Avapritinib Achieves Deep and Durable Symptom Control With a Well-Tolerated Safety Profile in ISM: Long-Term Outcomes From PIONEER

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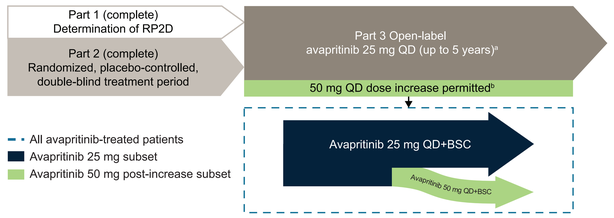
Introduction

- Indolent systemic mastocytosis (ISM) is a chronic clonal mast cell disease primarily driven by the *KIT* D816V mutation in ~95% of cases,[1,2] and is associated with symptoms of mast cell activation and tissue infiltration. ISM can cause a broad spectrum of debilitating cutaneous, gastrointestinal, neurological, and musculoskeletal symptoms that can lead to life-threatening anaphylaxis, poor quality-of-life (QoL), and significant morbidity[3–6]
- The prevalence of systemic mastocytosis (SM) has been estimated at up to 1 in 5,000 people[7–10]
- Historically, most SM patients have relied on symptom-directed best supportive care (BSC) medications that do not treat the underlying driver of ISM
- PIONEER (NCT03731260) is a randomized, double-blind, three-part trial examining the efficacy and safety of avapritinib, an oral, potent, and selective KIT D816V inhibitor, as a treatment for patients with ISM[11,12]
- In the placebo-controlled portion of PIONEER, patients treated with avapritinib showed rapid, durable, and clinically meaningful improvements in QoL and the breadth of ISM symptoms *versus* placebo through 24 weeks of treatment. After 6 months of blinded therapy, the safety profile of avapritinib was comparable to placebo, with the exception of higher rates of low-grade edema, flushing, and insomnia[11–13]
  - From baseline to Week 24 of treatment patients receiving avapritinib experienced significant improvement in the ISM-Symptom Assessment Form Total Symptom Score (ISM-SAF TSS) *versus* patients receiving placebo (–15.6 points vs –9.2; P=0.003)[12]
- Based on these outcomes, avapritinib, was approved at 25 mg once daily (QD) for treatment of adults with ISM in the USA and in patients with moderate-to-severe symptoms in the EU[14,15]
- Given the chronic nature of ISM, data on the long-term safety and efficacy of avapritinib are needed
- Here we present extended avapritinib findings from PIONEER through a median follow-up of 40 months

Figure 1. Study design



[a]n=226, includes patients from Part 1 who continued avapritinib 25 mg QD or crossed over from placebo to avapritinib 25 mg QD. This also includes patients from Part 2 who received avapritinib 25 mg QD or who crossed over from placebo to avapritinib 25 mg. [b]Patients could dose increase to 50 mg QD in Part 3.
BSC, best supportive care; QD, once daily; RP2D, recommended Part 2 dose.

Methods

- Patients with moderate-to-severe ISM symptoms who completed the randomized dose-finding (Part 1), or randomized, double-blind, placebo-controlled (Part 2) portions of PIONEER rolled over to the open-label, long-term extension (Part 3) with up to 5-year follow-up (**Figure 1**)
- Across all parts of the study, 226 patients initiated avapritinib therapy at 25 mg QD + BSC; the long-term efficacy and safety of avapritinib in this group of patients, as assessed by changes in symptoms and QoL, is presented
  - Symptoms were assessed using the ISM-SAF (©2018 Blueprint Medicines Corporation), a validated symptom assessment tool specifically developed for evaluation of ISM symptomology based on self-reported severity of 11 ISM symptoms; scores range from 0–110, with moderate to severe defined as TSS ≥28[16]
  - QoL was assessed using the Mastocytosis Quality-of-Life Questionnaire (MC-QoL), on which scores range from 0–100, where 100 is worst QoL impairment[17,18]
- Long-term efficacy data and cumulative long-term safety from initiation of avapritinib at 25 mg QD are presented up to the data cut-off date of February 21, 2025
  - Safety was evaluated by the rate of adverse events (AEs); relatedness of AEs was determined by the treating clinician
- Per investigator discretion, for patients with an increase in symptoms and markers of mast cell burden, a dose increase up to 50 mg QD of avapritinib was permitted in Part 3
- Analyses were conducted in three patient groups:
  1. **All avapritinib-treated patients:** All patients who initiated avapritinib 25 mg QD including those who dose increased to 50 mg in Part 3
  2. **Avapritinib 25 mg subset:** The same population as (1), but excluding data post-dose increase in the subset of patients who dose escalated to avapritinib 50 mg QD
  3. **Avapritinib 50 mg post-increase subset:** The subset of patients who dose increased to 50 mg QD, using the time of dose escalation as baseline

Results

Patient demographics

- A total of 226 patients started avapritinib 25 mg QD treatment in Parts 1, 2, or 3 (**Table 1**)
- The median duration of treatment (range) was 40.0 (0.7–67.2) months

Table 1. Baseline demographics

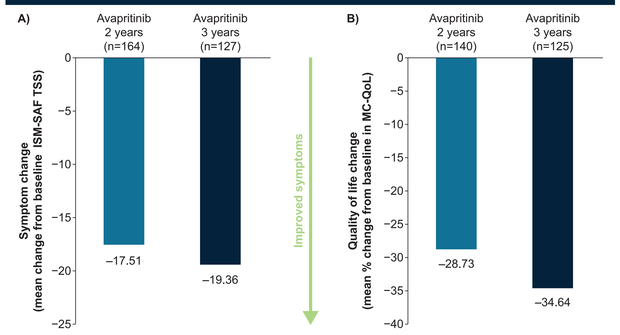
Patient demographic	Avapritinib 25 mg QD (n=226)
Age (years), median (range)	51 (18–79)
Female, n (%)	166 (73)
Baseline BMI (kg/m²), median (range)	28.1 (17.6–51.4)
ISM symptom burden	
Baseline ISM-SAF TSS, mean (SD)	48.1 (19.5)
Mast cell burden	
Median (range) serum tryptase (central), ng/mL	39.2 (3.6–590.4)
Median (range) bone marrow biopsy mast cells (central), %	7.0 (1.0–60.0)
Median (range) *KIT* D816V VAF in peripheral blood[a], %	0.39 (undetectable–41.29)

[a]Digital droplet PCR was used to measure *KIT* D816V VAF.
BMI, body mass index; ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis - Symptom Assessment Form; PCR, polymerase chain reaction; SD, standard deviation; TSS, total symptom score; VAF, variant allele frequency.

All avapritinib-treated patients

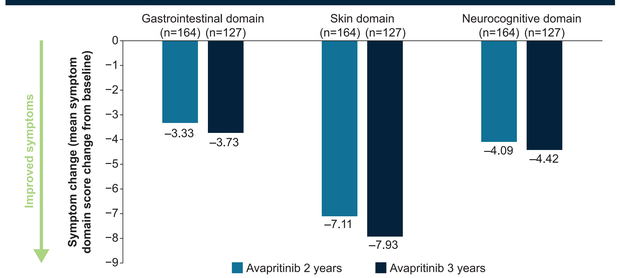
- Longer-term efficacy data with median ~40 months of follow-up demonstrates durable improvements in overall symptoms and QoL per MC-QoL
  - The mean change (standard deviation [SD]) in ISM-SAF TSS was –17.51 (22.25) at Week 96 (henceforth known as 2 years) and –19.39 (20.06) at 156 weeks (henceforth known as 3 years) (**Figure 2A**)
  - The mean percentage change (SD) from baseline in MC-QoL was –28.73 (53.29) at 2 years and –34.64 (35.75) at 3 years in all avapritinib-treated patients (**Figure 2B**)
- Continued responses were seen in all symptom domains and the most severe symptom in all avapritinib-treated patients (**Figure 3**)
  - The mean change (SD) from baseline in most severe symptom score was –3.02 (3.02) at 2 years and –3.31 (3.11) at 3 years

Figure 2. Longer-term efficacy for A) ISM-SAF TSS and B) MC-QoL in all avapritinib-treated patients at 2 and 3 years



MC-QoL, Mastocytosis Quality-of-Life Questionnaire.

Figure 3. Longer-term efficacy for ISM-SAF symptom domains in all avapritinib-treated patients at 2 and 3 years



Avapritinib 25 mg subset

- The majority of patients remained on avapritinib 25 mg, with a median duration of treatment (range) of 37.1 months (0.7–67.2) in the avapritinib 25 mg subset
- Longer follow-up showed continued responses in symptoms and QoL measures with durable improvements in ISM-SAF TSS and MC-QoL
  - The mean change in ISM-SAF TSS was –17.89 (SD 21.89; n=154) at 2 years and –20.27 (SD 18.87; n=98) at 3 years
  - The mean percentage change from baseline in MC-QoL was –28.02 (SD 54.18; n=133) at 2 years and –38.20 (SD 35.40; n=95) at 3 years

Safety

- The safety profile of avapritinib remained consistent with the previously reported placebo-controlled portion with no new safety concerns observed with longer-term median follow-up of three years (**Table 2**)
- Consistent with the placebo-controlled portion of the study, Grade ≥3 treatment-related adverse events (TRAEs) in Part 3 remained low
- Discontinuations due to TRAEs remained limited, occurring in seven patients (3%)
- The most frequently reported adverse events (AEs) associated with treatment were edema events, with the majority being Grade 1
- The rate of cognitive AEs was similar to placebo in the placebo-controlled portion of the study; these events remained low with longer exposure (8% treatment-emergent AE [TEAE], 3% TRAE; all TRAEs were Grade 1–2)
- No intracranial bleeds were observed
- Avapritinib was not associated with an increased risk of liver injury, with a limited number of patients experiencing AEs of increased transaminase (pooled term); 9% TEAE, 4% TRAE, all TRAEs were Grade 1 or 2
- The rates of TRAE hair color changes and altered taste (pooled term) were low (4% and 1%, respectively), indicative of the selectivity of avapritinib for the *KIT* D816V mutation over wild-type *KIT*

Table 2. Safety profile of avapritinib

	Part 2[a]		Parts 1, 2, 3 combined[b]
	Avapritinib 25 mg QD + BSC (n=141)	Placebo + BSC (n=71)	All avapritinib-treated patients (N=226)
Median length of follow-up (months)	5.6	5.6	40.0
Any AEs, n (%)	128 (91)	66 (93)	224 (99)
Any TRAEs, n (%)	77 (55)	32 (45)	170 (75)
Grade ≥3 AEs	30 (21)	15 (21)	108 (48)[c]
Grade ≥3 TRAEs	3 (2)	2 (3)	15 (7)
Serious adverse events	7 (5)	8 (11)	47 (21)
Serious TRAEs	0 (0)	0 (0)	3 (1)[d]
TRAEs leading to discontinuation	2 (1)	1 (1)	7 (3)
Most common TRAEs (≥5% of patients), n (%)			
Peripheral edema	9 (6)	1 (1)	30 (13)
Periorbital edema	9 (6)	2 (3)	23 (10)
Headache	11 (8)	7 (10)	22 (10)
Nausea	9 (6)	6 (8)	19 (8)
Fatigue	6 (4)	2 (3)	16 (7)
Diarrhea	4 (3)	2 (3)	15 (7)
Alopecia	5 (4)	3 (4)	13 (6)

[a]Data cut June 23, 2022. [b]Data cut February 21, 2025. [c]One death (Grade 5 AE) occurred during the study and was unrelated to treatment; the patient had a medical history of anaphylaxis and atrial fibrillation, and the event was assessed as due to anaphylaxis in the context of atrial fibrillation. [d]Serious TRAEs included transient loss of vision (1), gastric hemorrhage (1), and peripheral edema (1). None of these events led to discontinuation.
AEs, adverse events; TRAEs, treatment-related adverse events.

Avapritinib 50 mg post-dose increase subset

- Sixty-five patients (29%) who received avapritinib 25 mg QD in PIONEER increased up to 50 mg QD in the open-label extension
- The median time to dose increase (range) was 28.4 months (11.3–50.3)
- Patients who dose increased had a higher *KIT* D816V VAF and higher symptom burden at the beginning of avapritinib treatment compared with patients who remained on 25 mg (**Table 3**)

Table 3. Baseline demographics

Patient demographic[a]	Patients who did not dose increase (n=161)	Patients who did dose increase (n=65)[b]	P-values
Age (years), median (range)	51 (18–77)	50 (22–79)	0.3966
Female, n (%)	116 (72)	50 (77)	0.5083
ISM symptom burden			
Baseline ISM-SAF TSS, mean (SD)	46.2 (19.0)	52.6 (19.9)	0.0266
Mast cell burden			
Median (range) serum tryptase (central), ng/mL	38.8 (3.6–284.0)	41.6 (5.5–590.4)	0.4037
Median (range) bone marrow biopsy mast cells (central), %	7.0 (1.0–50.0)	10.0 (2.0–60.0)	0.0519
Median (range) *KIT* D816V VAF in peripheral blood[c], %	0.23 (undetectable–29.18)	0.60 (undetectable–41.29)	0.0076

[a]Data represent baseline values at initiation of avapritinib 25 mg QD. [b]The avapritinib 50 mg QD post increase subset. [c]Digital droplet PCR was used to measure *KIT* D816V VAF.

- After 24 weeks of avapritinib 50 mg QD, 36 out of 42 patients with available ISM-SAF TSS data at the 24-week timepoint experienced stable-to-improved TSS (33 with improvement in ISM-SAF TSS, three with stable TSS; where stable is defined as 0–10% increase in TSS)
- After 24 weeks of avapritinib 50 mg QD, 34 out of 39 patients with available MC-QoL data at the 24-week timepoint had stable-to-improved MC-QoL (32 with improvement in MC-QoL, two with stable MC-QoL; where stable is defined as 0–10% increase in MC-QoL)

Table 4. Safety profile of patients receiving 50 mg QD avapritinib

	50 mg dose increase (n=65)
Median time on avapritinib 50 mg QD (range), months	12.3 (0.1–30.3)
Any AEs, n (%)	50 (77)
Any treatment-related AEs, n (%)	23 (35)
Grade ≥3 AEs	10 (15)
Grade ≥3 treatment-related AEs	1 (2)[a]
Serious AEs	7 (11)
Treatment-related serious AEs	0

Includes only new, recurrent, or worsening AEs after initiation of 50 mg QD avapritinib.
[a]One event (Grade 3) of weight increase.

- The safety profile at 50 mg was similar to the overall safety population with no new safety concerns observed (**Table 4**)
- The only new, recurrent or worsening TRAE that was observed at 50 mg QD in ≥5% patients was peripheral edema
- No patients discontinued treatment due to AEs after receiving 50 mg QD

Conclusions

- Patients with ISM can suffer from a wide range of debilitating symptoms often not adequately controlled by BSC medications
- With over 200 patients, PIONEER is the first and largest, randomized, double-blind, placebo-controlled trial of a highly selective KIT D816V-targeting agent in patients with ISM and led to FDA and EMA approval of avapritinib for the treatment of this disease
- Avapritinib robustly reduces disease-related symptoms and achieves durable improvements in QoL after a median of over 3 years of follow-up
- Avapritinib was well-tolerated at doses of 25 mg QD and 50 mg QD, with no new safety concerns identified at either dose
- Avapritinib is an effective and well-tolerated therapeutic option with a favorable longer-term benefit-risk ratio across the spectrum of disease seen in patients with ISM

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Conflicts of interest/disclosures

Dr Tashi has served on advisory board for Blueprint Medicines Corporation and PharmaEssentia. He is a principal investigator on several clinical trials for Blueprint Medicines Corporation, including PIONEER. For full author disclosures, please contact medinfo@blueprintmedicines.com.

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