HARBOR: A phase 2/3 study of elenestinib (BLU-263) in patients with indolent systemic mastocytosis (mCAS) and monoclonal mast cell activation syndrome (mMCAS)

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with indolent systemic mastocytosis (ISM) and monoclonal mast...MI, USA; 18Blueprint Medicines Corporation, Cambridge, MA, USA; 19UT Health San Antonio, MD Anderson Cancer Center, TX, USA; 20Mona Lisa Health, Ltd. On the behalf of Blueprint Medicines Corporation.

Introduction

• Systemic mastocytosis (SM) is a clonal mast cell disease driven by the PTGER4 D816V mutation.
• The KIT D816V mutation leads to increased accumulation of aberrant mast cells (MCs) in bone marrow, skin, the gastrointestinal tract, and other organs, which leads to chronic, debilitating, and potentially life-threatening symptoms due to the release of MC-derived mediators.
• Most patients with SM have non-advanced forms, including the World Health Organization (WHO)-classified variant of indolent SM (ISM).
• ISM is commonly associated with skin lesions.
• Approximately 5% of patients with ISM progress to advanced forms of SM associated with poor survival.
• Monoclonal mast cell activation syndrome (mMCAS) is a rare MC disease that does not meet the WHO diagnostic criteria for SM but is defined by the presence of the KIT D816V mutation.
• Despite conventional therapy, there remains an unmet need in ISM and mMCAS to reduce symptom burden and/or alter the disease course.
• Avapritinib, a potent and highly selective oral therapy targeting KIT D816V, is approved in the USA for adult patients with ISM; avapritinib is not recommended for patients with platelet counts <50x109/L.
• Currently, there are no approved KIT D816V disease-modifying therapies designed to target the underlying driver of mMCAS.
• Elenestinib (BLU-263) is a novel, oral, next-generation investigational KIT inhibitor therapy, and in whom symptoms are not adequately controlled by best supportive care (BSC).
• MC burden measures of elenestinib efficacy include changes from baseline in bone marrow MC burden, serum tryptase, and peripheral blood KIT D816V variant allele fraction.
• All patients will also be receiving BSC.
• In Part 1, patients may receive placebo or avapritinib at 25 mg, 50 mg, or 100 mg.
• Once an RD is determined from Part 1, patients will roll over to Part 3 to evaluate open-label long-term safety and efficacy of elenestinib.
• In Part 2, patients receive elenestinib or placebo at the recommended RD determined from Part 1 for 24 weeks to evaluate the proportion of patients achieving a meaningful reduction in symptom scores, as assessed by the ISM Symptom Assessment Form total symptom score, a validated patient-reported outcome tool developed to assess ISM symptom burden.
• Two PK groups, enrolling approximately 80 patients receiving elenestinib in an open-label fashion, prior to or concurrent with Part 1 and Part 2, will better characterize the PK and safety of elenestinib in patients with ISM with varying symptom burden.
• In the exploratory, open-label Part M, patients with mMCAS will receive elenestinib RD for up to 5 years.

Study objectives and design

• The phase 2/3 HARBOR trial (NCT04910685) is a randomized, double-blind, placebo-controlled study designed to determine the recommended dose (RD) of elenestinib and to evaluate its safety, tolerability, and efficacy in patients with ISM or mMCAS who have not previously received any targeted KIT inhibitor therapy, and in whom symptoms are not adequately controlled by best supportive care (BSC).
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Key eligibility criteria

Inclusion criteria

• Patients have been diagnosed with ISM or mMCAS and meet the diagnostic criteria set forth in the following textbooks.

Exclusion criteria

• Patients have been diagnosed with other SM subclassifications or organ damage C-findings attributable to SM.
• Diagnosis of another myeloproliferative disorder (e.g., polycythemia vera, primary myelofibrosis).
• A patient who has received treatment with a KIT inhibitor therapy at any time in the past.

Key study endpoints

Primary endpoints

• Part 1 – Determination of RD
• Part 2 – Mean change in ISM-SAF individual symptom scores
• Part 3 – Long-term safety, tolerability and efficacy

Secondary endpoints

• Part 1 – Progression of patients who achieve ≥30% reduction in ISM-SAF TSS from baseline to Week 24
• Part 2 – Safety and tolerability of elenestinib in ISM or mMCAS
• Part 3

Exploratory endpoints

• Part M (mMCAS)
• Pharmacokinetics: Patients achieving ≥30% reduction in MC-C
• ≥SD reduction and mean change in measures of MC burden

Enrollment and current status

• Enrollment in Part 1 and PK groups has recently completed, and Part 2 will open following RD determination from Part 1; overall, enrollment is planned at approximately 70 sites in 15 countries worldwide.

Current study sites

• https://www.blueprintclinicaltrials.com/

Summary

• The phase 2/3 HARBOR study is designed to assess the safety, efficacy, and tolerability of elenestinib as a potential treatment option to reduce symptom burden for patients with ISM and mMCAS. Enrollment in Part 1 and PK groups has recently completed, and Part 2 will open following RD determination from Part 1.

For more information visit:

https://www.blueprintclinicaltrials.com/en-us/study/HARBOR

References


Disclosures

The clinical study is supported by Blueprint Medicines Corporation. The authors of the manuscript were not involved in the conduct of the clinical study and are not employees of Blueprint Medicines Corporation.