Avapritinib Continues to Demonstrate Durable Symptom Control With a Well-Tolerated Safety Profile: Long-term Outcomes From PIONEER

Poster Number 509

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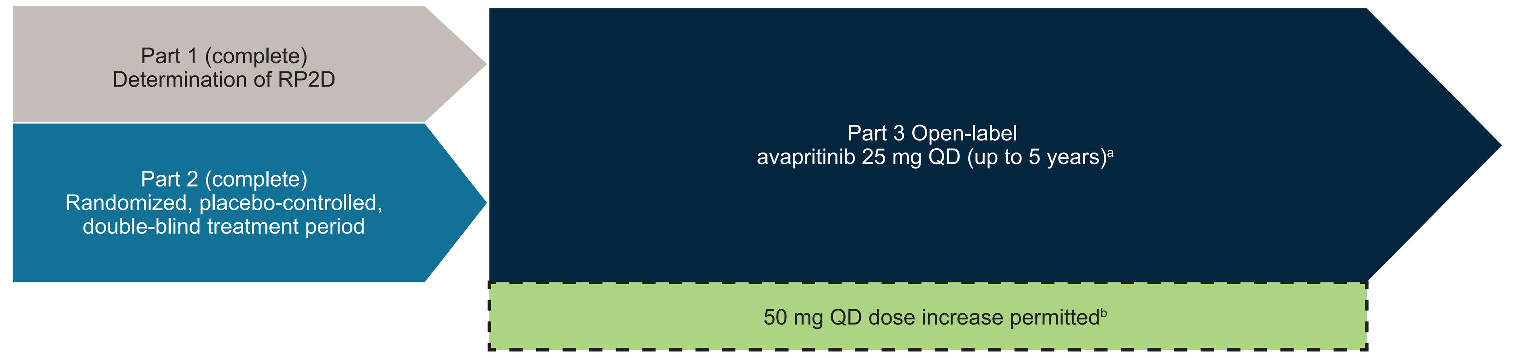
Introduction

- Indolent systemic mastocytosis (ISM) is a chronic clonal mast cell disease primarily driven by the *KIT* D816V mutation in ~95% of cases,[1–4] and is associated with symptoms of mast cell activation and tissue infiltration. ISM can cause debilitating cutaneous, gastrointestinal, neurologic, musculoskeletal, and cardiorespiratory symptoms which can lead to life-threatening anaphylaxis, poor quality-of-life (QoL), and significant morbidity[4–7]
- The prevalence of systemic mastocytosis has been estimated at up to 1 in 5,000 people[8–11]
- Historically, most patients have relied on symptom-directed medications, which 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, a potent and selective KIT D816V inhibitor, as a treatment for patients with ISM
- In Part 2, the placebo-controlled portion of PIONEER, patients treated with avapritinib showed rapid, durable, and clinically meaningful improvements in ISM symptoms and QoL *versus* placebo through 24 weeks of treatment, and avapritinib was well-tolerated with a safety profile similar to placebo[12–14]
- Based on these outcomes, avapritinib was approved at 25 mg once daily (QD) in adult patients with ISM in the USA and in patients with moderate-to-severe ISM in the EU[15,16]
- Here, we present extended findings with avapritinib from PIONEER through median ~4 years of treatment

Methods

Figure 1. Study design



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

- 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 years follow-up (**Figure 1**)
- Across all parts of the study, 226 patients initiated avapritinib therapy at 25 mg QD + best supportive care
- 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 September 17, 2025
  - Symptoms were assessed using the ISM-Symptom Assessment Form (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 total symptom score (TSS) ≥28[17]
  - 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[18,19]
  - Safety was evaluated by the rate and severity of adverse events (AEs); relatedness of AEs was determined by the treating clinician
- Per investigator discretion, for patients with an increase in symptoms and biomarkers of mast cell burden, a dose increase to 50 mg QD of avapritinib was permitted in Part 3
- Analyses were conducted in two 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 50 mg post-increase subset**: The subset of patients who dose increased to 50 mg QD, using the time of dose escalation in Part 3 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 46.5 (0.7–67.2) months

Table 1. Baseline demographics

Patient demographic	Avapritinib 25 mg QD (n=226)
Age (years), median (range)[a]	51.0 (18–79)
Female, n (%)	166 (73)
Baseline BMI (kg/m²), median (range)[b]	28.1 (17.6–51.4)
ISM symptom burden	
Baseline ISM-SAF TSS, mean (SD)[b]	48.1 (19.5)
Mast cell burden[b]	
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[c], %	0.39 (undetectable–41.3)

[a]Age at the time of informed consent. [b]Baseline is based on the last observations prior to the first administration of avapritinib in the study. [c]Digital droplet PCR was used to measure *KIT* D816V VAF.
BMI, body mass index; ISM, indolent systemic mastocytosis; ISM-SAF, ISM-symptom assessment form; SD, standard deviation; TSS, total symptom score; VAF, variant allele frequency.

All avapritinib-treated patients

Efficacy

- Longer-term efficacy data with a median ~4 years of treatment demonstrate durable, sustained improvements in overall symptoms and QoL
- The mean change (standard deviation [SD]) in ISM-SAF TSS was –17.66 (19.32) at Week 48 (henceforth 1 year) and –17.66 (19.07) at Week 204 (henceforth 4 years), in all patients treated with avapritinib (**Figure 2A**)
  - Continued responses were seen in all ISM-SAF symptom domains (**Figure 2B**) and most severe symptom (**Figure 3**) in all patients treated with avapritinib
- The mean percentage change (SD) from baseline in MC-QoL was −30.96 (37.48) at 1 year, and –35.41 (35.71) at 4 years in all patients treated with avapritinib

Figure 2. Longer-term efficacy for ISM-SAF TSS (A) and symptom domains (B) in all patients treated with avapritinib at 1 year and 4 years

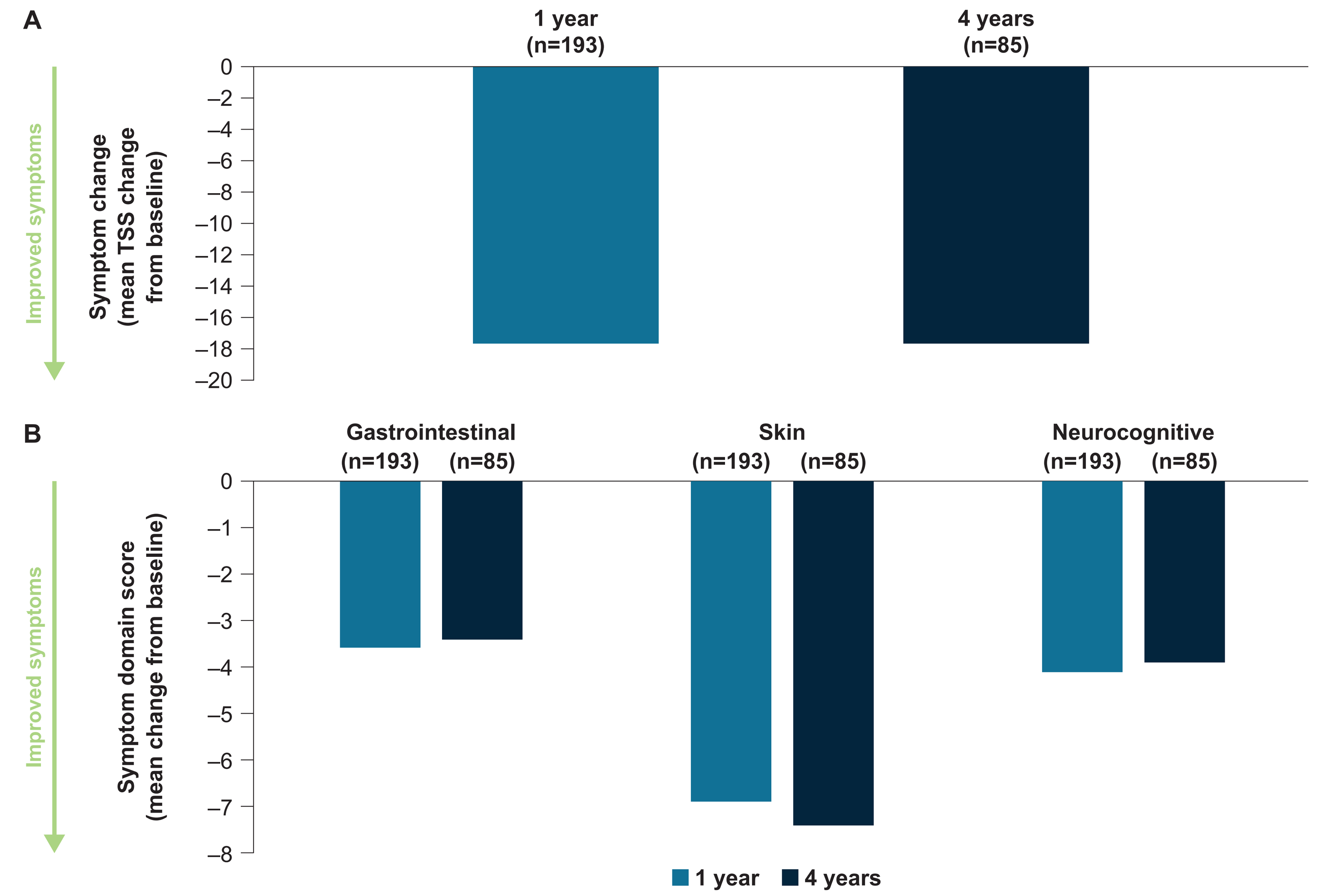
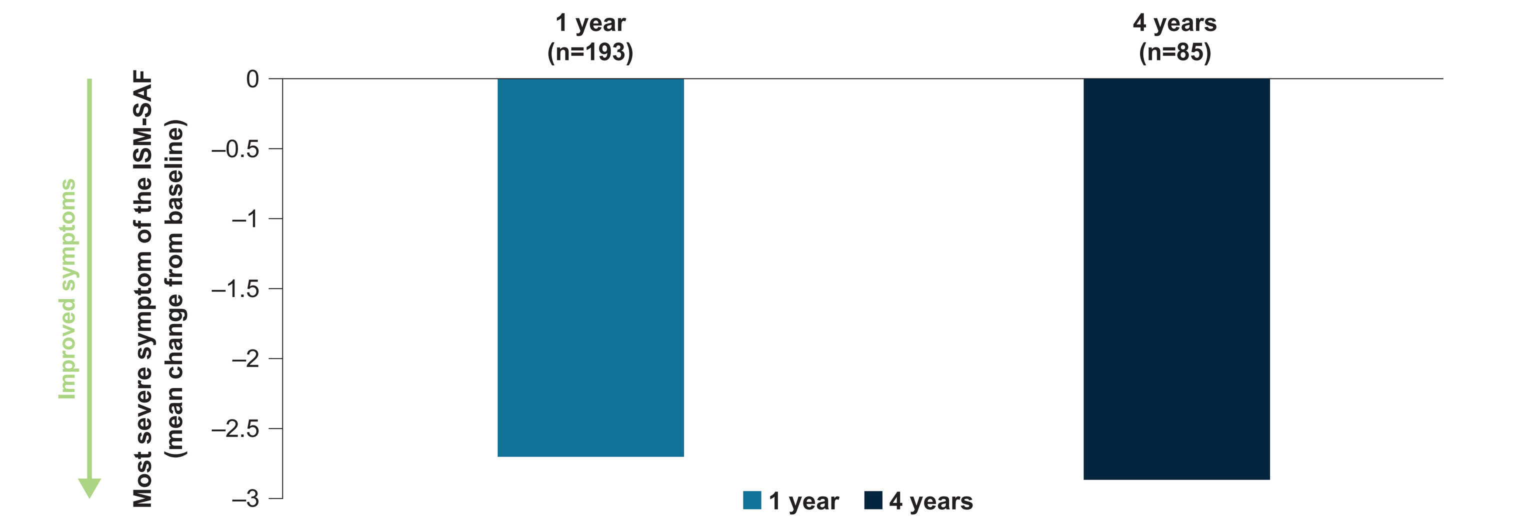


Figure 3. Longer-term efficacy for ISM-SAF most severe symptom in all patients treated with avapritinib at 1 year and 4 years



Safety (median follow-up of 4 years)

- The safety profile of avapritinib with longer-term median follow-up of 4 years remained consistent with the previously reported placebo-controlled portion (**Table 2**)
- Grade ≥3 treatment-related adverse events (TRAEs) remained low
- Discontinuations due to TRAEs remained limited, occurring in six patients (3%)
- The most frequently reported AEs related to treatment were edema events, with the majority being Grade 1, consistent with previous reports
- 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. The rate of AEs of increased transaminase (pooled term) was similar to placebo in the placebo-controlled portion of the study; these events remained low with longer exposure (9% TEAE, 4% TRAEs, all TRAEs were Grade 1–2)
- The rates of TRAE hair color changes and altered taste (pooled term) were low (4% and 2% 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 patients who initiated avapritinib 25 mg QD + BSC (N=226)
Median length of follow-up (months)	5.6	5.6	46.5
Any AEs, n (%)	128 (91)	66 (93)	224 (99)
Any TRAEs, n (%)	77 (55)	32 (45)	168 (74)
Grade ≥3 AEs, n (%)	30 (21)	15 (21)	108 (48)[c]
Grade ≥3 TRAEs, n (%)	3 (2)	2 (3)	14 (6)
Serious AEs, n (%)	7 (5)	8 (11)	53 (23)
Serious TRAEs, n (%)	0 (0)	0 (0)	3 (1)[d]
TRAEs leading to discontinuation, n (%)	2 (1)	1 (1)	6 (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)	18 (8)
Fatigue	6 (4)	2 (3)	17 (8)
Diarrhea	4 (3)	2 (3)	16 (7)
Alopecia	5 (4)	3 (4)	13 (6)

[a]Data cut June 23, 2022. [b]Data cut September 17, 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; BSC, best supportive care; TRAEs, treatment-related adverse events.

Avapritinib 50 mg post-dose increase subset

- A total of 74 patients (33%) who received avapritinib 25 mg QD in PIONEER increased to 50 mg QD in the open-label extension
- The median time to dose increase (range) was 31.4 (11.3–52.5) months
- Patients who dose-increased had a higher *KIT* D816V VAF and symptom burden at the beginning of avapritinib treatment compared with patients who remained on 25 mg
- After 24 weeks of avapritinib 50 mg QD, 42 out of 48 patients with available ISM-SAF TSS data experienced stable-to-improved TSS (38 with improvement in ISM-SAF TSS, four with stable TSS; where stable is defined as 0–10% increase in TSS)
- After 24 weeks of avapritinib 50 mg QD, 40 out of 46 patients with available MC-QoL data had stable-to-improved MC-QoL (38 with improvement in MC-QoL, two with stable MC-QoL; where stable is defined as 0–10% increase in MC-QoL)

Table 3. Safety profile of patients after dose escalation to 50 mg QD avapritinib in Part 3[a]

	50 mg dose escalation (n=74)
Median time on avapritinib 50 mg QD (range), months	16.5 (0.2–33.6)
Any AEs, n (%)	64 (86)
Any TRAEs, n (%)	24 (32)
Grade ≥ 3 AEs, n (%)	13 (18)
Grade ≥ 3 TRAEs, n (%)	1 (1)
Serious AEs, n (%)	10 (14)
Serious TRAEs, n (%)	0

[a]Includes only new, recurrent, or worsening AEs after initiation of 50 mg QD avapritinib in Part 3.

- The safety profile of dose escalation at 50 mg was similar to 25 mg, with no new safety concerns identified (**Table 3**)
- The most commonly reported (≥5% of patients) new, recurrent, or worsening TRAE that was observed after dose increase to 50 mg QD was peripheral edema in 6 (8%) patients, all Grade 1–2
- No patients discontinued treatment due to AEs after receiving 50 mg QD

Conclusions

- Avapritinib robustly reduces disease-related symptoms across all symptom domains and improves QoL after a median treatment duration of ~4 years
- Avapritinib was well tolerated after a median of 4 years of treatment with no new safety concerns identified and a very low rate of discontinuations due to treatment related AEs
- In the subset of primarily high-disease-burden patients who increased their dose, the majority experienced further improvements in ISM-SAF TSS and MC-QoL from time of dose increase, with a well-tolerated safety profile over a median of 1 year of treatment that was consistent with the safety profile of the 25 mg dose
- Avapritinib is an effective and well-tolerated therapeutic option for patients with ISM and appropriate for chronic use, with a positive long-term benefit-risk ratio across the spectrum of disease seen in ISM

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Conflicts of interest/disclosures

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