Durable Symptom and Quality of Life Improvement in Patients With Indolent Systemic Mastocytosis Treated With Avapritinib: Updated 4-Year Results From the PIONEER Trial

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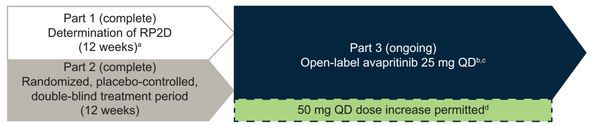
Introduction

- Indolent systemic mastocytosis (ISM) is a chronic clonal mast cell disease primarily driven by the *KIT* D816V mutation in ~95% of cases.[1–4] It is characterized by a broad spectrum of debilitating cutaneous, gastrointestinal, neurologic, and musculoskeletal symptoms which can lead to life-threatening anaphylaxis, poor quality of life (QoL), and significant morbidity[1,5–7]
- The prevalence of systemic mastocytosis has been estimated at up to 1 in 5000 people[8–11]
- Historically, management of ISM has centered on symptom-directed therapies that do not target the underlying disease biology, leaving many patients with ongoing symptom burden despite best supportive care (BSC) treatment
- 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 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]
- These outcomes supported the approval of avapritinib 25 mg once daily (QD) in the EU for adults with moderate to severe ISM and in the USA for adults with ISM[13,14]
- Here, we present extended findings from PIONEER for avapritinib, with a median treatment duration of ~4 years

Methods

Figure 1. Study design

- 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 of avapritinib treatment (**Figure 1**)



[a]Part 1 patients received treatment for 12 weeks, then continued assigned therapy and dose until the RP2D was determined. [b]All avapritinib-treated patients group; n=226, includes patients from Part 1 who started and 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. [c]Up to 5 years. [d]Per investigator discretion, for patients with an increase in symptoms and biomarkers of mast cell burden, dose increase to 50 mg QD was permitted in Part 3.
QD, once daily; RP2D, recommended phase 2 dose.

- Long-term efficacy 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). ISM-SAF is a validated symptom assessment tool specifically developed for the evaluation of ISM symptomology based on self-reported severity of 11 ISM symptoms; scores range from 0 to 110, with moderate to severe defined as a total symptom score (TSS) of ≥28[15]
  - QoL was assessed using the Mastocytosis Quality of Life Questionnaire (MC-QoL), a validated, disease-specific patient-reported outcome instrument consisting of 27 items across four domains (symptoms, emotional impact, social/life functioning, and skin impact). The MC-QoL assesses the impact of mastocytosis over the previous 2 weeks. Items are rated on a five-point Likert scale (never, seldom, occasionally, often, very often) and summarized into domain and total scores, typically transformed to a 0–100 scale, with higher scores indicating a greater impact of disease on QoL[16]
    - Changes in individual MC-QoL questions were also assessed. Improvement in QoL for an individual MC-QoL question was defined as a patient-reported shift at year 4 to an impact category at least one level lower than the corresponding baseline category on the Likert scale
  - Dose and/or frequency of BSC medications could be reduced gradually in patients experiencing symptomatic improvement during avapritinib treatment. Changes in the dose and/or frequency of BSC medications used to manage ISM-related symptoms were assessed at 1 year (48 weeks) and 3 years (156 weeks) from the initiation of avapritinib 25 mg QD. As of the data cut-off date, all enrolled patients had reached this minimum 3-year treatment duration or discontinued the study
  - Safety was evaluated by the rate and severity of adverse events (AEs); relatedness of AEs was determined by the treating clinician

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. Overall baseline demographics for Parts 1, 2, and 3

	Avapritinib 25 mg QD (n=226)
Patient demographic	
Age (years), median (range)[a]	51.0 (18–79)
Female, n (%)	166 (73)
Baseline number of BSC medications used, median (range)[b]	3.0 (0–10)
ISM symptom burden	
Baseline ISM-SAF TSS, mean (SD)[b]	48.1 (19.5)
MC-QoL	
Baseline MC-QoL, mean (SD)[b]	54.3 (18.3)
Mast cell burden[b]	
Serum tryptase, median (range), ng/mL	39.2 (3.6–590.4)
Bone marrow biopsy mast cells, median (range), %	7.0 (1.0–60.0)
KIT D816V VAF in peripheral blood[c], median (range), %	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 polymerase chain reaction was used to measure *KIT* D816V VAF.
BSC, best supportive care; ISM, indolent systemic mastocytosis; ISM-SAF, ISM-Symptom Assessment Form; MC-QoL, Mastocytosis Quality of Life Questionnaire; SD, standard deviation; TSS, total symptom score; VAF, variant allele fraction.

All avapritinib-treated patients

Efficacy

- Longer-term efficacy data with a median ~4 years of treatment demonstrated 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 2**)
- 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 3**)

Figure 2. Long-term efficacy of avapritinib on mean change in ISM-SAF TSS from baseline to 6 months, 1 year, and 4 years

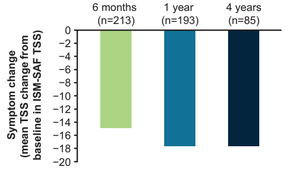
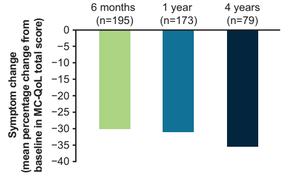


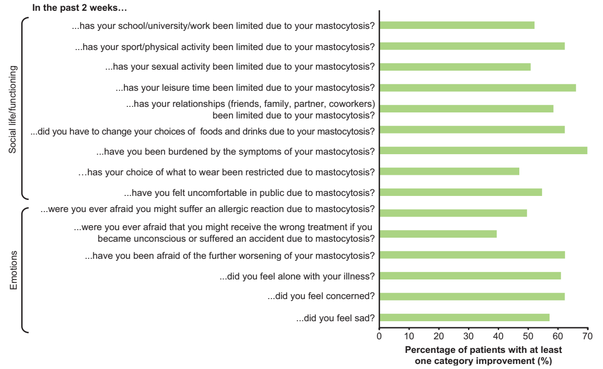
Figure 3. Long-term efficacy of avapritinib on mean percentage change in MC-QoL total score from baseline to 6 months, 1 year, and 4 years



MC-QoL

- Patients showed improvements of at least one Likert category across MC-QoL questions related to social function and emotions at 4 years (**Figure 4**). Among patients reporting improvement in these domains, the majority indicated that mastocytosis never or seldom affected their daily lives during treatment with avapritinib. For example, of patients treated with avapritinib for ~4 years:
  - 51.9% reported a reduction in how often mastocytosis limits their ability to attend school or work. Among these patients, 73% reported that mastocytosis "never" or "seldom" affected their school or work activities while on avapritinib
  - 58.2% reported a reduction in how often mastocytosis limits their interpersonal relationships. Among these patients, 76% reported that mastocytosis never or seldom impacted their relationships while on avapritinib

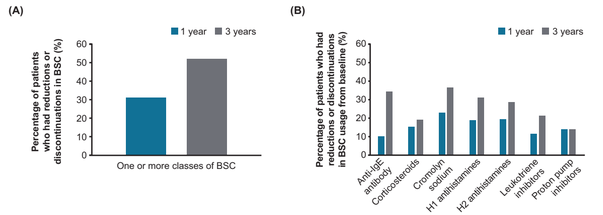
Figure 4. Percentage of patients with improvement in at least one Likert-scale category of the MC-QoL related to social life/functioning and emotions at 4 years of avapritinib treatment



Change in BSC medication usage

- At 1 year, 31% (n=69/226) of patients had reductions/discontinuations in one or more classes of BSC; by 3 years (latest timepoint assessed), 52% (n=118/226) of patients had reductions/discontinuations in one or more BSC classes (**Figure 5A**)
- Patients showed reductions across all individual BSC classes from baseline to 1 year and 3 years
  - The largest percentage of patients with reductions or discontinuations of BSC usage at 3 years were observed for cromolyn sodium (36.5%, n=27/74), anti-immunoglobulin E therapy (34.5%, n=10/29), and H1 (31.2%, n=69/221) and H2 (28.8%, n=44/153) antihistamines (**Figure 5B**)

Figure 5. Percentage of patients who had reductions or discontinuations in (A) one or more classes of BSC and (B) individual classes of BSC from baseline to 1 year and 3 years



Long-term safety

- The safety profile of avapritinib with longer-term median treatment duration of ~4 years remained consistent with the previously reported placebo-controlled portion[14] (**Table 2**)
- Grade ≥3 treatment-related adverse events (TRAEs) remained low
- The rate of discontinuations due to TRAEs remained limited occurring in 3% (n=6/226) of patients
- The most frequently reported AEs related to treatment were edema events, with the majority being Grade 1, consistent with previous reports[12]
- The rate of cognitive AEs was similar to placebo in the placebo-controlled portion of the study[12]; 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[12]; these events remained low with longer exposure (9% TEAE, 4% TRAEs, all TRAEs were Grade 1–2)

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 treatment duration (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. dSerious TRAEs included transient loss of vision (1), gastric hemorrhage (1), and peripheral edema (1). None of these events led to discontinuation.
AE, adverse event; TRAE, treatment-related adverse event.

Conclusions

- Avapritinib robustly reduces disease-related symptoms over ~4 years of treatment
- Long-term treatment with avapritinib was associated with sustained and clinically meaningful benefits including symptom and QoL improvements
- A progressively reduced use of symptom-directed medications (BSC) was seen with long-term treatment, reflecting meaningful improvements in disease burden
  - By year 3, over 50% of patients had reductions in one or more BSC classes
  - Notably, sustained improvements in symptoms and QoL were observed despite a concomitant reduction in BSC usage, which would otherwise be expected to exacerbate symptom burden
- Avapritinib remained well tolerated over a median treatment duration of ~4 years, with no new safety concerns, a low rate of treatment-related discontinuations, and a safety profile supportive of long-term use
- Overall, these 4-year data demonstrate that avapritinib can simultaneously achieve durable reductions in disease-related symptoms, long-term improvements in QoL, and decrease the amount of BSC medications used, all while maintaining a well-tolerated and well-characterized safety profile

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Conflicts of interest/disclosures

Dr Broesby-Olsen has received honoraria from Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi, Novartis, Thermo Fisher Scientific; and is a study steering committee member for Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi. For full author disclosures, please contact medinfo@blueprintmedicines.com.

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