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

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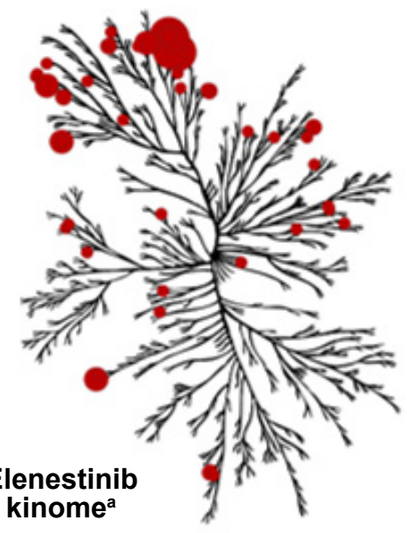
Introduction

- Systemic mastocytosis (SM) is a clonal mast cell disease driven by the *KIT* D816V mutation in ~95% of cases[1–5]
- The *KIT* D816V mutation leads to increased accumulation of aberrant mast cells (MCs) in bone marrow, skin, the gastrointestinal tract, and other organs, which can lead to chronic, debilitating, and potentially life-threatening symptoms due to the release of MC-derived mediators[5]
- Most patients with SM have non-advanced forms, including the World Health Organization (WHO)-classified variant of indolent SM (ISM)[6,7]
  - ISM is commonly associated with skin lesions[8,9]
  - Approximately 5% of patients with ISM progress to advanced forms of SM associated with poor survival[10]
- Monoclonal mast cell activation syndrome (mMCAS) is a rare MC disease which does not meet the WHO diagnostic criteria for SM but is defined by the presence of the *KIT* D816V mutation[11,12]
- Despite conventional therapy, there remains an unmet need in ISM and mMCAS to reduce symptom burden and/or alter the disease course[13]
- 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 <50x10^9/L[14]
  - 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 tyrosine kinase inhibitor with high selectivity and potency for KIT D816V[15]
- Preclinical data has demonstrated the high potency of elenestinib for KIT D816V in both biochemical (Kd=0.24 nM) and cellular (IC_{50}=4.3 nM) assays
- Phase 1 findings demonstrated the safety of elenestinib across all tested doses in healthy participants, and the corresponding pharmacokinetics (PK) were linear across the dose ranges in single ascending and multiple ascending dose cohorts, with the half-life supporting once daily (QD) dosing[15]



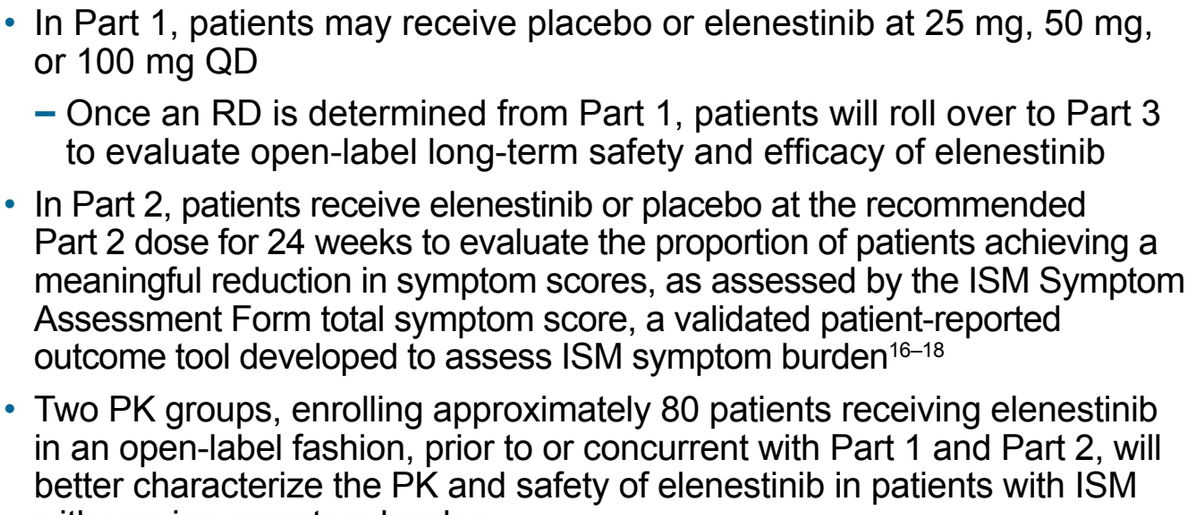
Elenestinib kinome[a]

[a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines is not responsible for its content.

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)
- 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 elenestinib at 25 mg, 50 mg, or 100 mg QD
  - 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 Part 2 dose 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[16–18]
- 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

HARBOR study design



BSC, best supportive care; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; MC, mast cell; mMCAS, monoclonal mast cell activation syndrome; PK, pharmacokinetic; QD, once daily; RD, recommended dose; TSS, total symptom score.

Key eligibility criteria

Inclusion criteria

- ≥18 years of age (≥16 years allowed if permitted by local regulations)
- ECOG performance status 0–2
- Moderate to severe symptoms based on the ISM-SAF mean TSS (Part 1)
- Pathologically and centrally confirmed diagnosis of ISM by BM biopsy and central review of B- and C-findings according to WHO diagnostic criteria (Part 1, Part 2, PK groups); or of mMCAS by BM biopsy[a] (Part M)
- Failure to achieve adequate symptom control for ≥1 baseline symptoms (Part 1, Part 2, PK groups)[b]
- BSC for ISM symptom management and ISM symptomatic therapies[c] must be stable for ≥14 days prior to starting screening procedures (Part 1, Part 2, PK groups)
- Patients must have symptoms consistent with MC activation (despite BSC) in at least 2 organ systems (Part M)[d]

Exclusion criteria

- Patients have been diagnosed with other SM subclassifications or organ damage C-findings attributable to SM[e]
- Diagnosis of another myeloproliferative disorder (e.g., myelodysplastic syndrome, myeloproliferative neoplasm)
- Prior treatment with any targeted KIT inhibitors[f]
- Received the following therapy prior to first dose of the study drug:
  - Radiotherapy or psoralen and ultraviolet A therapy <14 days before beginning the screening assessments
  - Any hematopoietic growth factor <14 days before beginning the screening assessments
- 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[g]

[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. [c]No new medications ≥14 days before beginning the 14-day eligibility screening period. [d]Characterized by cutaneous flushing, tachycardia, syncope, hypotension, diarrhea, nausea, vomiting, and gastro-intestinal cramping, and sBT levels above 8 ng/mL OR severe (Ring and Messmer grading ≥II), recurrent anaphylaxis, including but not limited to hymenoptera venom, drug or food, regardless of sBT levels. [e]WHO SM subclassification (cutaneous SM only, smoldering SM, SM with associated hematological neoplasm of non-MC lineage, aggressive SM, MC leukemia, MC sarcoma). [f]Masitinib and midostaurin are not considered targeted KIT inhibitors. [g]The following prior malignancies are not exclusionary: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ of any site.
BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; ISM, indolent systemic mastocytosis; sBT, serum blood tryptase; SM, systemic mastocytosis; WHO, World Health Organization.

Key study endpoints

Primary endpoints

- **Part 1**
  - Determination of RD
  - PK and PD
- **Part 2**
  - Proportion of patients who achieve a ≥30% reduction in ISM-SAF TSS from baseline at Week 25
- **Parts 1 and 3**
  - Safety and tolerability
  - Mean change in ISM-SAF TSS[a,b]

Secondary endpoints

- **Part 1**
  - Mean change in ISM-SAF individual symptom scores[a]
- **Part 2**
  - ≥50% reduction in measures of MC burden[c]
  - Mean change in ISM-SAF
- **Parts 1 and 2**
  - Mean change in measures of MC burden[a,c]
- **Part 3**
  - Mean change in serum tryptase and *KIT* D816V VAF in the blood[b]
  - Mean change in ISM-SAF individual and lead symptom scores from baseline

Exploratory endpoints

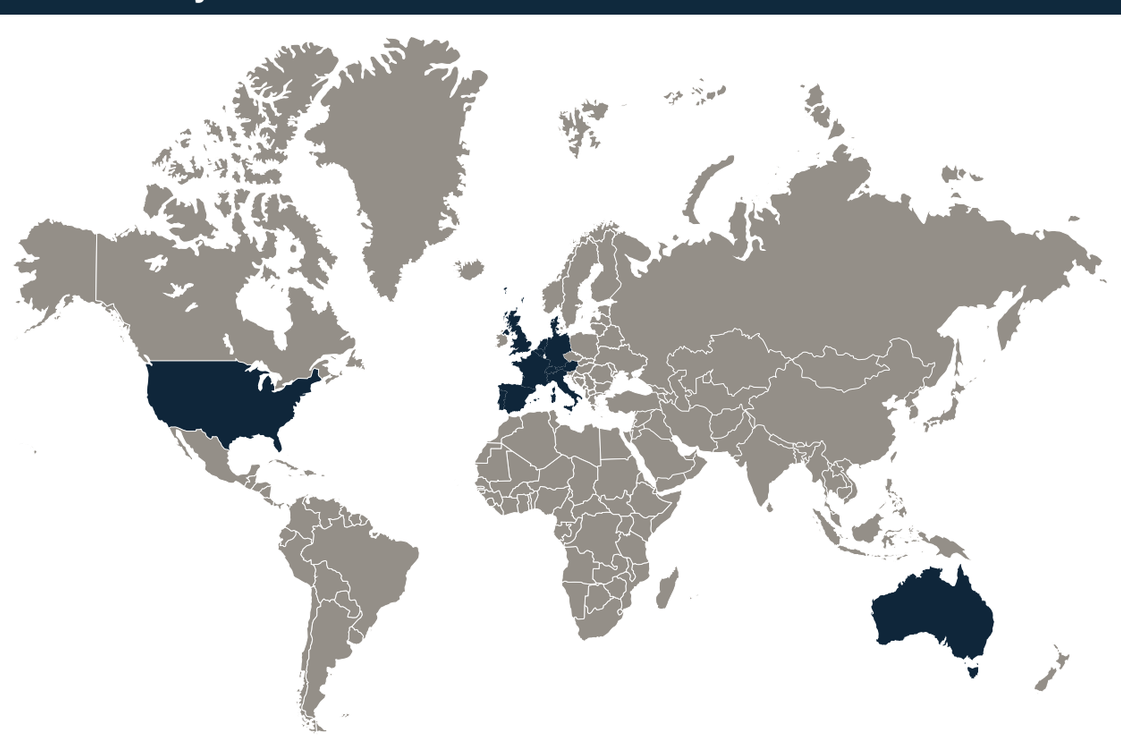
- **Part M (mMCAS)**
  - Proportion of patients achieving ≥30% reduction in MC-QoL
  - ≥50% reduction and mean change in measures of MC burden[c]

[a]From baseline at Week 13 (Part 1). [b]From elenestinib baseline (Part 3). [c]Serum tryptase, *KIT* D816V VAF, and BM MCs.
MC-QoL, validated mastocytosis quality of life questionnaire; PD, pharmacodynamics; VAF, variant allele fraction.

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



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

https://clinicaltrials.gov/ct2/show/NCT04910685

- To learn more about our clinical trials, visit blueprintclinicaltrials.com or contact us in the USA at medinfo@blueprintmedicines.com or 1-888-BLU-PRNT (1-888-258-7768), and in Europe at medinfoeurope@blueprintmedicines.com or +31 85 064 4001

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