Efficacy and Safety of Avapritinib in Indolent Systemic Mastocytosis (ISM): Results from the Double-Blind Placebo-Controlled PIONEER Study

Mariana Castells,1* Jason Gotlib,2* Hanneke Oude Elberink,3 Frank Siebenhaar,4,5 Karin Hartmann,6,7 Sigurd Broesby-Olsen,8 Tracy I. George,9 Jens Panse,10 Ivan Alvarez-Twoo,11 Deepti H. Radia,12 Tsewang Tashi,13 Cristina Bulai Livideanu,14 Vito Sabato,15 Paul Van Daele,16 Sonia Cerquozzi,17 Ingunn Dybedal,18 Andreas Reiter,19 Thanai Pongdee,20 Stéphane Barete,21 Lawrence Schwartz,22 Prithviraj Bose,23 Massimo Triggiani,24 William Shomali,25 Matthew Giannetti,25 Ilda Bidollari,26 Hui-Min Lin,26 Robyn Scherber,26 Maria Roche,26 Cem Akin,27** Marcus Maurer4,5**

*Mariana Castells,
1Department of Medicine, Brigham and Women’s Hospital, Boston, MA, USA; 2Stanford Cancer Institute / Stanford University School of Medicine, Stanford, CA, USA; 3Department of Allergology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; 4Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; 5Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany; 6Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland; 7Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland; 8Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark; 9ARUP Laboratories, Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT, USA; 10Department of Hematology, Hemostaseology and Stem Cell Transplantation, University Hospital Aachen, Medical Faculty, RWTH Aachen University, Aachen, Germany; 11Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; 12Département de dermatologie, CEREMAST CHU de Toulouse, Toulouse, France; 13Department of Immunology, Allergology and Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; 14Department of Medical Research, Erasmus Medical Center, Rotterdam, Netherlands; 15Department of Medicine, Alberta Health Services and Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; 16Department of Allergy, Oslo University Hospital, Oslo, Norway; 17University Hospital Mannheim, Heidelberg University, Mannheim, Germany; 18Division of Allergic Diseases, Mayo Clinic, Rochester, MN, USA; 19Unit of Dermatology Reference Centre for Mastocytosis (CEREMAST) AP-HP, Pitié-Salpêtrière Hospital, Sorbonne Université, Paris, France; 20Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA, USA; 21The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 22Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy; 23Division of Allergy and Clinical Immunology, Brigham and Women’s Hospital, Boston, MA, USA; 24Blueprint Medicines Corporation, Cambridge, MA, USA; 25University of Michigan, Ann Arbor, MI, USA.

*Equally contributing first authors; **Equally contributing last authors

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Indolent systemic mastocytosis (ISM) is a clonal mast cell disease driven by the KIT D816V mutation in ~ 95% of adult cases\textsuperscript{1–3}

- Patients with ISM can have lifelong \textbf{debilitating symptoms} across multiple organ systems\textsuperscript{4–8}

- Most patients rely on polypharmacy for the management of symptoms with \textbf{best supportive care (BSC) medications}\textsuperscript{8–10}

- Symptoms are \textbf{not adequately controlled} with BSC medications in many patients with ISM\textsuperscript{8–10}

- Currently, there are \textbf{no approved therapies} that target the KIT D816V-mutated tyrosine kinase in ISM

BSC, best supportive care; ISM, indolent systemic mastocytosis.
Avapritinib is a potent and highly selective oral therapy targeting KIT D816V, the underlying driver of systemic mastocytosis.

### Highly selective kinome profile

**Potently and selectively inhibits**
the autophosphorylation of KIT D816V, with an IC$_{50}$ of 0.27 nanomolar in selective cellular assays.$^{11}$

### Biochemical IC$_{50}$ (nM)

<table>
<thead>
<tr>
<th></th>
<th>KIT D816V</th>
<th>KIT wild type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avapritinib</td>
<td>0.27</td>
<td>73</td>
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</tbody>
</table>

nM, nanomolar concentration.
**Avapritinib in advanced systemic mastocytosis**

**Reduction in mast cell burden biomarkers**\(^{12,13}\)

**Improved symptom severity**\(^{12,13}\)

**Survival benefit vs. real-world best available therapy**\(^{14,b}\)

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**Avapritinib is approved in the US and EU for AdvSM with a starting dose of 200 mg once daily**\(^{15,16}\)

\(^{a}\)Patients with systemic mastocytosis and an associated hematologic neoplasm only. \(^{b}\)Data for best available therapy from retrospective real-world patient chart review, methodology described previously; shading represents 95% confidence interval.\(^{17}\) AdvSM, advanced systemic mastocytosis. AdvSM-SAF, advanced systemic mastocytosis symptom assessment form.
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

### Randomization

- Both groups continued optimized BSC as needed

### Double-blind treatment period (24 weeks)

- **Avapritinib 25 mg QD**
  - n=141
- **Placebo**
  - n=71

### Open-label extension (5 years)

- **Avapritinib 25 mg QD**
  - (ongoing)

### Biomarkers of mast cell burden

- ≥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

### Quality of life

- Mean % change in QoL score, as measured by MC-QoL

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*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.*
ISM-SAFA: Validated symptom assessment tool specifically developed for evaluation of ISM symptomology\textsuperscript{18–20}

- Total Symptom Score (TSS) based on severity of 11 ISM symptoms
- Developed over past 8 years with input from patients, disease experts, and global regulatory agencies\textsuperscript{19}

<table>
<thead>
<tr>
<th>ISM Symptom Assessment Form (ISM-SAF)</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoring 0–10 daily on handheld device</td>
<td></td>
</tr>
<tr>
<td>0 = no symptom</td>
<td></td>
</tr>
<tr>
<td>10 = worst imaginable symptom</td>
<td></td>
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<tr>
<td>Analyzed as a 14-day moving average</td>
<td></td>
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<tr>
<td>TSS (0–110)</td>
<td></td>
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<tr>
<td>Higher scores represent more severe symptoms</td>
<td></td>
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</tbody>
</table>
Baseline patient and disease characteristics were balanced between groups

<table>
<thead>
<tr>
<th>Patient demographic</th>
<th>Avapritinib 25 mg QD (n=141)</th>
<th>Placebo (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>50.0 (18–77)</td>
<td>54.0 (26–79)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>100 (70.9)</td>
<td>54 (76.1)</td>
</tr>
</tbody>
</table>

**ISM symptom burden**

| TSS score, mean (SD) | 50.2 (19.1) | 52.4 (19.8) |
| Most severe symptom score, mean (SD) | 7.7 (1.7) | 7.9 (1.7) |

**Mast cell burden**

| Median serum tryptase (central), ng/mL (range) | 38.4 (3.6–256.0) | 43.7 (5.7–501.6) |
| Median bone marrow biopsy mast-cells (central), % (range) | 7.0 (1.0–50.0) | 7.0 (1.0–70.0) |
| Mast-cell aggregates present, n (%) | 106 (75.2) | 57 (80.3) |
| Median KT D816V VAF in peripheral blood, % (range) | 0.4 (0.02–41.3) | 0.3 (0.02–36.7) |
| KT D816V positivity, n (%) | 131 (92.9) | 69 (97.2) |

**SM therapy**

| Avapritinib 25 mg QD (n=141) | Placebo (n=71) |
| Prior cytoreductive therapy, n (%) | 19 (13.5) | 7 (9.9) |
| Prior TKI therapy, n (%) | 10 (7.1) | 4 (5.6) |

**BSC use**

| Number of BSC treatments, median (range) | 3 (0-11) | 4 (1-8) |
| BSC use at baseline, n (%) | 140 (99.3) | 71 (100.0) |

| H1 Antihistamines | 137 (97.2) | 71 (100.0) |
| H2 Antihistamines | 93 (66.0) | 47 (66.2) |
| Leukotriene receptor antagonists | 49 (34.8) | 25 (35.2) |
| Cromolyn sodium | 43 (30.5) | 25 (35.2) |
| Proton pump inhibitors | 22 (15.6) | 20 (28.2) |
| Corticosteroids | 17 (12.1) | 7 (9.9) |
| Anti-IgE antibody (omalizumab) | 14 (9.9) | 7 (9.9) |
| Other | 33 (23.4) | 19 (26.8) |

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*aThe limit of detection was 0.02%.

*bCytoreductive therapies included dasatinib, imatinib, masitinib, nilotinib, midostaurin, brentuximab vedotin, cladribine, hydroxyurea, rapamycin, and interferon alfa. Includes treatments received by patients at baseline; patients may have received BSC treatments previously that had been discontinued at the time of enrollment/baseline.

cAll patients had at least two BSC prior to or at screening. A total of 10 (7.1%) patients treated with avapritinib and 5 (7.0%) patients treated with placebo had <2 BSC at the start of the study.

ISM, indolent systemic mastocytosis; SD, standard deviation; SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor; TSS, total symptom score.
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

- Avapritinib 25 mg QD
- Placebo

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

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

- Avapritinib 25 mg QD
- Placebo

At Week 24
- Proportion of patients with ≥50% reduction or undetected KIT D816V (%)
  - Avapritinib 25 mg QD: 67.8% (58.6–76.1)
  - Placebo: 6.3% (1.8–15.5)
  - P-value: <0.0001

Number of patients

- Avapritinib: 141
- Placebo: 71

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

**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.
Avapritinib demonstrated improvement in all individual ISM symptoms versus placebo including the most severe symptom at baseline

Mean TSS absolute change from baseline to 24 weeks, individual ISM-SAF, by treatment group

Avapritinib 25 mg QD (n=131) vs Placebo (n=66)

Regardles of which symptom was rated most severe at baseline, avapritinib patients had a significant reduction in this versus placebo
Continued improvement was observed in all individual symptoms among avapritinib-treated patients at 48 weeks.
Avapritinib-treated patients were significantly more likely than placebo to reach the TSS ≥30% and TSS ≥50% reduction thresholds over time.

### 30% Reduction in ISM-SAF TSS Score Over Time

- **≥30% reduction in ISM-SAF TSS score over time**
- **At Week 24**
  - **Avapritinib 25 mg QD (n=141)**: 45.4% (37.0–54.0)
  - **Placebo (n=71)**: 29.6% (19.3–41.6)
  - **P-value**: 0.009

### 50% Reduction in ISM-SAF TSS Score Over Time

- **≥50% reduction in ISM-SAF TSS score over time**
- **At Week 24**
  - **Avapritinib 25 mg QD (n=141)**: 24.8% (17.9–32.8)
  - **Placebo (n=71)**: 9.9% (4.1–19.3)
  - **P-value**: 0.005

**Graph Details**:
- **Treatment groups**: Avapritinib 25 mg QD, Placebo
- **Number of patients**:
  - **Avapritinib**: 139, 135, 133, 133, 135, 134, 131, 121, 104, 89, 74, 69, 58
  - **Placebo**: 71, 71, 71, 68, 66, 66, 60, 51, 41, 39, 33, 26
- **Visit weeks**: Baseline, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48
- **Proportion of patients with ≥30% reduction in TSS (%) at Week 48**: 60.7%
- **Proportion of patients with ≥50% reduction in TSS (%) at Week 48**: 39.3%
Avapritinib demonstrated sustained improvement in MC-QoL versus placebo, an established and validated disease-specific QoL measure.

Change in mean MC-QoL component score from baseline to Week 24 in the ITT population

<table>
<thead>
<tr>
<th>Component</th>
<th>Avapritinib 25 mg QD (n=141)</th>
<th>Placebo (n=71)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>-34.3% (-39.9, -28.7)</td>
<td>-17.9% (-25.1, -10.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Life/Functioning</td>
<td>-14.58</td>
<td>-16.58</td>
<td></td>
</tr>
<tr>
<td>Emotions</td>
<td>-23.44</td>
<td>-24.11</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>-11.98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

At Week 24

Mean % change MC-QoL (95% CI)

-34.3% (-39.9, -28.7) vs -17.9% (-25.1, -10.8), p=0.001

ITT, intent-to-treat. *p<0.05.
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)

<table>
<thead>
<tr>
<th></th>
<th>Avapritinib 25 mg QD (N=141)</th>
<th>Placebo (N=71)</th>
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</thead>
<tbody>
<tr>
<td>Any AEs(^{a,b}), 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>SAEs, n (%)</td>
<td>7 (5.0)</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>Any grade TRAEs</td>
<td>77 (54.6)</td>
<td>32 (45.1)</td>
</tr>
<tr>
<td>Most frequently reported TRAEs (≥5% of patients)</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>TRAEs leading to discontinuation</td>
<td>2 (1.4)</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

\(^a\)AEs refer to treatment-emergent AEs (TEAEs), 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 cross over, then through 30 days after the last dose of study drug.

\(^b\)There 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

• ISM patients can suffer from a wide range of debilitating symptoms often not adequately controlled by BSC medications

• PIONEER is the first randomized, double-blind, placebo-controlled trial of a highly selective KIT D816V-targeting agent in patients with Indolent SM

• Avapritinib-treated patients showed rapid, durable and clinically meaningful improvements in mast cell burden, symptoms, and QoL compared to placebo-treated patients at 24 weeks of treatment

• Avapritinib was well tolerated with a similar safety profile to placebo

• Open-label extension assessing long-term safety and efficacy of 25 mg QD avapritinib ongoing

Conclusion

• Avapritinib selectively targets KIT D816V, the underlying driver of disease

• Avapritinib reduced mast cell burden, improved symptoms, and improved quality of life for patients, potentially offering a promising new treatment option for patients with ISM
References

16. Ayvakyt (avapritinib) Summary of Product Characteristics. Cambridge, MA; Blueprint Medicines Corporation; 2022
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