin lesions,[7,8] gastrointestinal and neurocognitive symptoms,[9] and osteoporosis and fracture risk[10–12] which can significantly impact patients' quality of life (QoL)[7,13,14]
- Elenestinib is a next-generation inhibitor designed for potent and highly selective KIT D816V inhibition (half-maximal inhibitory concentration of KIT D816V, 3.1 nM; kinase selectivity score, 0.035) with limited central nervous system penetration[15]
- Elenestinib is currently being evaluated in the double-blind, placebo-controlled, global, phase 2/3 HARBOR randomized controlled trial (RCT; NCT04910685)[16]
- HARBOR is an ongoing study designed to evaluate the disease-modifying efficacy and safety of elenestinib in patients with ISM and smoldering SM (SSM). The safety, tolerability, and efficacy in Part 1 supports the Part 2 and Part 3 design – Part 1 previously showed that elenestinib has a similar tolerability profile to placebo[15]
- HARBOR Part 2 will primarily evaluate the impact of elenestinib on symptom improvement; while secondary analyses will assess symptom control, anaphylaxis rates, bone mineral density (BMD), and disease burden markers such as *KIT* D816V variant allele frequency, serum tryptase normalization, and patient-reported QoL

Methods

- Key inclusion criteria for HARBOR Part 2 include centrally confirmed ISM diagnosis and a moderate to severe total symptom score (TSS) per the ISM-Symptom Assessment Form (ISM-SAF; ©2018 Blueprint Medicines Corporation) based on a 14-day average. A high-level overview of the key inclusion and exclusion criteria can be found in **Table 1**

Table 1. Key inclusion and exclusion criteria

Inclusion criteria

- ≥18 years of age
- Eastern Cooperative Oncology Group performance status of 0–2
- Centrally confirmed diagnosis of ISM; archival biopsy may be used if completed within the past 12 months
- Confirmed diagnosis of SSM, confirmed by Central Pathology Review of bone marrow biopsy and central review of B- and C-findings by WHO diagnostic criteria (**Part S only**)
- Moderate to severe TSS per the ISM-SAF (©2018 Blueprint Medicines Corporation) based on a 14-day average (**Part 2 only**)
- Symptom-directed therapy must be stable for ≥14 days prior to screening procedures (**Part 2 only**)
- Inadequate symptom control for ≥1 baseline symptoms (**Part 2 only**)

Exclusion criteria (all parts)

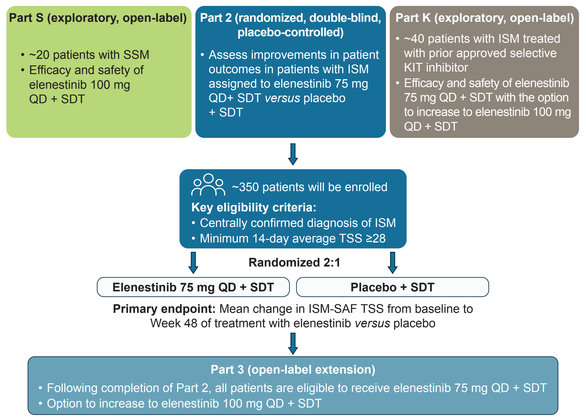
- Diagnosis of another myeloproliferative disorder, or any of the following WHO SM subclassifications: CM, SM-AHN, ASM, MCL, mast cell sarcoma
- Patient is receiving another investigational agent from another interventional study ≤24 weeks prior to screening
- Patient has a history of a primary malignancy that has been diagnosed or required therapy ≤3 years prior to the study
- Prior treatment with any selective KIT inhibitors (**except Part K**)
- All TEAEs from previous selective KIT inhibitor must be resolved to ≤ Grade 1 prior to first dose of elenestinib (**Part K only**)

ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form (©2018 Blueprint Medicines Corporation); MCL, mast cell leukemia; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; SM, systemic mastocytosis; SSM, smoldering systemic mastocytosis; TEAE, treatment emergent adverse event; TSS, total symptom score; WHO, World Health Organization.

Methods

- In HARBOR Part 2, ~350 patients will be randomized 2:1 to elenestinib 75 mg QD + symptom-directed therapy (SDT) or placebo + SDT. After completing the double-blind Part 2 (Week 48), patients may roll over to 75 mg QD + SDT in Part 3 (open-label) with an option to increase to 100 mg elenestinib QD + SDT, for a total treatment duration of ~5 years (**Figure 1**)
- There will be two additional open-label cohorts: one evaluating the efficacy and tolerability of elenestinib 75 mg QD (with optional increase to 100 mg QD) in ~40 patients previously treated with an approved selective KIT D816V inhibitor (Part K) and one evaluating the safety and efficacy of elenestinib 100 mg QD + SDT in ~20 patients with SSM (Part S)

Figure 1. Study design of the phase 2/3 HARBOR study (NCT04910685)



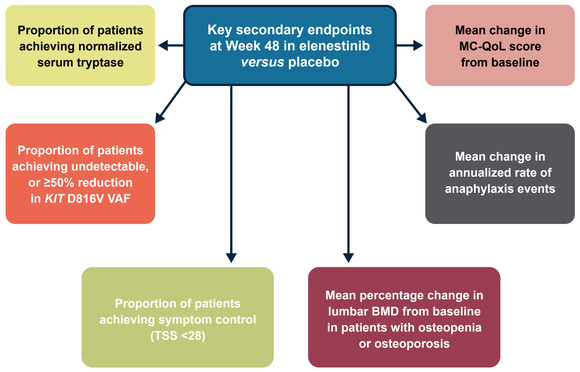
SDT, symptom-directed therapy.

- HARBOR is the largest RCT in ISM to date, Part 2 has initiated and is expanding globally, currently planned to be open in 24 countries (**Figure 2**)

Figure 2. HARBOR currently participating countries

- The primary endpoint of HARBOR Part 2 is the mean change in ISM-SAF TSS from baseline to Week 48, to determine if treatment with elenestinib + SDT provides greater symptom improvement over placebo + SDT
- While the primary endpoint of HARBOR Part 2 is symptom improvement, additional novel and relevant key secondary endpoints will assess the disease-modifying capabilities of treatment with elenestinib + SDT *versus* placebo + SDT
- Key secondary endpoints are shown in **Figure 3**

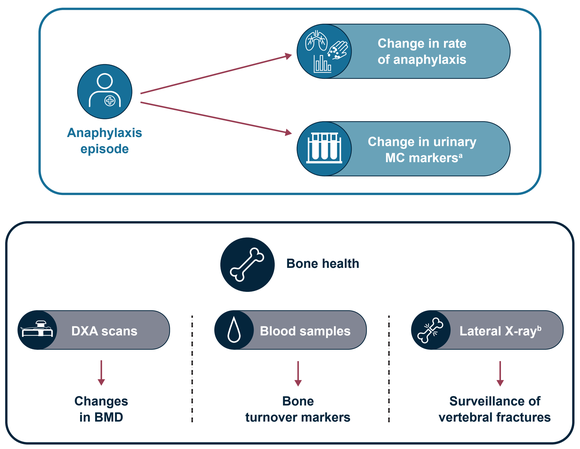
Figure 3. Key secondary endpoints of HARBOR Part 2



BMD, bone mineral density; MC-QoL, Mastocytosis Quality of Life Questionnaire; VAF, variant allele frequency

- For the assessment of anaphylaxis, urinary biomarker data of MC reactions will be collected from patients in the USA. Patient-reported anaphylaxis data, along with healthcare provider data, will supplement the findings from the physician's report and the anaphylaxis adjudication committee (**Figure 4**).

Figure 4. 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.
DXA, dual-energy X-ray absorptiometry; MC, mast cell.

- For the assessment of bone health, HARBOR Part 2 will assess changes in BMD through dual-energy X-ray absorptiometry scans; bone turnover biomarkers through blood sample assessment; and the surveillance of vertebral fractures through vertebral x-rays

Conclusions

- Elenestinib is a highly selective and potent next-generation KIT D816V inhibitor that has limited central nervous system penetration
- HARBOR Part 2 has been designed to assess the impact of a selective KIT inhibitor more robustly than in any other non-advanced SM trial
- The primary endpoint of HARBOR Part 2 aims to assess the impact of elenestinib on patient symptom improvement; and additional novel and relevant endpoints, including bone health and anaphylaxis, will enable the assessment of disease modification
- Dosing has been optimized to include treatment flexibility by evaluating multiple active dosing regimens, and the study timelines reflect the chronic nature of the disease

References

1. Kristensen T et al. *Am J Hematol*. 2014;89:493–498.
2. Ungerstedt J et al. *Cancers*. 2022;14:3942.
3. Garcia-Montero AC et al. *Blood*. 2006;108:2366–2372.
4. Gülen T et al. *Immunol Allergy Clin North Am*. 2022;42:45–63.
5. Buonomo A et al. *Mediterr J Hematol Infect Dis*. 2022;14:e2022040.
6. Brockow K. *Allergy*. 2008;63:226–232.
7. Hermine O et al. *PLoS One*. 2008;3:e2266.
8. Hartmann K et al. *J Allergy Clin Immunol*. 2016;137:35–45.
9. Zeiger RS et al. *J Allergy Clin Immunol Pract*. 2025;13(1):202–212e7.
10. Degboé Y et al. *Bone*. 2017;105:219–225.
11. van der Veer E et al. *Allergy*. 2012; 67:431–438.
12. Farmer I et al. Presented at BSH 2023. Abstract P032.
13. Mesa RA et al. *Cancer*. 2022;128:3691–3699.
14. van Anrooij B et al. *Allergy*. 2016;71:1585–1593.
15. Tashi T et al. Presented at ASH 2023. Oral #76.
16. ClinicalTrials.gov identifier: NCT04910685. https://clinicaltrials.gov/study/ NCT04910685. Accessed March 19, 2026.

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