PIONEER part 2: a randomized, double-blind, placebo-controlled, phase 2 study to evaluate safety and efficacy of avapritinib in indolent systemic mastocytosis

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AYVAKIT™ (avapritinib) is approved by the US Food and Drug Administration (FDA) for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

In Europe, AYVAKYT® (avapritinib) is approved by the European Medicines Agency (EMA) for the treatment of adult patients with unresectable or metastatic gastrointestinal GIST harboring the PDGFRA D842V mutation.

Avapritinib is not approved as safe or effective for use in systemic mastocytosis or any other indication by the FDA, EMA, or any healthcare authority in any jurisdiction.
Systemic mastocytosis is a rare, clonal mast cell neoplasm driven by KIT D816V\(^1\)

- Mast cell hyperactivation and proliferation\(^2,3\)
- Debilitating mediator symptoms in skin, gastrointestinal, and neurological symptoms\(^2,3\)
- Significant symptom-directed polypharmacy, including mast cell stabilizers, antihistamines, LTRAs, and anti-IgE\(^2,3\)
- No targeted approved therapies to reduce disease burden; significant use of symptom-directed polypharmacy\(^2,3\)

Approximately 1:10,000 people worldwide have SM\(^4,5\)

\(~5\%\) AdvSM
Organ damage and decreased survival

\(~95\%\) non-AdvSM
Indolent and smoldering SM
Suffer long-term with significant morbidity and poor quality of life\(^2,3,6\)
Avapritinib targets KIT D816V with objective and symptomatic responses in patients with systemic mastocytosis

**Highly potent against KIT D816V**

Biochemical IC₅₀ = 0.27 nM²

**Objective responses in AdvSM**

Phase 1 EXPLORER trial

77% confirmed ORR at ≥12 weeks² in AdvSM at ≥200 mg once daily

Responses deepen over time

FDA Breakthrough Designation for AdvSM

Registration-enabling PATHFINDER trial in AdvSM is currently ongoing

**Efficacy against AdvSM symptoms**

Significant reduction in AdvSM-SAF TSS³

Potential for resolution of mastocytosis in skin²

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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. AdvSM, advanced systemic mastocytosis; AdvSM-SAF, Advanced Systemic Mastocytosis-Symptom Assessment Form; FDA, Food and Drug Administration; IC₅₀, half-maximal inhibitory concentration; ORR, overall response rate; TSS, total symptom score.

Highly selective kinome profile
Objective: determine the safety and efficacy of avapritinib in patients with indolent SM and symptoms inadequately controlled by BSC

**PIioneer Part 1**
- Assessed safety profile
- Determined pharmacokinetic profile
- Identified recommended phase 2 dose:
  - 25 mg QD in continuous 28-day cycles

**PIioneer Part 2**
- Assess safety profile
- Determine efficacy of avapritinib at recommended phase 2 dose (25 mg QD)

PIONEER (NCT03731260): An international, multicenter, randomized, double-blind, placebo-controlled, phase 2 study

BSC, best supportive care; QD, once daily.

Key eligibility criteria

Inclusion criteria

• Age ≥18 years
• ECOG PS 0–2
• Indolent SM confirmed by central pathology review of bone marrow biopsy and central review of B- and C-findings according to WHO criteria
• Moderate-to-severe symptoms based on ISM-SAF$^a$ minimum mean TSS over the 14-day eligibility screening period
• Failure to achieve symptom control for ≥1 baseline symptom measured by ISM-SAF with ≥2 therapies considered BSC

Exclusion criteria

• Diagnosis with other WHO SM subclassifications: cutaneous mastocytosis only, smoldering SM, SM with associated hematologic neoplasm, aggressive SM, mast cell leukemia, or mast cell sarcoma
• Any anti-neoplastic therapy <28 days or TKI therapy <14 days before the ISM-SAF eligibility TSS assessment

$^a$The ISM-SAF TSS is composed of 11 individual 24-hour recall patient-reported symptoms (score 0–110 total) within the gastrointestinal, skin, and neurologic domains plus bone pain and fatigue, using a 14-day moving average.

ECOG PS, Eastern Cooperative Oncology Group performance status; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.
**PIONEER study design**

**Part 1: Dose escalation (fully enrolled)**

- **Primary endpoint**
  - Determination of RP2D
- **Secondary endpoints**
  - PK, safety, changes in MC burden, and PROs

<table>
<thead>
<tr>
<th>Dose</th>
<th>No.</th>
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<tbody>
<tr>
<td>Avapritinib 25 mg QD + BSC</td>
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<tr>
<td>Avapritinib 50 mg QD + BSC</td>
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<td>Avapritinib 100 mg QD + BSC</td>
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<tr>
<td>Placebo QD + BSC</td>
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Rollover: Avapritinib 25 mg QD + BSC

**Part 2: Pivotal efficacy (enrolling)**

- **Primary endpoint**
  - Response at 24 weeks

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<td>Avapritinib 25 mg QD BSC</td>
<td>136</td>
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<tr>
<td>Placebo QD + BSC</td>
<td>68</td>
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Rollover: Avapritinib 25 mg QD + BSC

30% or greater reduction in ISM-SAF TSS determined as clinically important response

- **Key secondary endpoints**
  - Proportions of patients with ≥50% reduction in serum tryptase, blood KIT D816V allele fraction, and BM MCs; mean change in TSS to Week 24

Patients who complete PIONEER part 1 or part 2 will be eligible to enter an open-label extension (rollover) to evaluate the long-term safety and efficacy of avapritinib 25 mg QD

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- **Measured by reduction of serum tryptase, peripheral blood KIT D816V allele fraction and BM MCs.**
- **Enrollment will be capped at approximately 20% of patients.**
- **BM, bone marrow; MC, mast cell; PK, pharmacokinetics; PROs, patient reported outcomes; R, randomize; RP2D, recommended phase 2 dose.**
Enrolling 204 patients in PIONEER part 2 is predicted to provide >97% power to detect superiority of avapritinib compared with placebo using a 2-sample Fisher Exact test, with a 1-sided type I error rate of 0.025, for the primary endpoint at Week 24.

Contact medinfo@blueprintmedicines.com for more information on study sites and enrollment.
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