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

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Indolent systemic mastocytosis

- 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]

1. Kristensen T, et al. *Am J Hematol*. 2014;89:493–498; 2. Ungerstedt J, et al. *Cancers*. 2022;14:3942; 3. Garcia-Montero AC et al. *Blood*. 2006;108:2366–2372; 4. Pardanani A. *Am J Hematol*. 2023;98:1097–1116; 5. Mesa RA, et al. *Cancer*. 2022;128:3700–3708;6. Mesa RA, et al. *Cancer*. 2022;128:3691–3699; 7. Hartmann K, et al. *J Allergy Clin Immunol*. 2016;137:35–45; 8. Jensen B, et al. *J Clin Nurs*. 2019;28:1114–1124; 9. Nowak A, et al. *J Dtsch Dermatol Ges*. 2011;9:525–532; 10. Hermine O, et al. *PLoS One*. 2008;3:e2266; 11. Pardanani A. *Blood*. 2013;121:3085–3094;
ISM, indolent systemic mastocytosis; MC, mast cell; QoL, quality of life.

The PIONEER study of avapritinib in ISM

- 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[1,2]
- In the randomized, placebo-controlled Part 2 of PIONEER, avapritinib demonstrated improvements in skin manifestations compared with placebo at 24 weeks[3]
  - 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

1. Blueprint Medicines Corporation. AYVAKIT® (avapritinib).Prescribing Information. 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212608s020lbl.pdf.Accessed June 2025; 2. Blueprint Medicines Corporation. AYVAKYT® (avapritinib). Summary of Product Characteristics. 2024.Available at: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf. Accessed June 2025; 3. Maurer M, et al. Presented at the Annual Meeting of the American Academy of Allergy Asthma and Immunology 2023, Presentation L69.
QD, once daily

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

PIONEER Study Design

- Across all parts of the study, 226 patients initiated avapritinib therapy at 25 mg QD + best supportive care (BSC)
- 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 an artificial intelligence (AI) algorithm

ISM-SAF
(completed by all patients)

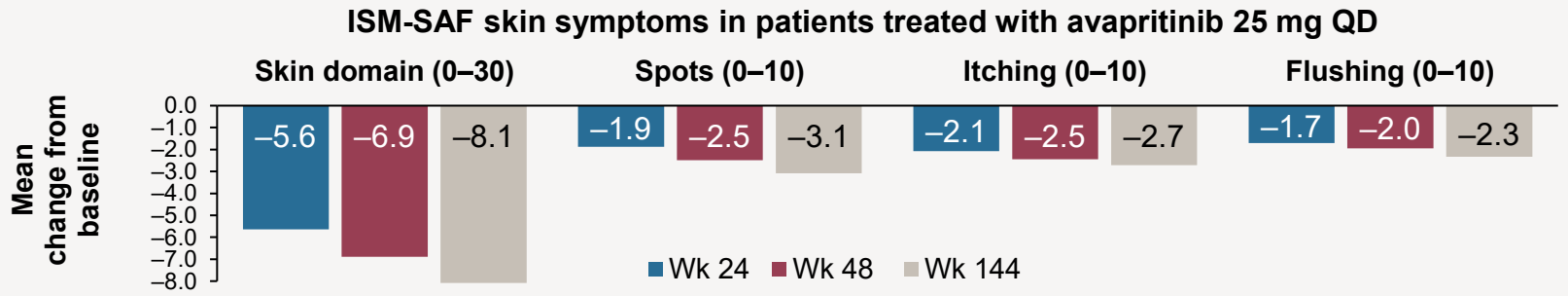
- Daily PRO assessment of 11 ISM-related symptoms up to Week 144 (3 years)
- Each evaluated on a 0–10 scale (no symptoms – worst imaginable)
- Skin domain is comprised of skin spots, flushing, and itching for a total scale of 0–30
- Median follow up: ~3 years

Skin photographs (Optional, for patients with skin lesions at screening)

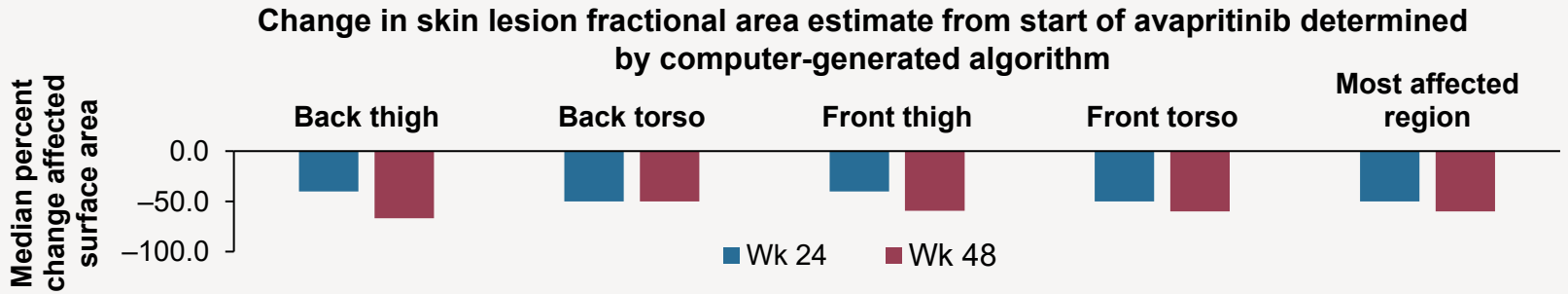
- High resolution photographs were taken at screening and at week 12, 24 and 48
- Photographs were assessed by:
  - AI algorithm that calculated the number of lesions, fractional area and percent fractional area
  - Blinded skin assessment committee, comprised of 4 dermatology experts in mastocytosis
- Reported here through up to 1 year of follow-up

BSC, best supportive care; ISM-SAF

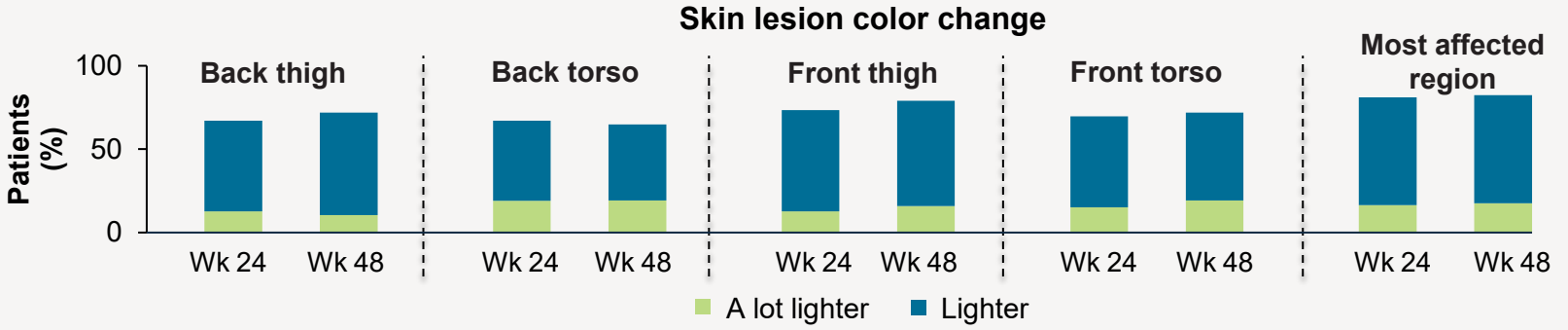
Results: Treatment with avapritinib demonstrates durable improvements in ISM skin symptoms



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. These improvements were sustained, and at Week 144 (3 years),the mean (SD) change in skin symptom domain was –8.1 (7.9)



The surface area of skin lesions was reduced at Week 24 in avapritinib-treated patients, especially compared with placebo. The reduction in the surface area of skin lesions was sustained after 48 weeks. 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, this was sustained at Week 48 (1 year)

SD, standard deviation; Wk, week

Results: Baseline demographics and safety profile of avapritinib

Baseline characteristics were comparable in n=79 patients with paired skin photographs and the pooled avapritinib 25 mg population at Week 24

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)	7.0 (1.0–60.0)
Median *KIT* D816V VAF in peripheral blood, % (range)[b]	0.48 (Undetectable–29.18)	0.39 (Undetectable–41.29)
SM 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 (0–10)	3 (0–10)

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

	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)**
Grade ≥3 TRAEs	3 (2)	2 (3)	14 (6)
Serious adverse events	**7 (5)**	**8 (11)**	**45 (20)[d]**
Serious TRAEs	0 (0)	0 (0)	3 (1)[e]
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)
TRAEs leading to discontinuation	**2 (1)**	**1 (1)**	**7 (3)**

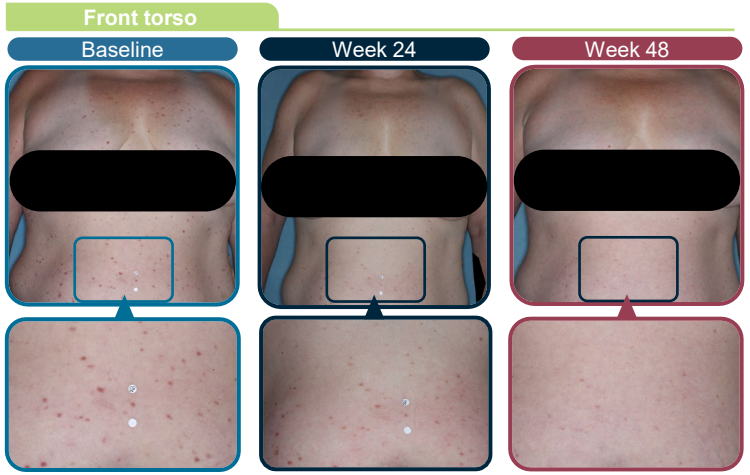
[a]Data cut: June 23, 2022. [b]Data cut: September 20, 2024. [c]Reflects median length of follow-up during the indicated study period. [d]One death (Grade 5 serious AE) occurred during the study and was unrelated to treatment; the patient had a medical history of anaphylaxis and atrial fibrillation, 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; BSC, best supportive care; TRAEs, treatment-related adverse events; TKI, tyrosine kinase inhibitor; TSS, total symptom score.

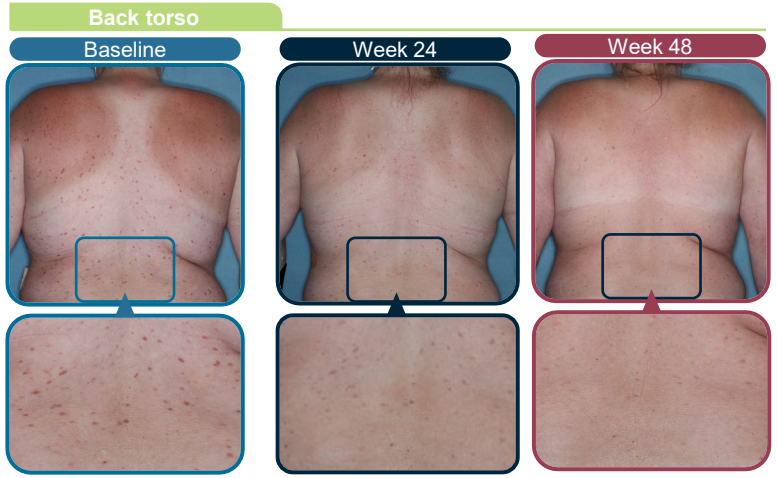
Results: Representative case study demonstrating improvements in skin lesion color and area and biomarkers of ISM disease burden with avapritinib

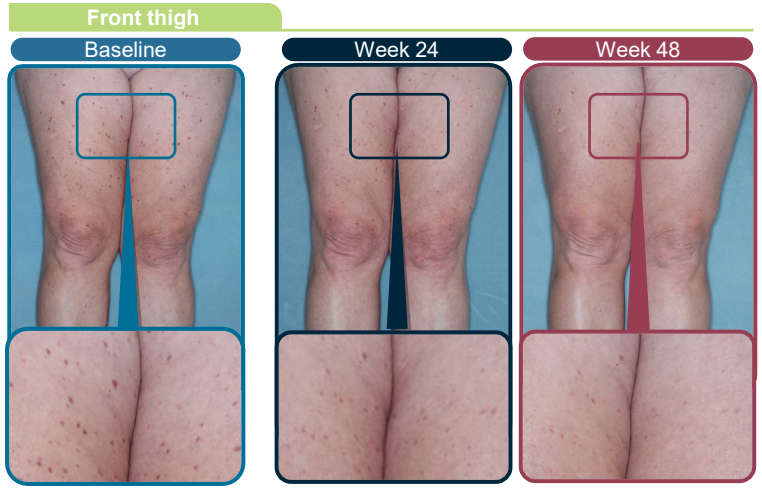
BSC: montelukast, promethazine, omeprazole

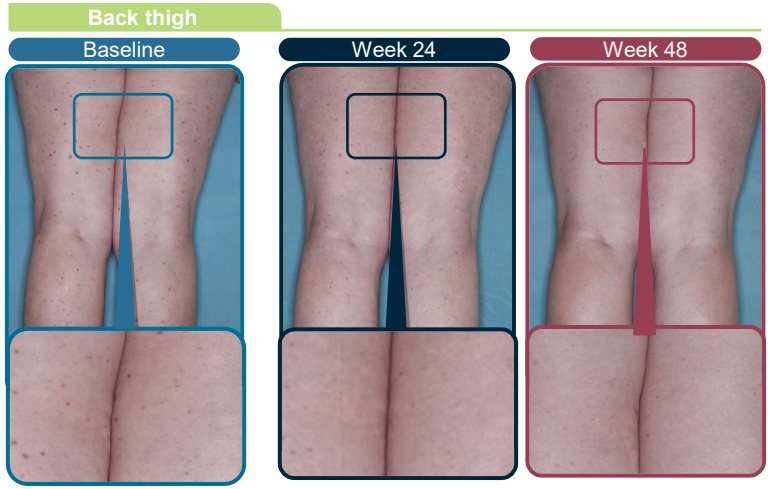
	% change from baseline to Week 48
ISM-SAF TSS	**−65.6**
Skin domain score	−62.2
MC-QoL total score	**−65.2**
Skin domain score	−57.1
Serum tryptase	**−71.6**

[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
  - Symptom improvements continued to be durable for up to 3 years
  - 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
- 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