**Results from PIONEER: A Randomized, Double-blind, Placebo-controlled, Phase 2 Study of Avapritinib in Patients with Indolent Systemic Mastocytosis (ISM)**

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**Background and methods**

**Systemic mastocytosis (SM)** is a rare condition caused by accumulation of clonal mast cells, mainly associated with KIT D816V mutation in the activation loop of KIT. Avapritinib is a selective, potent inhibitor of KIT D816V and has shown objective and symptomatic improvements in ISM.**

**Participants**

**Patients**

- Age ≥18 years
- Must meet WHO criteria for ISM
- KIT D816V allele fraction present
- Patients with indolent SM

**Exclusion criteria**

- Active or previous treatment with KIT inhibitors
- History of prior cytoreductive treatment
- Active systemic medical conditions

**Methods**

- **Background and methods**

  - **Trial design**
    - Part 1: Dose escalation (fully enrolled)
    - Part 2: Pivotal efficacy (pending)
  
  - **Study design**
    - Randomized, double-blind, placebo-controlled, phase 2 study of avapritinib vs placebo in patients with indolent SM
    - **Endpoints**
      - Efficacy assessed using the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF)
      - Symptom scores from 0 (none) to 10 (worst)
      - Abdominal pain, diarrhea, headache, flushing, skin, peripheral oedema, nail friability, and bone pain/fatigue

**Results**

**Patients**

- Patient baseline characteristics are shown in Table 1
- Overall, 95% (37/39) patients enrolled by data cut-off were continuing on the study
- Two patients discontinued due to patient decision and protocol non-compliance (n=1 each); median (range) time on study was 18 weeks (1–36)

**Safety**

- No grade 4 or 5 adverse events (AEs) were reported in the study; no grade 3 AEs were reported in the 25 mg cohort (Table 2)
- No patients discontinued due to AE progression or advanced SM
- No neoplasia, autoimmune disorders, or intercurrent infection

**Conclusion**

- Avapritinib significantly improves individual symptoms vs placebo (Figure 2)
- Avapritinib 25 mg once daily (QD) dose was selected as the recommended phase 2 dose
- Avapritinib 25 mg QD achieved similar reduction to 100 mg QD (Figure 2) and improved mastocytosis symptom groups by week 16 (Figure 6)
- Avapritinib 25 mg QD improved individual symptoms vs placebo (Figure 5)
- Avapritinib significantly improved health-related quality of life (MC-QoL) (Figure 6)
- Objective reductions in mast cell burden observed at 25 mg QD (Figure 7)

**Table 1: Baseline characteristics**

<table>
<thead>
<tr>
<th><strong>Patient demographics, n (%)</strong></th>
<th><strong>Avapritinib (n=39)</strong></th>
<th><strong>Placebo (n=9)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>51 (21–75)</td>
<td>57 (32–78)</td>
</tr>
<tr>
<td><strong>Prior cytoreductive therapy</strong></td>
<td>6 (15)</td>
<td>2 (22)</td>
</tr>
<tr>
<td><strong>MC-QoL</strong></td>
<td>72 (12)</td>
<td>72 (12)</td>
</tr>
<tr>
<td><strong>MC aggregates present, %</strong></td>
<td>100 (0)</td>
<td>100 (0)</td>
</tr>
</tbody>
</table>

**Table 2: Tolerability of avapritinib across all doses**

<table>
<thead>
<tr>
<th><strong>Placebo (n=9)</strong></th>
<th><strong>Avapritinib 50 mg (n=10)</strong></th>
<th><strong>Avapritinib 100 mg (n=10)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean % change from baseline</strong></td>
<td><strong>Midpoint Safety</strong></td>
<td><strong>Mean % change from baseline</strong></td>
</tr>
<tr>
<td>GI</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>UI</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Skin</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Headache</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Any grade 3 AEs</strong></td>
<td><strong>Placebo (n=9)</strong></td>
<td><strong>50 mg (n=10)</strong></td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Figure 1: PIONEER study design**

**Figure 2: Symptom burden at week 16 (all doses)**

**Figure 3: Symptom burden at week 16 (25 mg, 50 mg, 100 mg QD)**

**Figure 4: Improvements in most bothersome symptoms (25 mg QD)**

**Figure 5: Symptom reduction by week 16**

**Figure 6: Quality of life improvements by week 16**

**Figure 7: Mast cell burden in 25 mg vs placebo**