Avapritinib versus Placebo in Indolent Systemic Mastocytosis

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**WHO Criteria for ISM**

*If at least 1 major and 1 minor OR 3 minor criteria are fulfilled, the diagnosis of ISM can be established.*

**Major criteria:**
- Presence of dense infiltrates of mast cells (>15 mast cells in aggregates) in BM biopsies or sections of other extracutaneous organs

**Minor criteria:**
- *KIT* D816V mutation
- Expression of CD2 and/or CD25 on MCs
- Baseline serum tryptase > 20 ng/mL
- Spindled shaped MC morphology

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Brigham & Women’s Hospital–Department of Allergy & Clinical Immunology
ISM is the most common form of SM; driven by KITD816V mutation in ~95% of cases

- Patients with ISM can have lifelong debilitating symptoms across multiple organ systems\(^1\textsuperscript{-5}\)
- The vast majority of patients with ISM have highly heterogenous maculopapular skin lesions\(^5\textsuperscript{-10}\)
  - Lesions may be localized or diffuse, typically on the thighs and torso
  - Patients also experience Darier’s sign, pruritus, and flushing
- Avapritinib has previously demonstrated improvements in multiple SM symptoms including skin manifestations and QoL measurements\(^11\textsuperscript{-13}\)
- In Part 1 of PIONEER, avapritinib significantly reduced total mast cell burden and abnormal CD30+ mast cells in skin lesions

Avapritinib is approved in the USA and EU for AdvSM with a starting dose of 200 mg QD

Skin improvements with avapritinib in patients with AdvSM from the EXPLORER study

Baseline

On study

AdvSM, Advanced Systemic Mastocytosis; ISM, indolent systemic mastocytosis; QD, once-daily; QoL, quality of life; SM, systemic mastocytosis.
Registrational PIONEER Study: Randomized, double-blind, placebo-controlled study in patients with ISM

Screening period
- Best supportive care medications (BSC) optimized for up to a month
  - Antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc.
- Eligibility
  - Age ≥18 years
  - ISM by central pathology review
  - Moderate to severe symptoms (TSS ≥28) after ≥2 BSC medications

Symptoms
Primary endpoint
- Mean change in ISM-SAF Total Symptom Score (TSS) from baseline to Week 24
- Mean change in individual symptom scores of ISM-SAF
- Mean change in most severe symptom score

Biomarkers of mast cell burden
Key secondary endpoints
- ≥50% reduction in serum tryptase levels
- ≥50% reduction in KIT D816V VAF in peripheral blood (or below level of detection [<0.02%] for patients with a detectable mutation at baseline)
- ≥50% reduction in in bone marrow mast cell aggregates

Baseline (avapritinib vs placebo)
- Mean TSS: 50.2 vs 52.4
- Median (range) number of BSC treatment: 3 (0–11) vs 4 (1–8)
- Percentage of patients with SM involvement in skin by PI assessment: 72.3% vs 74.6%

*The recommended dose of avapritinib for the double-blind period and open-label extension was identified based on efficacy and safety results from Part 1 that included 4 cohorts: 25 mg avapritinib (n=10), 50 mg avapritinib (n=10), 100 mg avapritinib (n=10) and placebo (n=9). Patients treated with high dose steroids within 7 days of primary endpoint (n=4) were excluded from the week 24 analysis, but included at other timepoints of the study. Percentages were calculated based on available data at the timepoint. One-sided P-values are reported for primary and key secondary endpoints. ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; MC-QoL, Mastocytosis Quality of Life Questionnaire; QD, once daily; QoL, quality of life; R, randomized; TSS, total symptom score; VAF, variant allele fraction.
All enrolled patients met the following criteria:

- Met WHO diagnostic criteria for ISM
- Uncontrolled symptoms while on ≥ 2 BSC medications (prior to or at screening)
- Mean Total Symptom Score (TSS) score of ≥28 during the 14-day screening period

### Clinical TrialEndpoints

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Reduction in mean TSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Endpoints</td>
<td>≥50% reduction in baseline serum tryptase &amp; KIT D816V VAF</td>
</tr>
<tr>
<td></td>
<td>QoL measures</td>
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<tr>
<td></td>
<td>≥50% reduction in BM MC burden</td>
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<tr>
<td></td>
<td>≥50% and ≥30% Reduction in TSS</td>
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</tbody>
</table>
Rapid and sustained reductions in biomarkers of mast cell burden in avapritinib-treated patients versus placebo

**Key secondary endpoints**

**Patients with ≥50% reduction in serum tryptase**

- **Number of patients**
  - Avapritinib: 141
  - Placebo: 71

- **Visit (week)**
  - Baseline
  - 4
  - 8
  - 12
  - 16
  - 20
  - 24

- **≥50% reduction in tryptase level (%)**
  - **Avapritinib 25 mg QD**
    - Baseline: 0
    - 4: 118
    - 8: 63
    - 12: 110
    - 16: 57
    - 20: 113
    - 24: 54
  - **Placebo**
    - Baseline: 0
    - 4: 60
    - 8: 52
    - 12: 51
    - 16: 53
    - 20: 54

- **At Week 24**
  - Proportion of patients with ≥50% reduction in serum tryptase (95% CI)
    - **Avapritinib 25 mg QD** (n=141): 53.9% (45.3–62.3)
    - **Placebo** (n=71): 0.0% (0.0–5.1)
    - **P-value**: <0.0001

**Patients with ≥50% reduction in peripheral blood KIT D816V VAF**

- **Number of patients**
  - Avapritinib: 136
  - Placebo: 62

- **Visit (week)**
  - Baseline
  - 4
  - 8
  - 12
  - 16
  - 20
  - 24

- **≥50% reduction or undetected KIT D816V (%)**
  - **Avapritinib 25 mg QD**
    - Baseline: 0
    - 4: 118
    - 8: 110
    - 12: 113
    - 16: 109
    - 20: 107
    - 24: 104
  - **Placebo**
    - Baseline: 0
    - 4: 64
    - 8: 54
    - 12: 51
    - 16: 53
    - 20: 54

- **At Week 24**
  - Proportion of patients with ≥50% reduction in KIT D816V VAF (95% CI)
    - **Avapritinib 25 mg QD** (n=141): 67.8% (58.6–76.1)
    - **Placebo** (n=71): 6.3% (1.8–15.5)
    - **P-value**: <0.0001

**Patients with ≥50% reduction in BM mast cell aggregates**

- **Number of patients**
  - Avapritinib: 136
  - Placebo: 62

- **Visit (week)**
  - Baseline
  - 4
  - 8
  - 12
  - 16
  - 20
  - 24

- **≥50% reduction or undetected BM mast cell aggregates (%)**
  - **Avapritinib 25 mg QD**
    - Baseline: 0
    - 4: 118
    - 8: 110
    - 12: 113
    - 16: 109
    - 20: 107
    - 24: 104
  - **Placebo**
    - Baseline: 0
    - 4: 64
    - 8: 54
    - 12: 51
    - 16: 53
    - 20: 54

- **At Week 24**
  - Proportion of patients with ≥50% reduction in BM mast cell aggregates (95% CI)
    - **Avapritinib 25 mg QD** (n=141): 52.8% (42.9–62.6)
    - **Placebo** (n=71): 22.8% (12.7–35.8)
    - **P-value**: <0.0001

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BM, bone marrow; CI, confidence interval.
Avapritinib demonstrated significant and durable improvement in symptoms versus placebo

TSS over time

Primary endpoint

A one-sided P-value of <0.025 was needed to declare avapritinib as superior in reducing TSS versus placebo

SE, standard error of the mean.

All patients on avapritinib (ongoing)

Roll over from double-blind period:
Avapritinib: 135/141 (95.7%)
Placebo: 66/71 (93.0%)

At Week 24

<table>
<thead>
<tr>
<th></th>
<th>Avapritinib 25 mg QD (n=141)</th>
<th>Placebo (n=71)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in TSS (95% CI)</td>
<td>−15.58 (−18.61, −12.55)</td>
<td>−9.15 (−13.12, −5.18)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Visit (week)

Number of patients

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Avapritinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>139/71</td>
<td>137/71</td>
</tr>
<tr>
<td>4</td>
<td>135/71</td>
<td>135/71</td>
</tr>
<tr>
<td>8</td>
<td>135/68</td>
<td>137/67</td>
</tr>
<tr>
<td>12</td>
<td>136/66</td>
<td>133/60</td>
</tr>
<tr>
<td>16</td>
<td>136/66</td>
<td>123/51</td>
</tr>
<tr>
<td>20</td>
<td>136/66</td>
<td>123/41</td>
</tr>
<tr>
<td>24</td>
<td>136/66</td>
<td>91/39</td>
</tr>
<tr>
<td>28</td>
<td>135/66</td>
<td>76/33</td>
</tr>
<tr>
<td>32</td>
<td>135/66</td>
<td>70/33</td>
</tr>
<tr>
<td>36</td>
<td>135/66</td>
<td>60/26</td>
</tr>
<tr>
<td>40</td>
<td>133/66</td>
<td>51/26</td>
</tr>
<tr>
<td>44</td>
<td>133/66</td>
<td>41/26</td>
</tr>
<tr>
<td>48</td>
<td>133/66</td>
<td>39/26</td>
</tr>
</tbody>
</table>
Blind SAC Evaluation of Skin Photographs

- **Blinded SAC determined:**
  - Most affected region at baseline
  - Color change over time

- **Computer-generated algorithm for each patient**
  - Affected surface area was followed with computer generated detection method
  - Number of lesions, fractional area, and percent fractional area were determined

Baseline

- Photograph
- Computer detection

**Baseline**

- Affected surface area

- Photograph: 31%

**On study**

- Photograph
- Computer detection

- Affected surface area

Patient permission granted for use of photos.
Case study: Area and color of skin lesions improved at Week 24 with avapritinib treatment

Baseline

Week 24

Baseline

Week 24

Patient permission granted for use of photos
Case study: Area and color of skin lesions improved at Week 24 with avapritinib treatment

Patient permission granted for use of photos
Case Study

**Location of SM Involvement**

- 55 years old
- Female
- 27 years old
- History of cutaneous mastocytosis
- 7 years
- History of ISM
- Skin
- Bone marrow

**Screening**

- ISM-SAF TSS: -23.3
- Skin domain score: -44.4
- MC-QoL total score: -54.7
- Skin domain score: -77.3
- Serum tryptase: -26.3
- KIT D816V: Central lab: -63.2
- BM mast cells: No sample collected at Week 24

**Week 24**

- BSC: fexofenadine, montelukast, famotidine, omalizumab (all ongoing)
- levocetirizine, hydroxyzine (discontinued after ~3 months)

Brown staining indicated CD117 positivity.
Avapritinib treatment improved skin lesion color at Week 24 as assessed by blinded Skin Assessment Committee

- In patients with paired photographs, 86.2% of avapritinib-treated patients versus 0% of placebo had improved skin lesion color in most affected skin region at Week 24
- Rapid improvement in skin lesion color with avapritinib versus placebo was observed
  - At Week 12, 57.2% vs 3.8% of patients, respectively, had improved skin lesion color in most affected area

**Skin lesion color change**

<table>
<thead>
<tr>
<th></th>
<th>Back thigh</th>
<th>Back torso</th>
<th>Front thigh</th>
<th>Front torso</th>
<th>Most affected area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avapritinib 25 mg QD</td>
<td>58.8%</td>
<td>54.0%</td>
<td>66.7%</td>
<td>64.7%</td>
<td>72.5%</td>
</tr>
<tr>
<td>n=51</td>
<td>n=21</td>
<td>n=21</td>
<td>n=51</td>
<td>n=20</td>
<td>n=21</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.7%</td>
<td>16.0%</td>
<td>11.8%</td>
<td>11.8%</td>
<td>13.7%</td>
</tr>
<tr>
<td>n=21</td>
<td>n=50</td>
<td>n=21</td>
<td>n=51</td>
<td>n=20</td>
<td>n=21</td>
</tr>
</tbody>
</table>

Patients with no change or darkening of skin lesion color have not been included in the figure.
Avapritinib 25mg QD was well tolerated, with a similar safety profile to placebo

- Majority of AEs were Grade 1 or 2 with a low rate of discontinuation
- SAEs were reported more frequently in the placebo group (no treatment-related SAEs in either group)
- Edema adverse events were higher in the avapritinib group (majority Grade 1, and did not result in discontinuation)

### Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Avapritinib 25 mg QD (N=141)</th>
<th>Placebo (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AEs</strong>, n (%)</td>
<td>128 (90.8)</td>
<td>66 (93.0)</td>
</tr>
<tr>
<td>Grade 1–2 AEs</td>
<td>98 (69.5)</td>
<td>51 (71.8)</td>
</tr>
<tr>
<td>Grade 1–2 related AEs</td>
<td>74 (52.5)</td>
<td>30 (42.3)</td>
</tr>
<tr>
<td>Grade ≥3 AEs</td>
<td>30 (21.3)</td>
<td>15 (21.1)</td>
</tr>
<tr>
<td>Grade ≥3 related AEs</td>
<td>3 (2.1)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td><strong>SAEs, n (%)</strong></td>
<td>7 (5.0)</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td><strong>Any grade TRAEs</strong></td>
<td>77 (54.6)</td>
<td>32 (45.1)</td>
</tr>
<tr>
<td><strong>Most frequently reported TRAEs (≥5% of patients)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>11 (7.8)</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (6.4)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>9 (6.4)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>9 (6.4)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (2.8)</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td><strong>TRAEs leading to discontinuation</strong></td>
<td>2 (1.4)</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

*aAEs reported occurred between day 1 of Part 2 through to a day prior to day 1 of Part 3 if the patient crossed over to Part 3; if the patient did not crossover, then through 30 days after the last dose of study drug. Treatment-emergent AEs were defined as any AE that occurred between day 1 of Part 2 through to a day prior to day 1 of Part 3 if the patient crossed over to Part 3; if the patient did not crossover, then through 30 days after the last dose of study drug.*

*bThere were too few events (≤5 per group) to assess the impact of avapritinib on anaphylaxis.*

AEs, adverse events; SAEs, serious adverse events; TRAEs, treatment-related adverse events.
Summary

• Avapritinib demonstrated statistically significant and clinically meaningful improvement versus placebo in symptoms in the primary analysis, as measured with the TSS and biomarkers of mast cell burden
  – Of the patients with skin involvement, those treated with avapritinib experienced marked reductions in skin symptoms, skin color, surface area of skin lesions, and pathologic mast cell burden
  – Results confirmed the findings from Part 1, CD30 may be the most relevant biomarker of aberrant mast cells in skin lesions and further research is warranted
  – Improvements in skin symptoms were correlated with improvement in QoL
• Avapritinib was well tolerated and demonstrated a similar safety profile to placebo

Conclusions

• Avapritinib selectively targets KIT D816V, the underlying driver of disease
• Avapritinib substantially impacted ISM-related skin symptoms and skin lesion area and color in addition to providing overall disease improvement in mast cell burden, symptoms, and QoL for patients with ISM
Conclusions

• The PIONEER clinical trial found that avapritinib caused statistically significant improvements in patient-reported symptoms and decreases in objective measures of mast cell burden (serum tryptase, BM MC burden, KIT D816V VAF) after 24 weeks of treatment.

_The FDA approved avapritinib as a treatment for adults with ISM at the end of May 2023._

**Moving forward....**

• PIONEER is still ongoing! We are currently collecting data on the long-term side effects of avapritinib since they have not been fully characterized or understood.

• The pathology of symptoms and their severity (i.e. the relationship between individual symptoms and mast cell burden / mediator release) is not well understood.

• Hereditary Alpha Tryptasemia was not assessed in the PIONEER trial.

• The Mastocytosis Team also coordinates two other active Tyrosine Kinase Inhibitor (TKI) clinical trials: Harbor and Summit.