Avapritinib Durably Improves Cutaneous Involvement of Indolent Systemic Mastocytosis in Patients Treated in the PIONEER Study

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Introduction

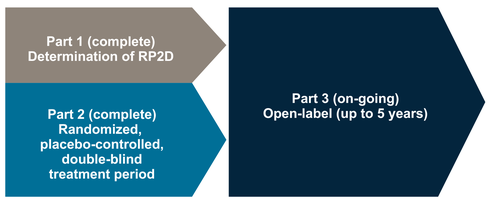
- Indolent systemic mastocytosis (ISM), the most common form of systemic mastocytosis, is a chronic clonal mast cell disease, and is primarily driven by the *KIT* D816V mutation in ~95% of cases[1-4]
- Patients with ISM may experience lifelong debilitating symptoms due to the accumulation and hyperactivation of aberrant mast cells (MCs) in various organs, including the skin[4,5]
- Skin manifestations include brown maculopapular skin lesions, pruritus, and wheals. Darier's sign is a hallmark of these skin lesions, and is related to the release of histamine and other mediators from MCs[6,7]
- Skin lesions also impact patients' self-image and can lead to social isolation and sleep disturbance, all contributing to a considerable decrease in quality of life (QoL)[8-10]
- Symptom-directed therapies are often insufficient at controlling skin manifestations and do not target the pathogenic driver of disease[11]
- Avapritinib, an oral, highly selective, potent inhibitor of D816V-mutated KIT, is the only therapy currently approved in the USA and Europe to treat adults with ISM[12,13]
- In the randomized, placebo-controlled Part 2 of PIONEER, avapritinib demonstrated improvements in skin manifestations compared with placebo at 24 weeks[14] (**Figure 1**)
  - Patients with skin involvement who were treated with avapritinib reported statistically significant reductions in the overall skin domain and in each of the individual mastocytosis-related cutaneous symptoms including spots, itching, and flushing compared with those who received placebo
  - Avapritinib reduced lesion surface area in the most affected skin region *versus* placebo (median –50% vs 0%, respectively). Additionally, the majority of patients treated with avapritinib experienced lightening of skin lesion color, whereas no change was observed among those receiving placebo
- Here, we report the impact of longer-term treatment in patients with ISM who started with avapritinib 25 mg once daily (QD) on skin symptoms, skin lesion area, and skin lesion color in the PIONEER study

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**)

Figure 1. Study design

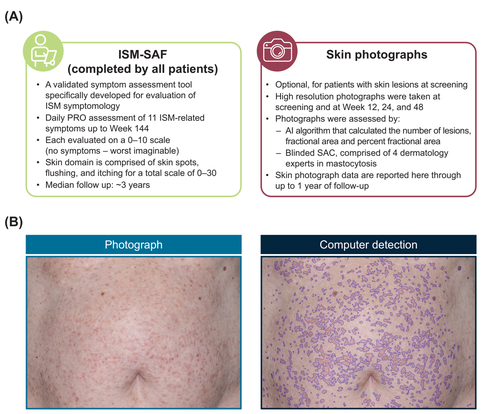
Overall, 226 patients initiated avapritinib 25mg QD across Parts 1, 2, and 3[a]



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

- Symptoms were assessed using the ISM Symptom Assessment Form (ISM-SAF; ©2018 Blueprint Medicines Corporation), and patients had the option of undergoing standardized clinical skin photography for assessment by the expert skin assessment committee and algorithm (**Figure 2A** and **2B**)
- Here, we present data at a cut-off of September 20, 2024

Figure 2. Comprehensive assessment of skin changes from baseline (A) and AI algorithm assessment of skin changes (B)



AI, artificial intelligence; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; PRO, patient-reported outcome; SAC, skin assessment committee.

Results

- Across all parts of the study, 226 patients initiated avapritinib therapy at 25 mg QD + best supportive care (BSC)
- Baseline characteristics were comparable in n=79 patients with paired skin photographs and the pooled avapritinib 25 mg QD population at Week 24 (**Table 1**)

Table 1. Baseline patient demographics and characteristics

Patient demographics	Patients with paired skin photographs (n=79)	Avapritinib 25 mg QD (n=226)
Age (years), median (range)	50 (22–77)	49.8 (18–79)
Female, n (%)	58 (73)	166 (73)
TSS baseline, mean (SD)[a]	49.1 (19.2)	48.1 (19.5)
Most severe symptom score, mean (SD)	7.7 (1.8)	7.5 (1.9)
Mast cell burden		
Median serum tryptase (central), ng/mL (range)	37.6 (3.6–248.8)	39.2 (3.6–590.4)
Median bone marrow biopsy mast cells (central), % (range)	10 (1–40)	7 (1–60)
Median *KIT* D816V VAF in peripheral blood, % (range)[b]	0.48 (Undetectable–29.18)	0.39 (Undetectable–41.29)
Systemic mastocytosis therapy		
Prior cytoreductive therapy, n (%)[c]	13 (16)	29 (13)
Prior TKI therapy, n (%)	8 (10)	17 (8)
Number of BSC treatments, median (range)[d]	3 (0–10)	3 (0–10)

[a]Eligibility for enrollment was based on TSS ≥28 at screening; patients may have a score <28 at baseline. [b]The limit of detection was 0.02%. [c]Cytoreductive therapies included dasatinib, imatinib, masitinib, nilotinib, midostaurin, brentuximab vedotin, cladribine, hydroxyurea, rapamycin, and interferon α. Includes treatments received by patients at baseline; patients may have received BSC treatments previously discontinued at the time of enrollment/baseline. [d]All patients had at least two BSC treatments prior to or at screening.
BSC, best supportive care; TSS, total symptom score; SD, standard deviation; TKI, tyrosine kinase inhibitor; VAF, variant allele fraction.

- Improvements in the ISM-SAF continued at Week 48 in patients who started with avapritinib 25 mg QD, the mean (standard deviation [SD]) change from baseline in the skin symptom domain was −6.9 (7.1) at Week 48 (1 year) and −2.5 (2.5), –2.5 (2.8), –2.0 (2.7) for spot severity, itching, and flushing, respectively (**Figure 3**)
  - These improvements were sustained, and at Week 144 (3 years), the mean (SD) change in skin symptom domain was –8.1 (7.9)

Results (continued)

Figure 3. ISM-SAF skin symptoms in patients treated with avapritinib 25 mg QD

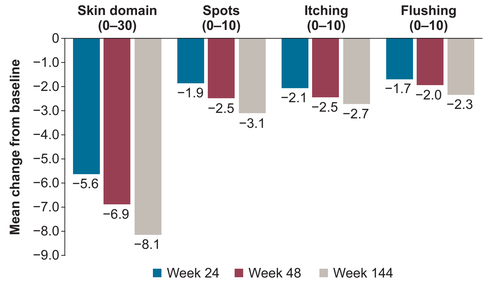


Figure 4. Change in skin lesion fractional area estimate from start of avapritinib determined by a computer-generated algorithm

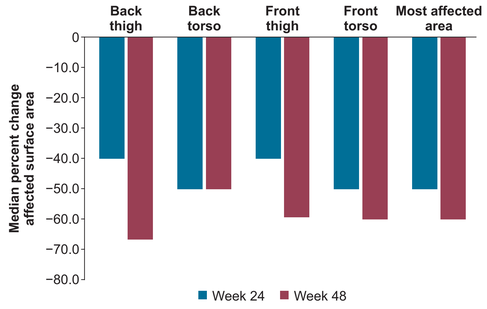
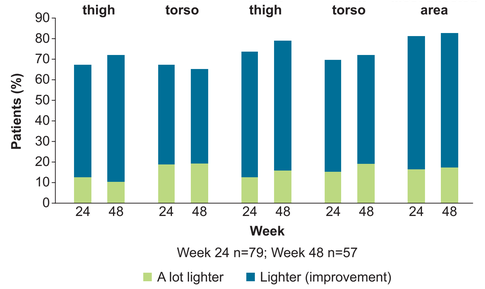


Figure 5. Skin lesion color change



Week 24 n=79; Week 48 n=57

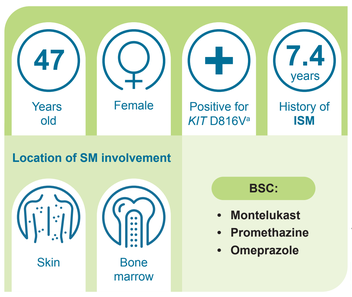
- The surface area of skin lesions was reduced at Week 24 in avapritinib-treated patients and was sustained at Week 48 (1 year) (**Figure 4**)
- Patients with paired photographs showed a median percent reduction in lesion surface area in the most affected skin region of –60% at Week 48
- As assessed by a blinded skin assessment committee, the majority of patients had an improvement in skin lesion color at Week 24 while treated with avapritinib and was sustained at Week 48 (1 year) (**Figure 5**)
- The safety profile of avapritinib was similar to placebo in the randomized, blinded part of the trial, and remained favorable in the longer-term open-label extension part of the trial, with a median follow-up of 3 years (**Table 2**)
- The most frequently reported adverse events associated with avapritinib were edema events, with the majority being Grade 1
- Grade ≥3 treatment-related adverse events (TRAEs) remained low and consistent with the randomized portion of the study
- Treatment discontinuations due to TRAEs remained limited occurring in seven patients (3%)

Table 2. Safety profile of avapritinib

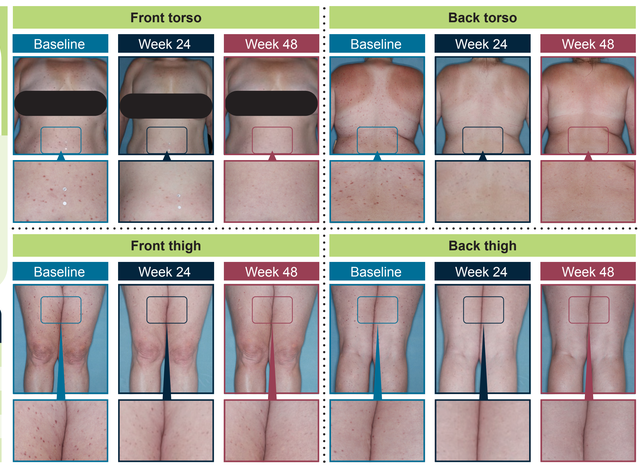
	Part 2[a]		Parts 1, 2, 3 combined[b]
	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	All patients who initiated avapritinib 25 mg QD + BSC (N=226)
Median length of follow-up (months)[c]	**5.6**	**5.6**	**35.3**
Any AEs, n (%)	**128 (91)**	**66 (93)**	**224 (99)**
Any TRAEs, n (%)	77 (55)	32 (45)	168 (74)
Grade ≥3 AEs	**30 (21)**	**15 (21)**	**103 (46)[d]**
Grade ≥3 TRAEs	3 (2)	2 (3)	14 (6)
Serious AEs	**7 (5)**	**8 (11)**	**45 (20)**
Serious TRAEs	0 (0)	0 (0)	3 (1)[e]
TRAEs leading to discontinuation	**2 (1)**	**1 (1)**	**7 (3)**
Most common TRAEs (≥5% of patients), n (%)			
Peripheral edema	9 (6)	1 (1)	29 (13)
Periorbital edema	9 (6)	2 (3)	22 (10)
Headache	11 (8)	7 (10)	21 (9)
Nausea	9 (6)	6 (8)	18 (8)
Fatigue	6 (4)	2 (3)	16 (7)
Diarrhea	4 (3)	2 (3)	14 (6)
Alopecia	5 (4)	3 (4)	13 (6)
Dizziness	4 (3)	5 (7)	11 (5)

[a]Data cut: June 23, 2022. [b]Data cut: September 20, 2024. [c]Reflects median length of follow-up during the indicated study period. [d]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. [e]Serious TRAEs included peripheral edema (1), gastric hemorrhage (1), and transient loss of vision (1). None of these events led to discontinuation.
AEs, adverse events; TRAEs, treatment-related adverse events.

Case study



	% change from baseline to Week 48
ISM-SAF TSS	**–65.6**
Skin domain score	–62.2
MC-QoL total score	**–65.2**
Skin domain score	–57.1
Serum tryptase	**–71.6**



[a]*KIT* point mutation at codon 816 in the BM or another extracutaneous organ.

Conclusions

- These results support previous analyses in which avapritinib demonstrated statistically significant and clinically meaningful improvements *versus* placebo (both with BSC) in symptoms, as measured with the TSS
  - Of the patients with skin involvement, those treated with avapritinib 25 mg QD experienced marked reductions in skin symptoms, skin color, and surface area of skin lesions
- We show that these improvements were persistent with a longer-term follow-up
  - Symptom improvements continued to be durable for up to 3 years
- Improvements in skin lesion size and color were also detected in clinical photographs for up to 1 year, corresponding to the predefined duration of photographic follow-up
- Avapritinib was generally well tolerated with no new safety concerns observed, with a median follow-up of 3 years
- Avapritinib achieved sustained and durable improvements in the skin manifestations of ISM while maintaining a long-term favorable benefit-risk profile in patients with ISM. These data highlight the ability of avapritinib to achieve long-term disease modification

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Acknowledgements

We thank the patients and their families for making the PIONEER study possible. We also thank the investigators and clinical trial teams who participated in the study. Medical writing support was provided by Matthew Nicolas, MSc, and Sarah Christopher, PhD, of Paragon (a division of Prime, Knutsford, UK). Funded by Blueprint Medicines Corporation. The sponsor reviewed and provided feedback on the presentation. However, the authors had full editorial control and provided final approval of all content.

Conflicts of interest / Disclosures

Dr. Siebenhaar has received honoraria (advisory board, speaker) and/or institutional grant/research support from Allakos, Blueprint Medicines Corporation, Celldex Therapeutics, Cogent Biosciences, Escient, GSK, Granular Therapeutics, Invea Therapeutics, Moxie Therapeutics, Noucor, Novartis, Sanofi/Regeneron, Telios Pharma, and Third Harmonic Bio. For all author disclosures, please contact medinfo@blueprintmedicines.com.

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Presented at the 2025 Fall Clinical Dermatology Conference, October 23–26, 2025, Las Vegas, NV, USA. Please contact medinfo@blueprintmedicines.com for permission to reprint and/or distribute.