Efficacy and Safety of Avapritinib in Indolent Systemic Mastocytosis: Results From the Double Blinded Placebo-Controlled PIONEER Study

Poster Number S7

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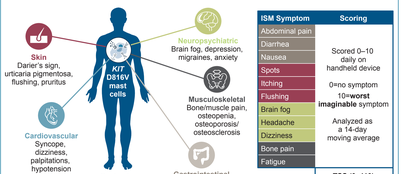
Background

- Indolent systemic mastocytosis (ISM) is a clonal mast-cell disease driven by the *KIT* D816V mutation in ~95% of adult cases[1–3]
- Patients with ISM often experience life-long debilitating skin, gastrointestinal, neurocognitive, musculoskeletal, and systemic manifestations, including anaphylaxis (**Figure 1**). These symptoms commonly result in impaired daily functioning and poor quality of life (QoL)[4–9]
- Most patients rely on polypharmacy for the management of symptoms with best supportive care (BSC) medications; however, many patients' symptoms are not adequately controlled with these medications and until recently there were no approved therapies that target the KIT D816V-mutated tyrosine kinase in ISM[5,10,11]
- Avapritinib is a potent and highly selective oral therapy targeting KIT D816V, the underlying driver of systemic mastocytosis (**Figure 2**)[12,13]
  - Avapritinib demonstrated reductions in mast-cell burden biomarkers and an improvement in all advanced systemic mastocytosis (AdvSM) symptoms, including skin manifestations and QoL measurements[12–14]
  - In addition, avapritinib demonstrated significantly better survival benefit *versus* best available therapy (including midostaurin and cladribine) in a retrospective real-world analysis[15,16]
- Avapritinib is approved in the USA for adult patients with AdvSM and in Europe for adult patients with AdvSM after ≥1 prior systemic therapy; avapritinib is not recommended for patients with platelet counts <50x10⁹/L[17,18]
- Avapritinib is approved in the USA for adult patients with ISM; avapritinib is not recommended for patients with platelet counts <50x10⁹/L[17]
- PIONEER (NCT03731260), a randomized, double-blind, placebo-controlled trial, evaluated avapritinib 25 mg once daily (QD) plus BSC (avapritinib) compared to placebo plus BSC (placebo) in patients with ISM with uncontrolled moderate to severe symptoms. Primary and secondary endpoints are summarized in **Figure 3**
- Here, we present key efficacy and safety data from Part 2 of the PIONEER trial

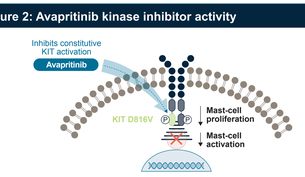
Figure 1: ISM symptoms[4–9] assessed by the validated ISM-SAF[a]



ISM Symptom	Scoring
Abdominal pain	Scored 0–10 daily on handheld device 0=no symptom 10=**worst imaginable** symptom Analyzed as a 14-day moving average **TSS (0–110) Higher scores represent more severe symptoms**
Diarrhea	
Nausea	
Spots	
Itching	
Flushing	
Brain fog	
Headache	
Dizziness	
Bone pain	
Fatigue	

[a]ISM-SAF is a validated symptom assessment tool specifically developed for evaluation of ISM symptomology.[19–21]
ISM, indolent systemic mastocytosis; ISM-SAF, indolent systemic mastocytosis Symptom Assessment Form; TSS, total symptom score.

Figure 2: Avapritinib kinase inhibitor activity



Highly selective kinome profile

Potently and selectively inhibits the autophosphorylation of KIT D816V, with an IC_{50} of 0.27 nM in selective cellular assays[22]

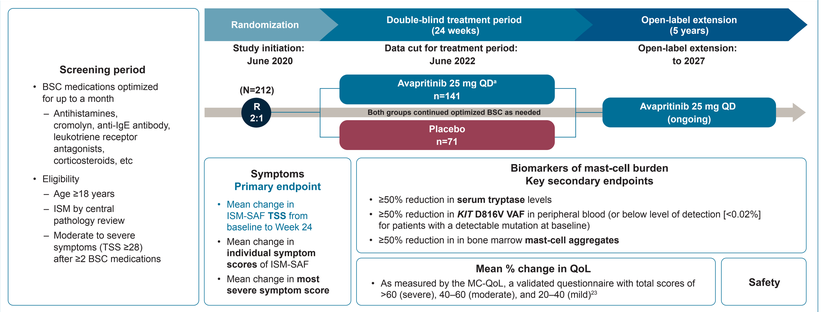
Biochemical IC_{50} (nM)

	KIT D816V	KIT wild type
Avapritinib	0.27	73

IC_{50}, half maximal inhibitory concentration; nM, nanomolar.

Methods

Figure 3: Study design



[a]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 four 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; IgE, immunoglobulin E; MC-QoL, Mastocytosis Quality of Life Questionnaire; QD, once daily; QoL, quality of life; R, randomized; VAF, variant allele fraction.

Results

- Baseline characteristics are described in **Table 1**
- More than 70% (n=167) of PIONEER patients had skin involvement at baseline; the patient population with skin biopsies at baseline had similar baseline characteristics to the intent-to-treat population (**data not shown**)

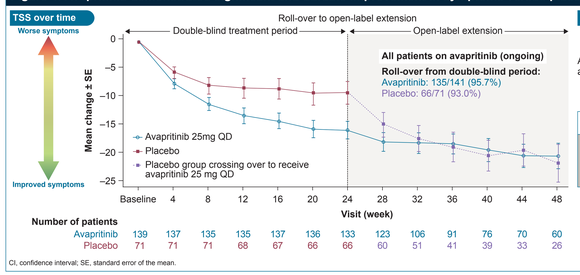
Improvements in TSS

- Avapritinib demonstrated significantly greater improvement in mean TSS (95% confidence interval [CI]) at 24 weeks *versus* placebo (–15.6 [–18.6 to –12.6] *vs* –9.2 [–13.1 to –5.2]; *P*=0.003) (**Figure 4**)
- A total of 66 patients crossed over from placebo to avapritinib in Part 3 and improvements in TSS were observed; in the 26 patients who completed an additional 24 weeks of treatment, the mean (95% CI) change in TSS was –21.4 (–28.0 to –14.9) at 48 weeks

Improvements in symptoms

- At 24 weeks, avapritinib demonstrated improvement in all individual ISM symptoms *versus* placebo, including the most severe symptom at baseline (**Figure 5**)
  - Regardless of which symptom was rated most severe at baseline, avapritinib patients had a notable reduction in this *versus* placebo
- In the majority of patients, the most severe symptom domain at baseline was the skin domain
  - At 24 weeks, in patients with skin disease, mean standard deviation (SD) change in skin domain was greater with avapritinib (n=107; –7.2 [6.4]) *vs* placebo (n=60; –2.8 [4.2]), *P*<0.0001; avapritinib *versus* placebo also improved spots (–2.3 [2.1] *vs* –0.6 [1.5]; *P*<0.0001), itching (–2.6 [2.8] *vs* –1.2 [2.0]; *P*<0.001), and flushing (–2.2 [2.6] *vs* –1.0 [1.9]; *P*<0.001)

Figure 4: Avapritinib demonstrated significant and durable improvement in symptoms *versus* placebo



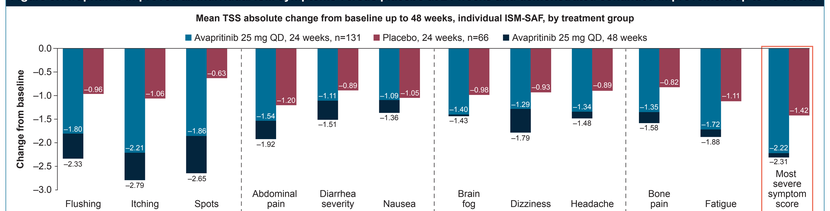
Primary endpoint

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

At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	*P*-value
Mean change in TSS (95% CI)	–15.58 (–18.61 to –12.55)	–9.15 (–13.12 to –5.18)	0.003

CI, confidence interval; SE, standard error of the mean.

Figure 5: Avapritinib improved all individual ISM symptoms *versus* placebo at 24 weeks and demonstrated continued improvement up to 48 weeks



At Week 24	Avapritinib 25 mg QD (n=131)	Placebo (n=66)	*P*-value
Mean change in most severe symptom score (SD)	–2.22 (2.30)	–1.42 (1.88)	0.015

SD, standard deviation.

- At 48 weeks, continued improvement was observed in all individual symptoms among avapritinib-treated patients (**Figure 5**)

Reductions in measures of mast-cell burden

- At Week 24, a significantly greater proportion of avapritinib-treated patients achieved ≥50% reductions in measures of mast-cell burden, including:
  - Serum tryptase levels (54% [95% CI, 45 to 62] *vs* 0% [0 to 5], *P*<0.0001; **Figure 6A**)
  - Bone marrow mast-cell burden (53% [95% CI, 43 to 63], *vs* 23% [13 to 36]; *P*<0.0001)
  - *KIT* D816V VAF (68% [95% CI, 59 to 76], *vs* 6% [2 to 16]; *P*<0.0001; **Figure 6B**)

Figure 6: Rapid and sustained reductions in biomarkers of mast-cell burden were observed in avapritinib-treated patients *versus* placebo

Key secondary endpoints

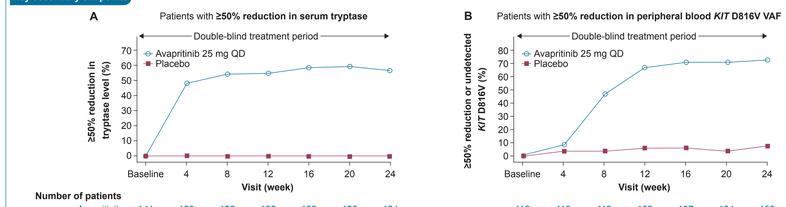
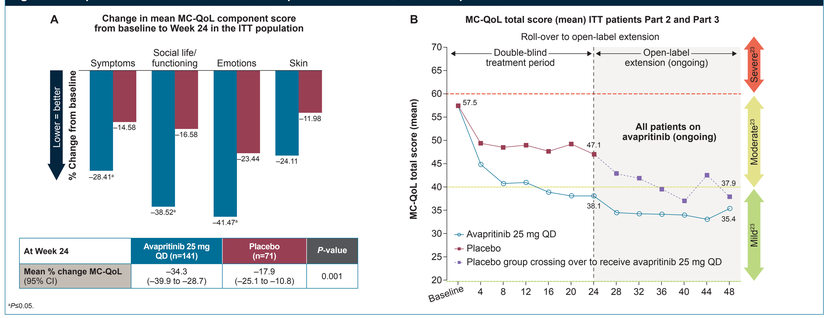


Table 1: Baseline patient demographics and characteristics

	ITT population (N=212)	
Patient demographics	**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 score, mean (SD)[a,b]	**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 *KIT* D816V VAF in peripheral blood, % (range)[c]	**0.4** (0.02–41.3)	**0.3** (0.02–36.7)
SM Therapy		
Prior cytoreductive therapy, n (%)[d]	**19** (13.5)	**7** (9.9)
Prior TKI therapy, n (%)	**10** (7.1)	**4** (5.6)
BSC use		
Number of BSC treatments, median (range)[e]	**3** (0–11)	**4** (1–8)

[a]Eligibility for enrollment was based on TSS ≥28 at screening; patients may have a score <28 at baseline. [b]Two patients in the avapritinib group had missing baseline TSS values; therefore, the denominator was based on patients with available data at baseline (n=139). [c]The limit of detection was 0.02%. [d]Cytoreductive therapies included dasatinib, imatinib, masitinib, 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. [e]All patients had at least two BSC prior to or at screening. A total of 10 (7.1%) patients treated with avapritinib and five (7.0%) patients treated with placebo had <2 BSC at the start of the study.
Note: A total of 72.3% of patients on avapritinib and 74.6% of patients receiving the placebo had PI-assessed skin involvement.
ITT, intent-to-treat; PI, principal investigator; TKI, tyrosine kinase inhibitor.

Figure 7: Avapritinib demonstrated sustained improvement in MC-QoL *versus* placebo



At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	*P*-value
Mean % change MC-QoL (95% CI)	–34.3 (–39.9 to –28.7)	–17.9 (–25.1 to –10.8)	0.001

*Ps0.05.

Improvement in QoL

- MC-QoL scores showed greater improvement with avapritinib *versus* placebo across domains (**Figure 7A**)
- Improvement in MC-QoL mean total score (SD) was greater with avapritinib (57.5 [16.0] to 38.1 [21.6]) *vs* placebo (57.5 [17.2] to 47.1 [20.9]), respectively, at baseline to Week 24 and overtime through to Week 48 (**Figure 7B**)

Well tolerated safety profile

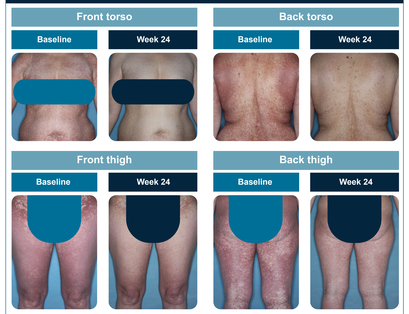
- Avapritinib was well tolerated, with a safety profile similar to placebo (**Table 2**):
  - Majority of adverse events (AEs) were Grade 1 or 2 with a low rate of discontinuation (~1% in both arms)
  - Serious adverse events (SAEs) were reported more frequently in the placebo group (no treatment-related SAEs in either group)
  - Edema AEs were higher in the avapritinib group (majority Grade 1, and did not result in discontinuation)
- In case studies, where photos of patient's skin lesions were assessed, area and color of skin lesions were shown to improve at Week 24 with avapritinib treatment (**Figure 8**)

Table 2: Summary of adverse events

	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[c]	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 at any group)		
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 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 (2 events in the avapritinib group and 3 events in the placebo group) to assess the impact of avapritinib on anaphylaxis [c]TRAEs refer to treatment-related AEs as assessed by investigators.
AEs, adverse events; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

Figure 8: Case study



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Conclusions

- By selectively targeting KIT D816V, the underlying driver of ISM, avapritinib treatment provided significant and clinically meaningful improvements in mast-cell burden, symptoms, and QoL compared with placebo
- Of the patients with skin involvement, those treated with avapritinib experienced marked reductions in skin symptoms, skin color, and surface area of skin lesions
- Avapritinib treatment was well tolerated, with a similar safety profile to placebo
- Avapritinib treatment offers a promising new treatment option for patients with ISM

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Disclosures

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