Marcus Maurer¹, Frank Siebenhaar¹, Karin Hartmann², Andreas Reiter³, Deepti Radia⁴, Michael W. Deininger⁵, Jayita Sen⁶, Hui-Mun Lin⁶, Brenton J. Mar⁶, Jason Gotlib⁷, Daniel J. DeAngelo⁸, Sigurd Broesby-Olsen⁹

Avapritinib improves overall symptoms, skin lesions and quality of life in patients with advanced systemic mastocytosis in the PATHFINDER study

¹Dermatological Allergology, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Berlin, Germany; ²Division of Allergy, Department of Dermatology, University Hospital of Basel and University of Basel, Basel, Switzerland; ³University Hospital Mannheim, Mannheim, Germany; ⁴Guy’s and St Thomas’ NHS Foundation Trust, London, UK; ⁵Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA; ⁶Blueprint Medicines Corporation, Cambridge, Massachusetts, USA; ⁷Stanford University School of Medicine/Stanford Cancer Institute, Stanford, California, USA; ⁸Dana-Farber Cancer Institute, Boston, Massachusetts, USA; ⁹Odense University Hospital, Odense, Denmark
Disclosure

In relation to this presentation, I declare the following, real or perceived conflicts of interest:

<table>
<thead>
<tr>
<th>Type</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment full time/part time</td>
<td>Dermatological Allergology, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin</td>
</tr>
<tr>
<td>Consulting, honoraria, reimbursement of travel expenses, and/or institutional grant/research support</td>
<td>Allakos, Amgen, Astra-Zeneca, Bayer, Blueprint Medicines Corporation, Celldex, Dr. Pfleger, FAES, Genentech, GI Innovation, GSK, Innate Pharma, Kyowa Kirin, Lilly, Merckle Recordati, Moxie, Novartis, Regeneron, Roche, Sanofi, Third Harmonic Bio, UCB, and Uriach/</td>
</tr>
<tr>
<td>Other research support</td>
<td>None</td>
</tr>
<tr>
<td>Ownership interest (stock, stock-options, patent or intellectual property)</td>
<td>None</td>
</tr>
</tbody>
</table>

AYVAKIT™ (avapritinib) is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with advanced systemic Mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL). Limitations of Use: AYVAKIT is not recommended for the treatment of patients with AdvSM with platelet counts of less than $50 \times 10^9$/L.

Avapritinib is not approved as safe or effective for use in non-advanced systemic mastocytosis by the FDA. Avapritinib is not approved for use in any subtype of systemic mastocytosis by the European Medicines Agency (EMA), or any healthcare authority in any jurisdiction.
Systemic mastocytosis (SM) is a rare, clonal mast cell (MC) neoplasm driven by KIT D816V mutation in ~95% of cases

- **KIT D816V** mutation drives MC proliferation and hyperactivation in various organs\(^1\)

- Severe skin, gastrointestinal, neurocognitive and systemic MC mediator symptoms diminish Quality of Life (QoL)\(^1,2\)

- In **Advanced SM**, MCs lead to organ damage resulting in poor survival\(^3\)

- Few effective treatment options\(^3\)

Patients’ permission granted for use of photos


MC, mast cell; QoL, quality of life.
Avapritinib is a potent and selective KIT D816V inhibitor which induced responses across SM subtypes

**Advanced SM**
**EXPLORER Phase 1 Study**
75% Overall Response Rate\(^a\) per mIWG-MRT-ECNM criteria\(^1\)

Improvements in MC burden, organ damage and patient symptoms and QoL were observed\(^2\)

**Baseline**

- Serum tryptase 367 ng/mL
- Weight loss of >50 pounds
- Hypoalbuminemia (2.3 mg/dL)
- Ascites with paracentesis (15 L/week)

**On study**

- Serum tryptase 1.9 ng/mL
- All weight gained back
- Albumin normalized
- Ascites resolved

**Non-Advanced SM**
**PIONEER Phase 2 Study (Part 1)**
60% Response\(^b\) in Total Symptom Score (TSS) at 24 weeks\(^3\)

Reductions in lesion surface area, color and skin MC number\(^3\)

**Baseline**

- Serum tryptase 367 ng/mL
- Weight loss of >50 pounds
- Hypoalbuminemia (2.3 mg/dL)
- Ascites with paracentesis (15 L/week)

**On study**

- Serum tryptase 1.9 ng/mL
- All weight gained back
- Albumin normalized
- Ascites resolved

---


Patients’ permission granted for use of photos.
**PATHFINDER Phase 2 pivotal study in Advanced SM (AdvSM)**

- Central diagnosis of AdvSM
- ≥18 years of age
- ECOG PS 0–3
- Platelets <50×10^9/L excluded

**Primary Endpoint (Cohort 1)**
- Adjudicated ORR by mIWG-MRT-ECNM criteria
  
  *Response primarily based on resolution of organ damage (C-findings)*

**Secondary Endpoints (both cohorts)**
- Reduction in MC burden (including serum tryptase)
- Safety

Based on data cut-off date of June 23, 2020

**Avapritinib 200 mg QD starting dose**

- **Enrolled (N=62)**
- **mIWG Evaluable, Cohort 1 (n=52)**
  - AdvSM with ≥1 evaluable C-finding
- **mIWG Non-Evaluable, Cohort 2 (n=10)**
  - AdvSM without any evaluable C-findings

**Symptom-related Secondary Endpoints (both cohorts)**
- **Total Symptom Score** of the AdvSM-Symptom Assessment Form (AdvSM-SAF), mean change from baseline
- **Global symptom severity** by Patient Global Impression of Symptom Severity (PGIS) Questionnaire
- **QoL** on the EORTC QLQ-C30 survey

**Symptom-related Exploratory Endpoints**
- **Cutaneous disease** in patients by photography

---

*60 patients received 200 mg and 2 patients received 100 mg. *Per mIWG-MRT ECNM criteria, response assessment requires ≥1 evaluable C-finding at baseline. MCL without an evaluable C-finding may be assessed for response based on disease burden alone (Gotlib et al. J Clin Oncol 2013;31:2393–2401). ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire- core questionnaire 30; MCL, mast cell leukemia; QD, once-daily.*
Baseline characteristics of PATHFINDER population

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>All doses (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>69 (31–88)</td>
</tr>
<tr>
<td>Sex, n (%), female</td>
<td>28 (45)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>43 (69)</td>
</tr>
<tr>
<td>2–3</td>
<td>19 (31)</td>
</tr>
<tr>
<td>AdvSM subtype per central assessment, n (%)</td>
<td></td>
</tr>
<tr>
<td>ASM</td>
<td>9 (15)</td>
</tr>
<tr>
<td>SM-AHN</td>
<td>43 (69)</td>
</tr>
<tr>
<td>MCL</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Bone marrow biopsy MC burden median percent (range)</td>
<td>45 (1–95)</td>
</tr>
<tr>
<td>Serum tryptase level, median ng/mL (range)</td>
<td>283 (24–1600)</td>
</tr>
<tr>
<td>KIT D816V positive in peripheral blood by central ddPCR, n (%)</td>
<td>59 (95)</td>
</tr>
<tr>
<td>Prior anti-neoplastic therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Midostaurin</td>
<td>34 (55)</td>
</tr>
<tr>
<td>Cladribine</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Baseline supportive medications, median (range)</td>
<td></td>
</tr>
<tr>
<td>H1 antihistamines</td>
<td>36 (58)</td>
</tr>
<tr>
<td>H2 antihistamines</td>
<td>24 (39)</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Corticosteroids (systemic)</td>
<td>20 (32)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (31)</td>
</tr>
</tbody>
</table>

ASM, aggressive systemic mastocytosis; ddPCR, droplet digital polymerase chain reaction; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.
**PATHFINDER high confirmed response rate of avapritinib in AdvSM**

- 75% confirmed ORR per mIWG-MRT-ECNM criteria
- 93% of patients achieved ≥50% reduction in serum tryptase

**Serum tryptase**

![Graph showing serum tryptase reduction](image)

- Overall, 43% of patients achieved reduction to <20 ng/mL

- Avapritinib was generally well tolerated; only 3 (5%) patients discontinued due to treatment-related AEs
- Cytopenias are the most common Grade ≥3 AEs

### Adverse Events (AEs) in ≥15%

<table>
<thead>
<tr>
<th>Non-hematologic, n (%)</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>31 (50)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>30 (48)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (23)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (18)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (18)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (15)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematologic, n (%)</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>28 (45)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Anemia</td>
<td>20 (32)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15 (24)</td>
<td>15 (24)a</td>
</tr>
</tbody>
</table>

AE table includes pooled similar AE terms for periorbital edema, thrombocytopenia, anemia, and neutropenia.
Patients with AdvSM, including highly symptomatic patients at baseline, improved on avapritinib

- Majority of patients reported severe (26%) or very severe (30%) SM symptoms at baseline.
- 78% of patients with improvement from baseline in global symptom severity.
- 71% of patients with severe/very severe symptoms improved to minimal/absent.

Baseline PGIS score (n=54):
- Very Severe: 30% (n=16)
- Severe: 26% (n=15)
- Moderate: 28% (n=16)
- Minimal: 11% (n=6)
- Absent: 6% (n=3)

Maximum change in global symptoms from baseline:
- Improvement from baseline symptoms on study
- Stable symptoms on study
- Worsening from baseline symptoms on study

*Includes patients with baseline and post-baseline assessments (n=51). PGIS was administered to patients at baseline and after 2, 4, 8, 16, 24, 32, and 40 weeks of therapy, and then every 12 weeks.
Patients reported a broad range of specific symptoms at baseline on the Advanced SM-Symptom Assessment Form (AdvSM-SAF)

AdvSM-SAF: Validated patient-reported outcome tool in AdvSM

- A total of 8 symptoms were scored (0–10) daily on an eDiary
- Scores were averaged over 7 days for analysis
- Patients have heterogenous symptoms in number and severity

Baseline AdvSM-SAF symptom scores

- A mean TSS of 18 is correlated to moderate to severe symptom burden on the PGIS

Concordance of AdvSM-SAF with PGIS

Mean TSS at baseline: 18.3
Avapritinib led to rapid and durable reduction in AdvSM symptoms

**Significant reduction in TSS**

Mean Baseline (BL) score: 18.3

Reduction in Symptoms

<table>
<thead>
<tr>
<th>Cycle</th>
<th>BL</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>56</td>
<td>53</td>
<td>51</td>
<td>49</td>
<td>45</td>
<td>41</td>
<td>36</td>
<td>35</td>
<td>28</td>
<td>24</td>
<td>22</td>
</tr>
</tbody>
</table>

- Week 8: -7.1
- Week 40: -9.8 (P<0.001)

**Individual Symptom Scores**

- Fatigue
- Abdominal pain
- Nausea
- Diarrhea
- Vomiting

BL, baseline; CI, confidence interval.
Avapritinib led to rapid and durable improvement in QoL and functional impairment

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ C30)

- AdvSM patients have poor QoL and functional impairment at Baseline
- Rapid improvement in QoL by week 8
- Sustained improvement at week 40, approaching scores in healthy patients from a historical study
- Improvements seen in all facets of QoL
Avapritinib reduced size of skin lesions in AdvSM

As captured

Detection of affected area

Week 12

Week 40

Surface area % change from baseline

8.1% of area affected

0.2% (−97.7% change)

0.1% (−98.5% change)

Patients’ permission granted for use of photos
Avapritinib reduced skin lesion color intensity

• Color change was judged by the Skin Assessment Committee

• No patients were assessed as “no change”, “darker” or “a lot darker”
Avapritinib led to profound reduction of disease burden and symptom improvement

- 75% confirmed ORR with significant reductions in serum tryptase in 93% of patients
- Reduced overall patient-reported symptom burden, with rapid and durable improvement in QoL and functional domains in patients with AdvSM
- Reduced affected area and lightened color of SM skin lesions
- Avapritinib was generally well tolerated; cytopenias were the most common Grade 3+ AEs
- Avapritinib for the treatment of AdvSM has been submitted to the EMA for approval
Acknowledgements

• Participating patients and families
• PATHFINDER Investigators
• Skin Assessment Committee

Medical writing support and editorial support were provided by Deborah Cantu, PhD, and Travis Taylor, BA both of Paragon, UK, supported by Blueprint Medicines Corporation, Cambridge, MA
Pivotal part 2 of PIONEER phase 2 study in Indolent SM now enrolling globally

Complete list of enrolling sites at: clinicaltrials.gov/ct2/show/NCT03731260

For more information email: medinfo@blueprintmedicines.com