Reductions in indolent systemic mastocytosis biomarker burden with avapritinib in the registrational, double-blind placebo-controlled PIONEER trial

Poster Number 1017

Jason Gotlib,[1*] Mariana Castells,[2*] Hanneke Oude Elberink,[3] Frank Siebenhaar,[4,5] Karin Hartmann,[6,7] Sigurd Broesby-Olsen,[8] Tracy I. George,[9] Jens Panse,[10,11] Iván Alvarez-Twose,[12] Deepti H. Radia,[13] Tsewang Tashi,[14] Cristina Bulai Livideanu,[15] Vito Sabato,[16] Paul Van Daele,[17] Sonia Cerquozzi,[18] Ingunn Dybedal,[19] Andreas Reiter,[20] Celalettin Ustun,[21] Philippe Schafhausen,[22] Prithviraj Bose,[23] Daniel J. DeAngelo,[24] Lindsay Rein,[25] Pankit Vachhani,[26] Massimo Triggiani,[27] Mark Rafferty,[28] Nauman M. Butt,[29] Stephen T. Oh,[30] Friederike Wortmann,[31] Johanna Ungerstedt,[32] Minakshi Taparia,[33] Andrew T. Kuykendall,[34] Cecilia Arana Yi,[35] Mattias Mattsson,[36] William Shomali,[1] Matthew P. Giannetti,[37] Ilda Bidollari,[38] Hui-Min Lin,[38] Robyn Scherber,[38] Maria Roché,[38] Cem Akin,[39**] Marcus Maurer[4,5**]

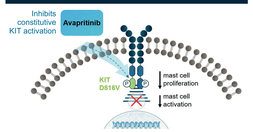
*Equally contributing first authors; **Equally contributing last authors

[1]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, USA; [2]Department of Medicine, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Department of Allergology, University Medical Center, Groningen Research Institute Asthma and COPD, University of Groningen, Groningen, The Netherlands; [4]Institute of Allergology, Charité–Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [5]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany; [6]Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland; [7]Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland; [8]Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark; [9]ARUP Laboratories, Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT, USA; [10]Department of Oncology, Hematology, Hemostaseology, and Stem Cell Transplantation, University Hospital Aachen, Medical Faculty, RWTH Aachen University, Aachen, Germany; [11]Center for Integrated Oncology (CIO), Aachen, Bonn, Cologne, Düsseldorf (ABCD), Aachen, Germany; [12]Institute of Mastocytosis Studies of Castilla-La Mancha, Virgen del Valle Hospital, Toledo, Spain; [13]Guy's & St Thomas' NHS Foundation Trust, London, UK; [14]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [15]Department of Dermatology, Expert Center of Mastocytosis (CEREMAST), Toulouse University Hospital, Toulouse, France; [16]Department of Immunology, Allergology and Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; [17]Department of Internal Medicine and Immunology, Erasmus Medical Center, Rotterdam, The Netherlands; [18]Department of Medicine, University of Calgary, Calgary, Alberta, Canada; [19]Department of Hematology, Oslo University Hospital, Oslo, Norway; [20]Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany; [21]Department of Internal Medicine, Division of Hematology, Oncology and Cell Therapy, Section of Bone Marrow Transplantation and Cellular Therapy, Rush Medical College Chicago, IL, USA; [22]Department of Oncology, Hematology, and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [23]Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [24]Dana-Farber Cancer Institute, Boston, MA, USA; [25]Department of Medicine, Duke University, School of Medicine, Durham, NC, USA; [26]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; [27]Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy; [28]The Beatson West of Scotland Cancer Centre, Glasgow, Scotland; [29]The Clatterbridge Cancer Centre, Bebington, Wirral, United Kingdom; [30]Sideman Cancer Center at Baptist Health Arkansas Children's Hospital and Washington University School of Medicine, Washington University Medical Campus, St. Louis, MO, USA; [31]Klinik für Hämatologie/Onkologie Campus Lübeck Universitätsklinikum Schleswig-Holstein Lübeck, Schleswig-Holstein, Germany; [32]H7 Department of Medicine, Huddinge, Karolinska University Hospitale, Stockholm, Sweden; [33]University of Alberta, Edmonton, Alberta, Canada; [34]Department of Malignant Hematology, H Lee Moffitt Cancer Center, Tampa, FL, USA; [35]Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, AZ, USA; [36]Department of Hematology, Uppsala University Hospital and Department of Immunology, Genetics and Pathology, Uppsala, Sweden; [37]Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Boston, MA, USA; [38]Blueprint Medicines Corporation, Cambridge, MA, USA; [39]University of Michigan, Ann Arbor, MI, USA.

Background

- Indolent systemic mastocytosis (ISM) is a clonal mast cell disease driven by the *KIT* D816V mutation in approximately 95% of adult cases[1–3]
- The *KIT* D816V mutation may lead to the uncontrolled proliferation and hyper-activation of aberrant mast cells[1-3]
- Patients with ISM often experience life-long debilitating skin, gastrointestinal, neurocognitive, cardiovascular, musculoskeletal, and systemic manifestations, including anaphylaxis. These symptoms commonly result in impaired daily functioning, ability to work, and poor quality of life (QoL)[4–8]
- For the management of these symptoms, most patients rely on polypharmacy with best supportive care (BSC) medications; however, symptoms are often not adequately controlled with BSC and until recently there were no approved therapies for the treatment of ISM which target KIT D816V[8–10]
- Avapritinib is an orally administered, potent, and highly selective inhibitor of KIT D816V with an IC_{50} of 0.27 nM in cellular assays (**Figure 1**)
  - Avapritinib is approved in the USA for adult patients with ISM, and advanced systemic mastocytosis (AdvSM) and in Europe for adult patients with AdvSM after ≥1 prior systemic therapy and has demonstrated rapid, deep, and durable responses in AdvSM[11–14]
  - Avapritinib is not recommended for patients with platelet counts <50x10^9/L
- Recently reported findings from the PIONEER trial (NCT03731260) showed patients with moderate to severe ISM treated with avapritinib achieved a significant reduction in biomarkers of mast cell burden, significant improvement in ISM-related symptoms, and an improved QoL[15]
- Here, we present expanded analyses demonstrating the impact of avapritinib *versus* placebo on measures of disease burden in patients with symptomatic ISM

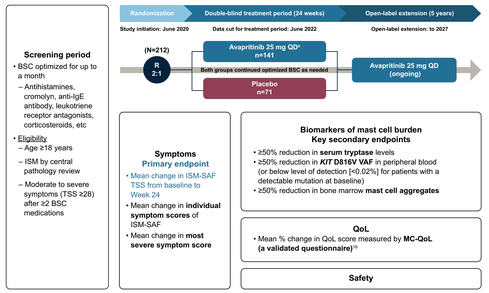
Figure 1. Avapritinib inhibits KIT D816V, the underlying driver of systemic mastocytosis



Methods

- PIONEER is a phase 2, multi-part, randomized, placebo-controlled, double-blind trial investigating avapritinib plus BSC in patients with symptomatic ISM. Primary and secondary endpoints are summarized in **Figure 2**
  - The primary endpoint measured by total symptom score (TSS) ranges from 0–110 based on severity of 11 ISM symptoms scored 0–10 daily (no symptom to worst imaginable) and analyzed as a 14-day moving average
- Additional analyses included reduction of serum tryptase to <20 ng/mL, reduction of *KIT* D816V variant allele fraction (VAF) to undetectable levels (<0.02%) , and clearance of bone marrow mast cell aggregates
- Quantification of mast cell infiltrates was performed by central pathology review and mast cell number and immunophenotype in bone marrow and skin biopsies were assessed via light microscopy and immunohistochemistry

Figure 2. Study design



*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.

BSC, best supportive care; 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.

Results

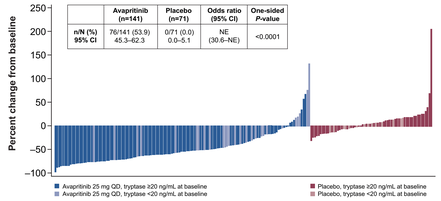
- As of June 23, 2022, 212 patients were enrolled in Part 2 of the PIONEER trial; 141 patients were randomized to avapritinib 25 mg QD and 71 patients were randomized to placebo. Baseline characteristics are summarized in **Table 1**

Table 1. Baseline characteristics

Patient demographic	Avapritinib 25 mg QD (n=141)	Placebo (n=71)
Age (years), median (range)	50.0 (18–77)	54.0 (26–79)
Female, n (%)	100 (70.9)	54 (76.1)
ISM symptom burden		
TSS, 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, ng/mL (range)[a]	38.4 (3.6–256.0)	43.7 (5.7–501.6)
Median bone marrow biopsy mast cells, % (range)[a]	7.0 (1.0–50.0)	7.0 (1.0–70.0)
Mast cell aggregates present, n (%)	106 (75.2)	57 (80.3)
Median *KIT* D816V VAF in peripheral blood, % (range)[b]	0.4 (0.02–41.3)	0.3 (0.02–36.7)
KIT D816V positivity, n (%)	131 (92.9)	69 (97.2)
QoL		
MC-QoL, mean (SD)	57.5 (16.0)	57.5 (17.2)
SM therapy[c]		
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)[c]	3 (0–11)	4 (1–8)

[a]A central laboratory tested serum tryptase and bone marrow mast cell burden. [b]The limit of detection was 0.02%. [c]Prior therapies included dasatinib, imatinib, masitinib, nilotinib, midostaurin, brentuximab vedotin, cladribine, hydroxyurea, rapamycin, and interferon alpha. Includes treatments received by patients at baseline; patients may have received BSC treatments previously that had been discontinued at the time of enrollment/baseline. [d]All patients had at least 2 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.
SD, standard deviation; SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor.

Figure 3. Avapritinib significantly reduced serum tryptase levels

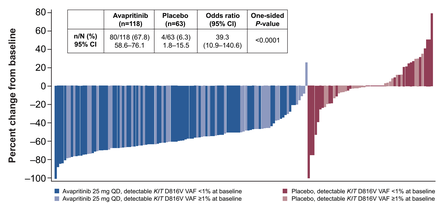


CI, confidence interval; NE, not evaluable.

Reductions in serum tryptase

- At Week 24, a significantly greater (*P*<0.0001) proportion of patients in the avapritinib group *versus* placebo group achieved ≥50% reduction in serum tryptase levels (54% [76/141] *versus* 0% [0/71]) (**Figure 3**)
- Reduction of serum tryptase to <20 ng/mL from ≥20 ng/mL at baseline was observed in 54% (58/107; <11.4 ng/mL, n=29; 11.4–<20 ng/mL, n=29) in the avapritinib group *versus* 2% (11.4–<20 ng/mL, n=1/50) in the placebo group

Figure 4. Avapritinib significantly reduced *KIT* D816V VAF

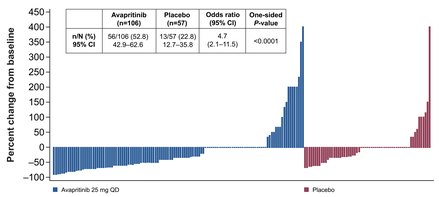


Reductions in KIT D816V VAF

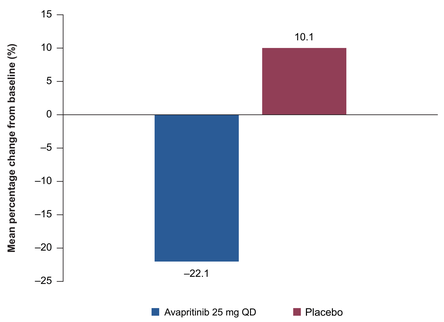
- At Week 24, a significantly greater (*P*<0.0001) proportion of patients in the avapritinib group *versus* placebo group achieved ≥50% reductions in *KIT* D816V VAF (68% [80/118] *versus* 6% [4/63]) (**Figure 4**)
- Of patients with detectable *KIT* D816V VAF at baseline, 11% (n=12/109) in the avapritinib group had undetectable *KIT* D816V VAF at 24 weeks *versus* 6% (n=3/54) in the placebo group

Figure 5. Avapritinib reduced mast cell burden in bone marrow and skin

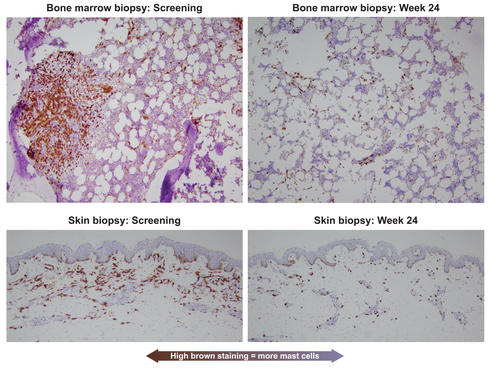
A. Bone marrow mast cell burden



B. Skin mast cell burden



C. Observed reduction in mast cell burden with avapritinib 25 mg QD evaluated by KIT (CD117) staining



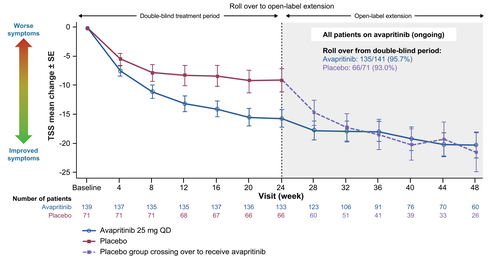
Brown staining indicated CD117 positivity.

Reductions of mast cells in bone marrow and skin

- At Week 24, a significantly greater (*P*<0.0001) proportion of patients in the avapritinib group *versus* placebo group achieved ≥50% reductions in bone marrow mast cell burden (53% [56/106] *versus* 23% [13/57]) (**Figure 5A**)
- Mean percent change of skin mast cell burden decreased at Week 24 with avapritinib but increased with placebo (**Figure 5B**)
- Reduction in mast cell burden was observed by pathological evaluations of KIT (CD117) in the bone marrow and skin (**Figure 5C**)
- Of patients with bone marrow mast cell aggregates at baseline, total clearance of bone marrow mast cell aggregates was 3 times more common in the avapritinib group than placebo (36% [n=33/91] *versus* 12% [n=6/50])
  - The 12% absence of bone marrow mast cell aggregates observed in the placebo group may be due to heterogeneity in the biopsy which has been previously reported in patients with ISM[17]

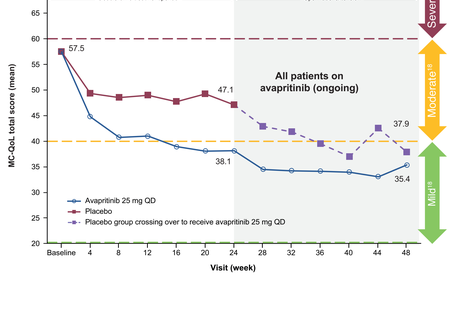
Figure 6. Patient-reported symptom burden and quality of life improved with avapritinib

A. TSS (mean change), ITT population Part 2 and Part 3



ITT, intent to treat. SE, standard error.

B. MC-QoL total score (mean), ITT population Part 2 and Part 3



Improvements in symptoms/quality of life

- Along with improvements in objective measures of disease burden, patients treated with avapritinib had improved symptoms and QoL
  - The avapritinib group had significantly greater mean change (95% CI) in TSS at 24 weeks *versus* placebo (–15.6 [–18.6, –12.6] *versus* –9.2 [–13.1, –5.2]; *P*=0.003) (**Figure 6A**)
  - In Part 3 (Week 48), a decrease in TSS was observed in patients who crossed over from placebo to avapritinib 25 mg QD (n=66)
- Greater improvement in QoL was observed in avapritinib-treated patients compared to those receiving placebo at Week 24 (*P*=0.001) and over time through Part 3 (**Figure 6B**)

Well tolerated safety profile

- Avapritinib was well tolerated with a safety profile similar to placebo (**Table 2**)
  - Majority of adverse events (AEs) were Grade 1 or 2 with a low rate of discontinuation
  - Serious AEs (SAEs) were reported more frequently in the placebo group (no treatment-related SAEs were observed in either group)
  - Edema AEs were higher in the avapritinib group (majority were Grade 1, and did not result in discontinuation)

Table 2. Summary of safety

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

[a]AEs refer to treatment-emergent AEs, 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 30days after the last dose of study drug. [b]There were too few events (2 events in avapritinib group and 3 event in placebo group) to assess the impact of avapritinib on anaphylaxis.
AEs, adverse events; SAEs, serious adverse events; TRAEs, treatment-related adverse events.

Conclusions

- In patients with ISM, avapritinib treatment provided rapid, durable, and clinically meaningful improvements in objective measures of disease burden
  - Patients with ISM who received avapritinib were more likely to experience normalization of disease burden measures with avapritinib than placebo
- ISM symptoms and patient QoL were improved with avapritinib *versus* placebo
- Avapritinib was well tolerated with a safety profile similar to placebo
- These results suggest avapritinib may represent a potentially disease-modifying therapy for patients with ISM

References

1. Kristensen T et al. *J Mol Diagn*. 2011;13:180–188; 2. Cohen SS et al. *Br J Haematol*. 2014;166:521–528; 3. Arber DA et al. *Blood*. 2022;140:1200–1228; 4. Mesa RA et al. *Cancer*. 2022;128:3691–3699; 5. Hermine O et al. *PLoS One*. 2008;3:e2266; 6. van Anrooij B et al. *Allergy*. 2016;71:1585–1593; 7. Hartmann K et al. *J Allergy Clin Immunol*. 2016;137:35–45; 8. Akin C et al. *J Allergy Clin Immunol*. 2022;149:1912–1918; 9. Pardanani A. *Blood*. 2013;121:3085–3094; 10. Pardanani A. *Am J Hematol*. 2021;96: 508–525; 11. DeAngelo D et al. *Nat Med*. 2021;27:2183–2191; 12. Gotlib J et al. *Nat Med*. 2021;27:2192–2199; 13. AYVAKIT® (avapritinib). Prescribing Information. May 2023. Blueprint Medicines Corporation; 14. AYVAKIT® (avapritinib). Summary of Product Characteristics. 2023. Blueprint Medicines Corporation; 15. Castells M et al. *J Allergy Clin Immunol*. 2023;151:AB204; 16. Siebenhaar F et al. *Allergy*. 2016;71(6): 869–877; 17. Butterfield J et al. *Am J Clin Pathol*. 2004;121:264–267;18. Pulfer S et al. *J Allergy Clin Immunol Pract*. 2021;9:3166–3175.e2

Acknowledgements

Medical writing support was provided by Danielle Scheunemann, MS, and editorial support was provided by Travis Taylor, BA, all of Paragon, Knutsford, UK, supported by Blueprint Medicines Corporation, Cambridge, MA, according to Good Publication Practice guidelines.

Figures 2 and 6 were adapted from *NEJM Evidence*, Gotlib J et al, Avapritinib versus Placebo in Indolent Systemic Mastocytosis, Volume 2 No. 6. Copyright © 2023 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Disclosures

This research was funded by Blueprint Medicines Corporation. Blueprint Medicines Corporation reviewed and provided feedback on the poster. The authors had full editorial control of the poster and provided their final approval of all content. Dr Gotlib is the Chair of the Response Adjudication Committee, has received research funding, served on advisory boards, and received honoraria and funding to cover travel expenses from Blueprint Medicines Corporation. Dr Gotlib has received research funding, is the co-chair of the Study Steering Committee, and has honoraria for these roles and serves on advisory boards for Deciphera. Full disclosures for all authors are available upon request at medinfo@blueprintmedicines.com.

SCAN ME