Avapritinib Improved Skin Findings In Patients With Indolent Systemic Mastocytosis (ISM) In the Registrational, Double-Blind, Placebo-Controlled PIONEER Study

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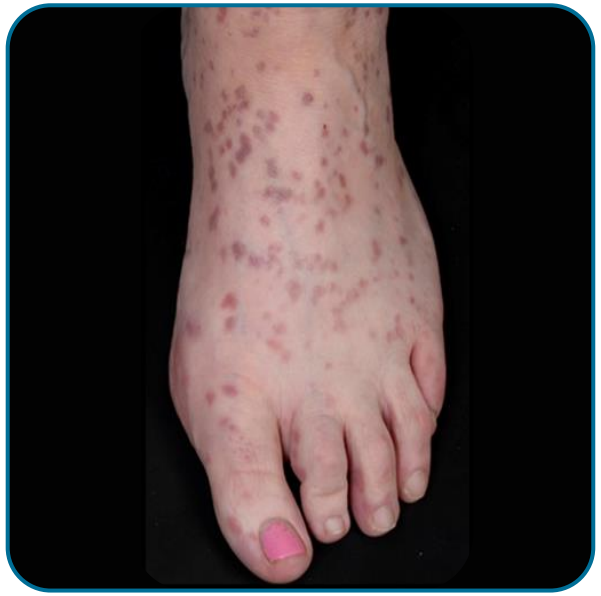
ISM is the most common form of SM; driven by the *KIT* D816V mutation in approximately 95% of cases[1–4]

- **Patients with ISM can have lifelong debilitating symptoms across multiple organ systems**[1–5]
- **The vast majority of patients with ISM have highly heterogenous maculopapular skin lesions**[5–10]
  - Lesions may be localized or diffuse, typically on the thighs and torso
  - Patients also experience Darier's sign, pruritus, and flushing
- **Avapritinib has previously demonstrated improvements in multiple SM symptoms including skin manifestations and QoL measurements**[11–13]
- **In Part 1 of PIONEER, avapritinib significantly reduced total mast cell burden and abnormal CD30+ mast cells in skin lesions**

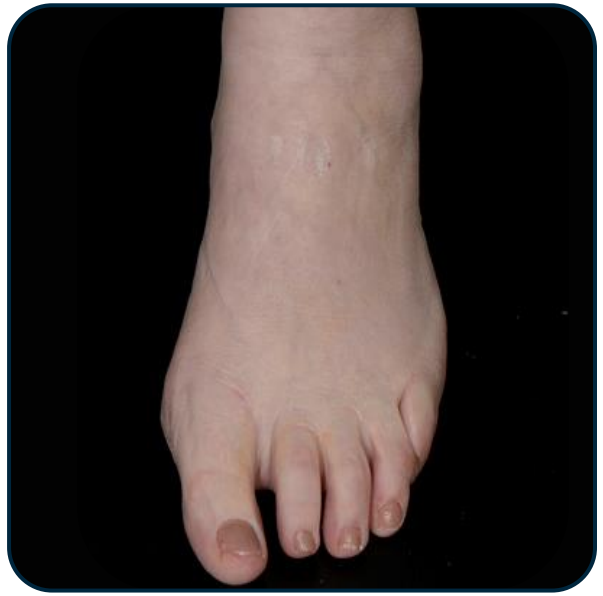
Avapritinib is approved in the USA and EU for AdvSM with a starting dose of 200 mg QD[14–15]

Skin improvements with avapritinib in patients with AdvSM from the EXPLORER study[11]

Baseline



On study



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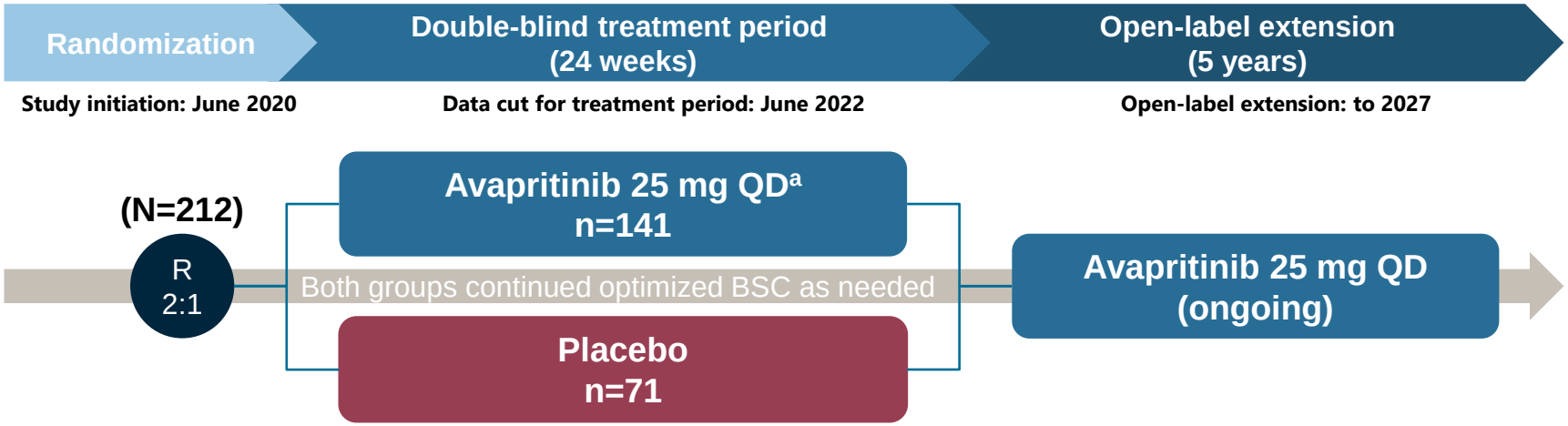
AdvSM, Advanced Systemic Mastocytosis; ISM, indolent systemic mastocytosis; QD, once-daily; QoL, quality of life; SM, systemic mastocytosis.

Registrational PIONEER study: Randomized, double-blind, placebo-controlled study in patients with ISM

Screening period

- Best supportive care medications (BSC) optimized for up to a month
  - Antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc.
- Eligibility
  - Age ≥18 years
  - ISM by central pathology review
  - Moderate to severe symptoms (TSS ≥28) after ≥2 BSC medications



Symptoms
Primary endpoint

- Mean change in ISM-SAF Total Symptom Score (**TSS**) from baseline to Week 24
- Mean change in **individual symptom scores** of ISM-SAF
- Mean change in **most severe symptom score**

Biomarkers of mast cell burden
Key secondary endpoints

- ≥50% reduction in **serum tryptase** levels
- ≥50% reduction in ***KIT* D816V VAF** in peripheral blood (or below level of detection [<0.02%] for patients with a detectable mutation at baseline)
- ≥50% reduction in in bone marrow **mast cell aggregates**

Baseline (avapritinib *vs* placebo)

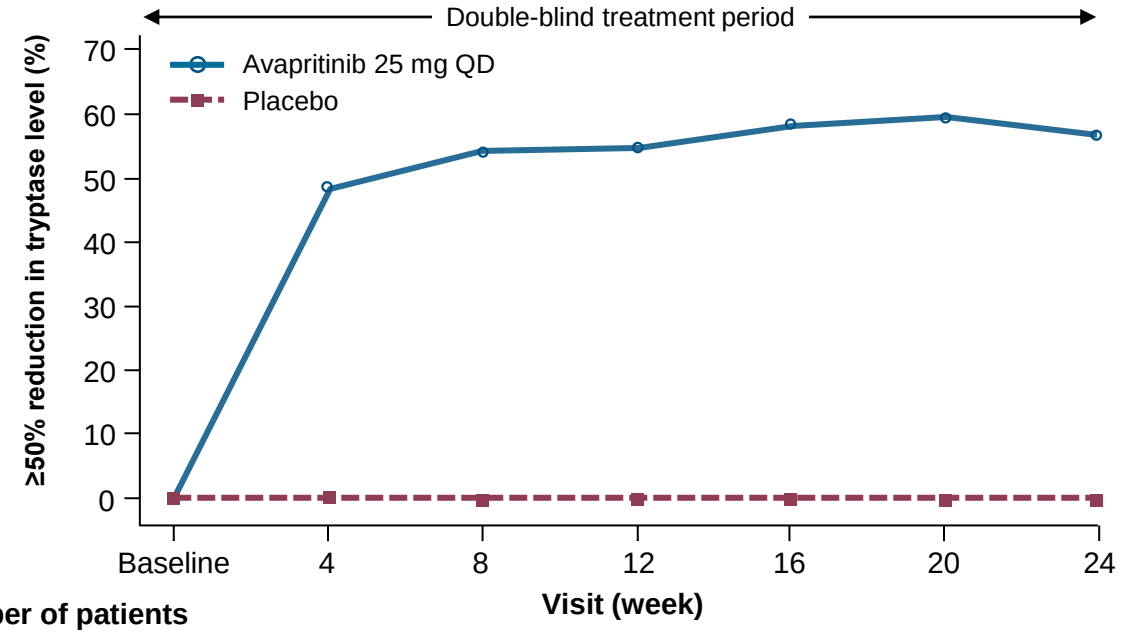
- Mean TSS: 50.2 *vs* 52.4
- Median (range) number of BSC treatment: 3 (0–11) *vs* 4 (1–8)
- Percentage of patients with SM involvement in skin by PI assessment: 72.3% vs 74.6%

[a]The recommended dose of avapritinib for the double-blind period and open-label extension was identified based on efficacy and safety results from Part 1 that included 4 cohorts: 25 mg avapritinib (n=10), 50 mg avapritinib (n=10), 100 mg avapritinib (n=10) and placebo (n=9). Patients treated with high dose steroids within 7 days of primary endpoint (n=4) were excluded from the week 24 analysis, but included at other timepoints of the study. Percentages were calculated based on available data at the timepoint. One-sided P-values are reported for primary and key secondary endpoints. ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; MC-QoL, Mastocytosis Quality of Life Questionnaire; QD, once daily; QoL, quality of life; R, randomized; TSS, total symptom score; VAF, variant allele fraction.

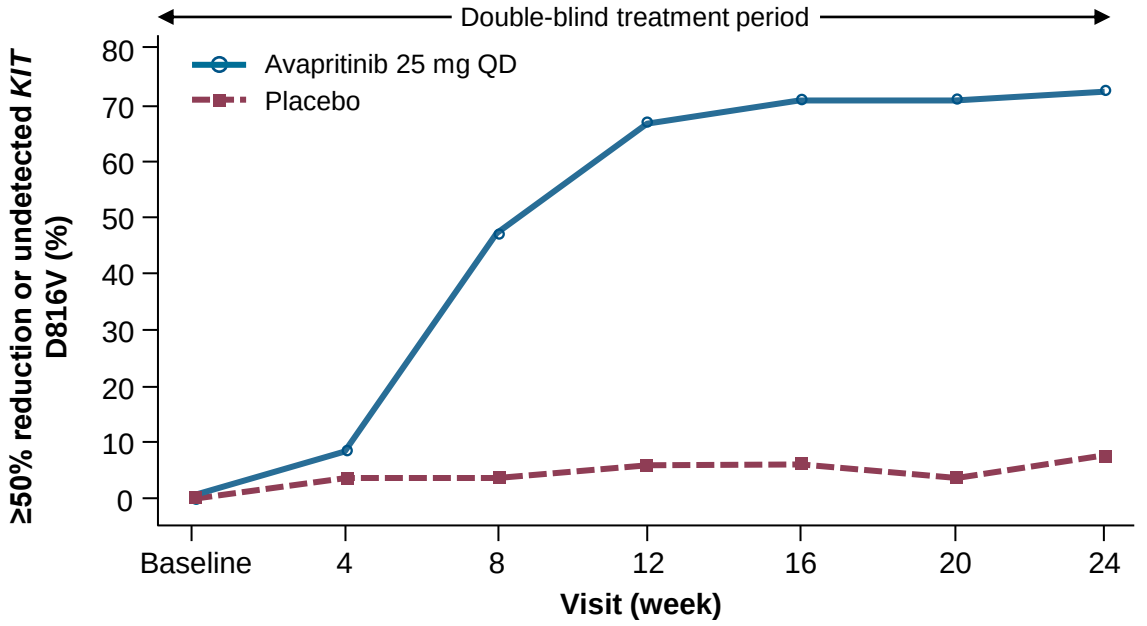
Rapid and sustained reductions in biomarkers of mast cell burden in avapritinib-treated patients *versus* placebo

Key secondary endpoints

Patients with ≥**50% reduction in serum tryptase**



Patients with ≥**50% reduction in peripheral blood *KIT* D816V VAF**



Number of patients

Avapritinib	141	133	136	132	133	128	134	118	110	113	109	107	104	109
Placebo	71	66	62	61	60	62	64	63	57	54	52	51	53	54

At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	P-value
Proportion of patients with **≥50% reduction in serum tryptase** (95% CI)	53.9% (45.3–62.3)	0.0% (0.0–5.1)	<0.0001

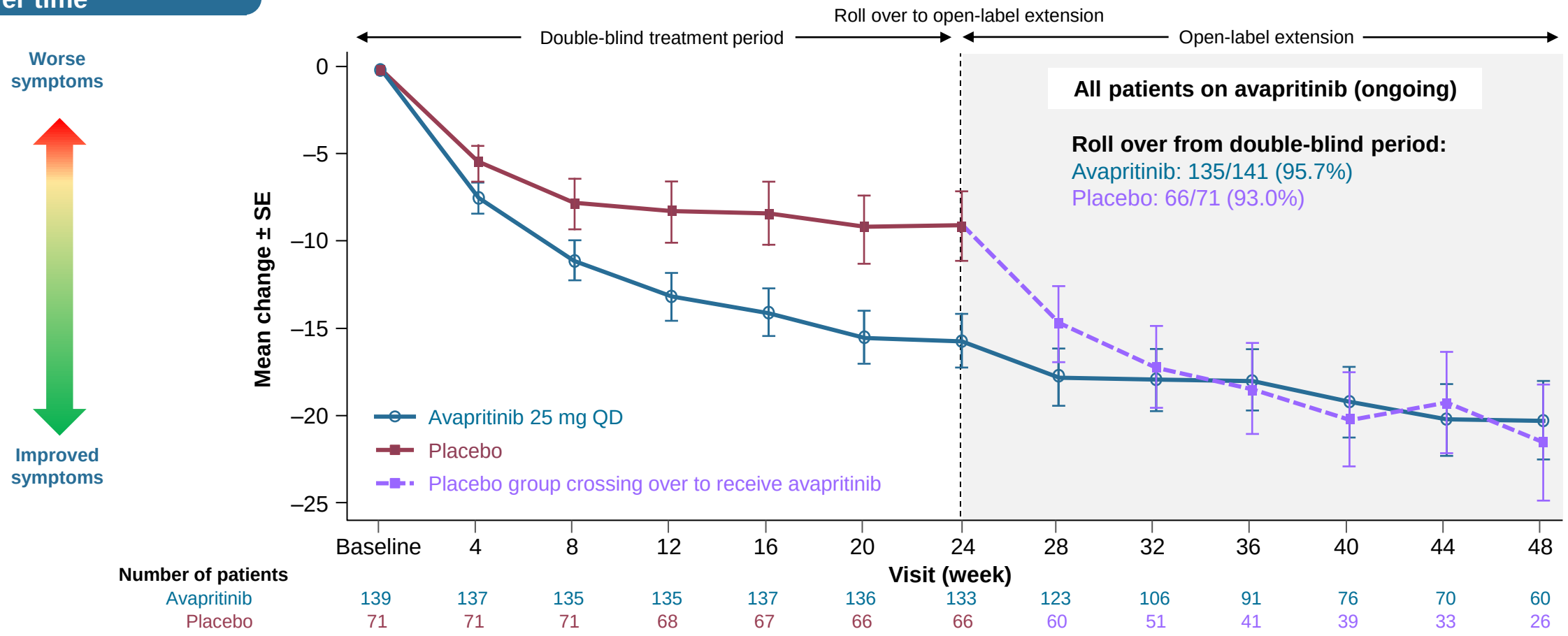
At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	P-value
Proportion of patients with **≥50% reduction in *KIT* D816V VAF** (95% CI)	67.8% (58.6–76.1)	6.3% (1.8–15.5)	<0.0001

At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	P-value
Proportion of patients with **≥50% reduction in BM mast cell aggregates** (95% CI)	52.8% (42.9–62.6)	22.8% (12.7–35.8)	<0.0001

BM, bone marrow; CI, confidence interval.

Avapritinib demonstrated significant and durable improvement in symptoms *versus* placebo

TSS over time



Number of patients	Baseline	4	8	12	16	20	24	28	32	36	40	44	48
Avapritinib	139	137	135	135	137	136	133	123	106	91	76	70	60
Placebo	71	71	71	68	67	66	66	60	51	41	39	33	26

Primary endpoint

A one-sided P-value of <0.025 was needed to declare avapritinib as superior in reducing TSS *versus* placebo

At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	P-value
Mean change in TSS (95% CI)	–15.58 (–18.61, –12.55)	–9.15 (–13.12, –5.18)	0.003

SE, standard error of the mean.

Comprehensive assessment of skin changes from baseline to Week 24

ISM-SAF
(completed by all patients)

- Daily PRO assessment of 11 ISM related symptoms
- Each evaluated on a 0–10 scale (no symptoms – worst imaginable)
- Skin domain is comprised of spot, flushing and itching for a total scale of 0–30

Skin photographs
(avapritinib n=74, placebo n=37)

- Optional, taken at baseline and every 12 weeks
- Photographs assessed by
  - *Computer-generated algorithm* - calculated affected surface area
  - *Blinded SAC*

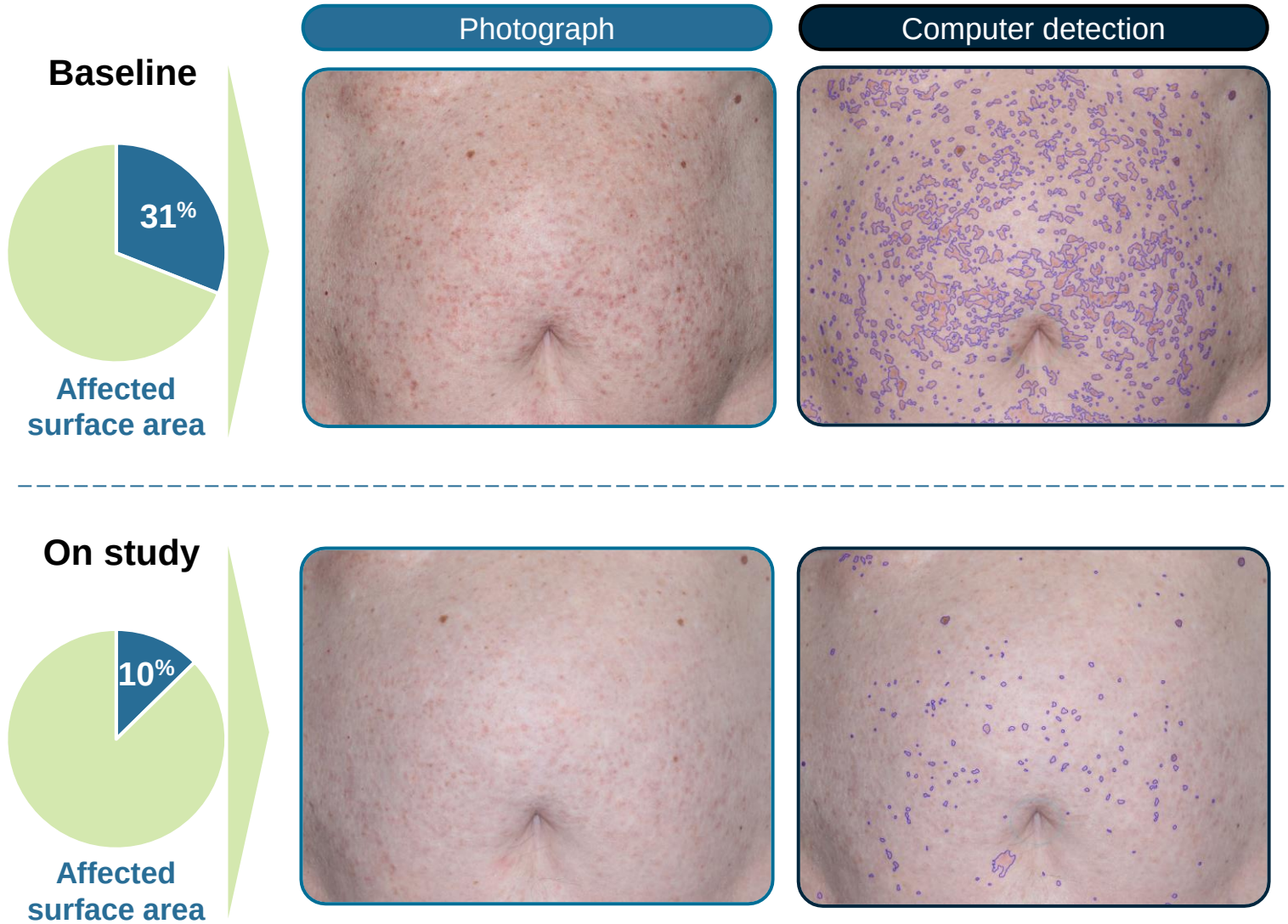
Skin biopsies
(avapritinib n=107, placebo n=60)

- Performed in patients with mastocytosis in skin at baseline and at Week 24
- Quantification of mast cell infiltrates was performed by central pathology
- Mast cell number and immunophenotype in skin biopsies were assessed via light microscopy and immunohistochemistry

MC-QoL, Mastocytosis Quality of Life questionnaire; PRO, patient-reported outcome; SAC, skin assessment committee.

Blinded SAC evaluation of skin photographs

- **Blinded SAC determined:**
  - Most affected region at baseline
  - Color change over time
- **Computer-generated algorithm for each patient**
  - Affected surface area was followed with computer generated detection method
  - Number of lesions, fractional area, and percent fractional area were determined



SAC, skin assessment committee.

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More than 70% of PIONEER patients had skin involvement; baseline characteristics were comparable to the ITT population

Patient demographics	Skin biopsy (n=167)		ITT population (N=212)	
	Avapritinib 25 mg QD (n=107)	Placebo (n=60)	Avapritinib 25 mg QD (n=141)	Placebo (n=71)
Age (years), median (range)	**49** (18–77)	**55** (29–79)	**50.0** (18–77)	**54.0** (26–79)
Female, n (%)	**78** (72.9)	**45** (75.0)	**100** (70.9)	**54** (76.1)
TSS baseline, mean (SD)[a,b]	**50.8** (19.1)	**53.9** (18.8)	**50.2** (19.1)	**52.4** (19.8)
Most severe symptom score, mean (SD)	**7.7** (1.7)	**8.1** (1.6)	**7.7** (1.7)	**7.9** (1.7)
Mast cell burden				
Median serum tryptase (central), ng/mL (range)	**39.5** (3.6–256.0)	**49.6** (5.7–501.6)	**38.4** (3.6–256.0)	**43.7** (5.7–501.6)
Median bone marrow biopsy mast cells (central), % (range)	**7.0** (1.0–50.0)	**7.0** (1.0–70.0)	**7.0** (1.0–50.0)	**7.0** (1.0–70.0)
Mast cell aggregates present, n (%)	**84** (78.5)	**50** (83.3)	**106** (75.2)	**57** (80.3)
Median *KIT* D816V VAF in peripheral blood, % (range)[c]	**0.5** (0.02–41.3)	**0.4** (0.02–36.7)	**0.4** (0.02–41.3)	**0.3** (0.02–36.7)
SM Therapy				
Prior cytoreductive therapy, n (%)[d]	**15** (14.0)	**6** (10.0)	**19** (13.5)	**7** (9.9)
Prior TKI therapy, n (%)	**8** (7.5)	**4** (6.7)	**10** (7.1)	**4** (5.6)
Number of BSC treatments, median (range)[e]	**3** (0–11)	**3** (1–8)	**3** (0-11)	**4** (1-8)

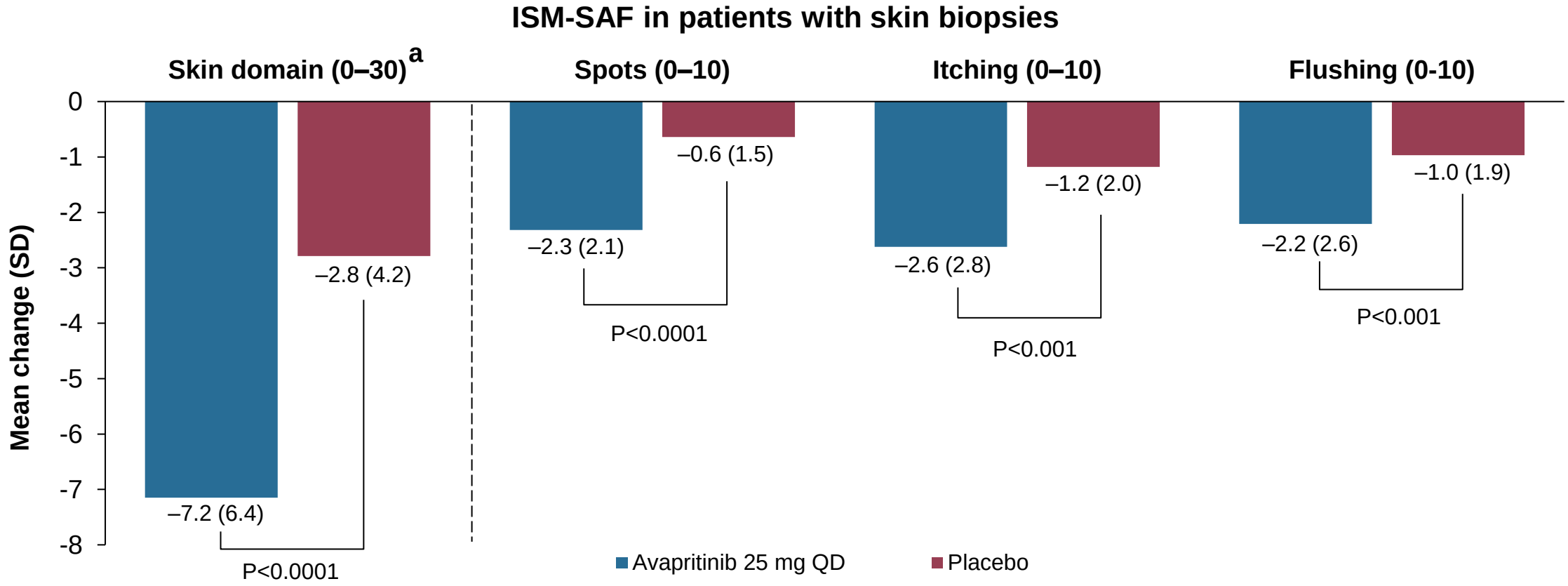
- **A subset of patients with skin biopsies agreed to optional skin photographs; baseline characteristics were similar to patients with skin biopsies and ITT population**

[a]Eligibility for enrollment was based on TSS ≥28 at screening; patients may have a score <28 at baseline. [b]Two patients in the avapritinib group had missing baseline TSS values; therefore, the denominator was based on patients with available data at baseline (n=139). [c]The limit of detection was 0.02%. [d]Cytoreductive therapies included dasatinib, imatinib, masitinib, nilotinib, midostaurin, brentuximab vedotin, cladribine, hydroxyurea, rapamycin, and interferon alpha. Includes treatments received by patients at baseline; patients may have received BSC treatments previously that had been discontinued at the time of enrollment/baseline. [e]All patients had at least 2 BSC prior to or at screening. A total of 10 (7.1%) patients treated with avapritinib and 5 (7.0%) patients treated with placebo had <2 BSC at the start of the study.

ITT; intent-to-treat; SD, standard deviation; TKI, tyrosine kinase inhibitor.

Significant improvements in ISM-SAF patient-reported skin domain, individual skin symptoms, and QoL in avapritinib-treated patients

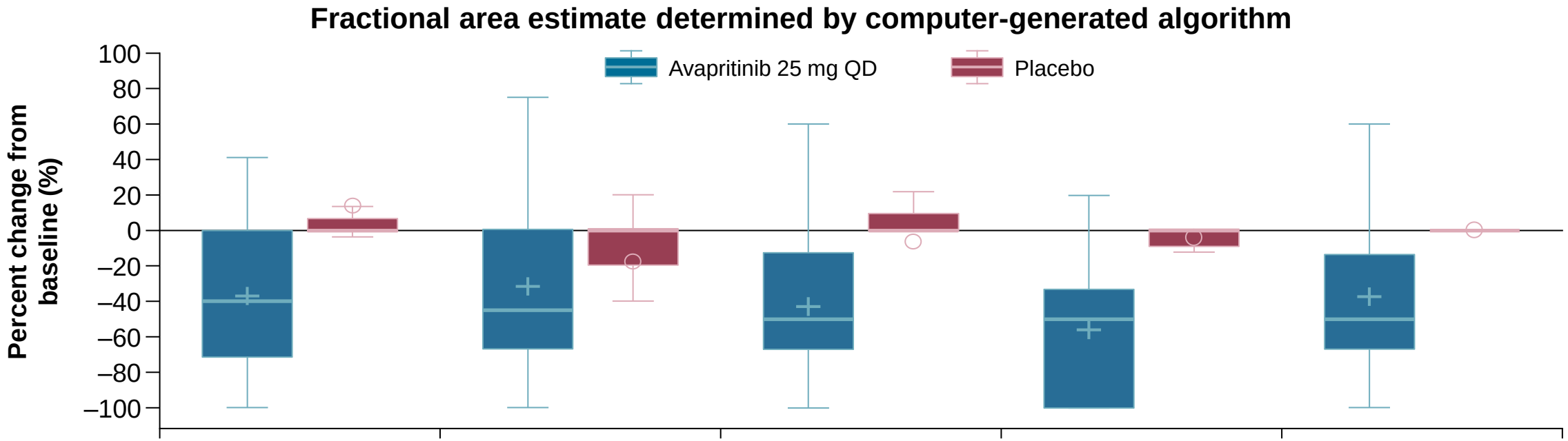
- In the majority of patients, the most severe symptom domain at baseline was the skin domain
- A correlation was observed between ISM-SAF skin domain score change from baseline and MC-QoL total score change from baseline



[a]Skin domain scores include the total score for spot, itching, and flushing severity.

Surface area of skin lesions was reduced at Week 24 in avapritinib-treated patients

- In patients with paired photographs (baseline and Week 24), mean percent reduction (SD) in lesion surface area was −36.6% (53.5) with avapritinib *versus* −1.8% (13.6) with placebo in most affected skin region

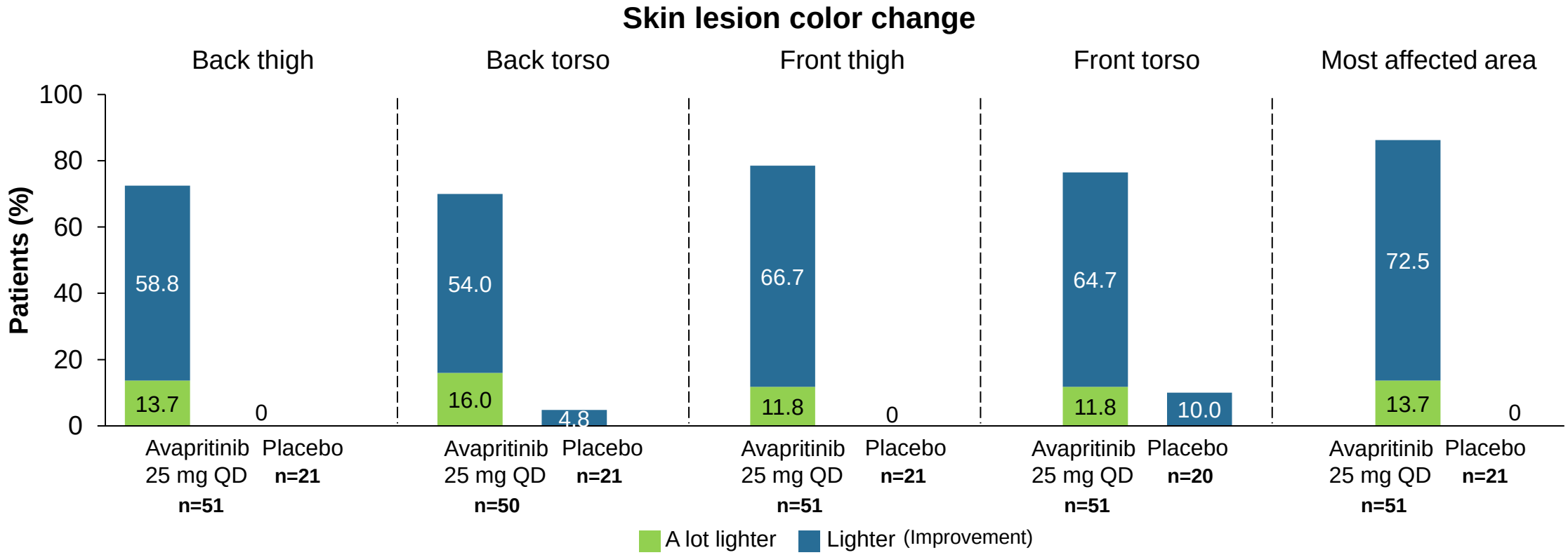


	Back thigh		Back torso		Front thigh		Front torso		Most affected	
N	37	17	40	16	44	19	39	14	45	17
Mean	**–35.8**	**14.6**	**–30.3**	**–15.2**	**–40.9**	**–7.7**	**–57.4**	**–4.3**	**–36.6**	**–1.8**
StdDev	54.4	55.5	66.9	35.9	52.8	30.8	34.3	22.6	53.5	13.6

Outliers are removed for visual presentation. The box represents the first and third quartile of the data. The symbol represents the mean, the line within the box represents the median, and the whiskers represent the upper 75th to 90th percentiles and lower 10th to 25th percentiles.

Avapritinib treatment improved skin lesion color at Week 24 as assessed by blinded Skin Assessment Committee

- In patients with paired photographs, 86.2% of avapritinib-treated patients *versus* 0% of placebo had improved skin lesion color in most affected skin region at Week 24
- Rapid improvement in skin lesion color with avapritinib *versus* placebo was observed
  – At Week 12, 57.2% vs 3.8% of patients, respectively, had improved skin lesion color in most affected area

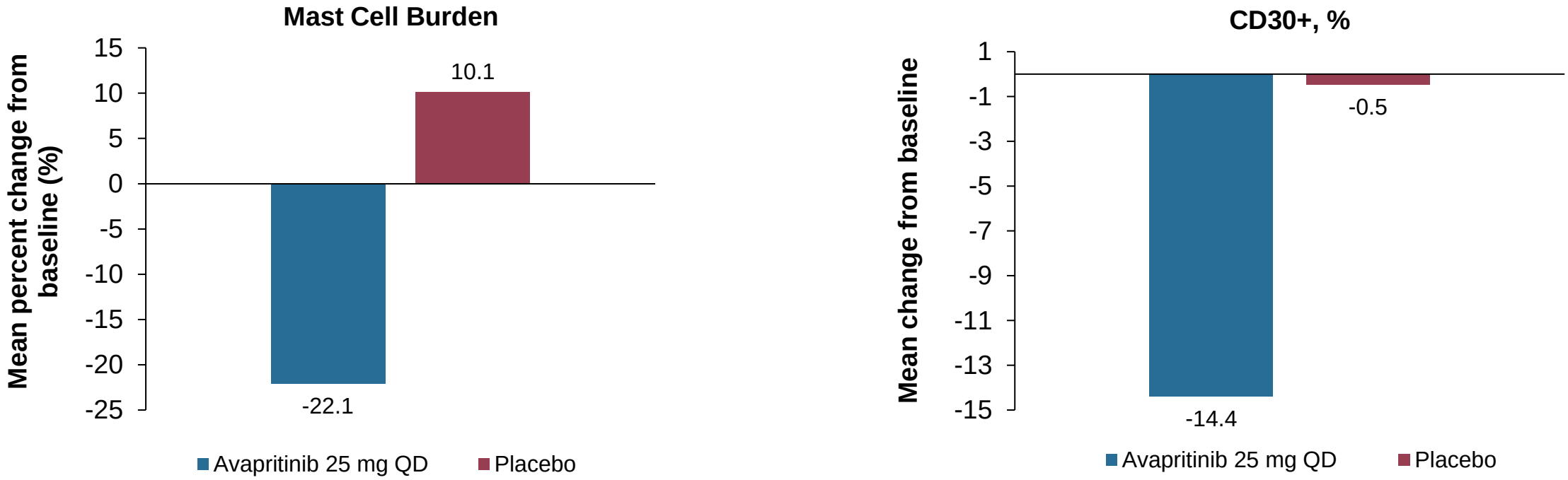


Patients with no change or darkening of skin lesion color have not been included in the figure.

Marked reduction of mast cell burden and CD30+ in skin lesions with avapritinib treatment

- Mean percent change (SD) of mast cell burden decreased at Week 24 with avapritinib (−22.1% [106], n=87) but increased with placebo (10.1% [121], n=49)
- Avapritinib significantly decreased CD30+ mast cell proportion in skin lesions at Week 24 *versus* placebo (−14.4% vs −0.5%; P=0.0015)

Skin lesional tissue pathology



Avapritinib 25mg QD was well tolerated, with a similar safety profile to placebo

- Majority of AEs were Grade 1 or 2 with a low rate of discontinuation
- SAEs were reported more frequently in the placebo group (no treatment-related SAEs in either group)
- Edema adverse events were higher in the avapritinib group (majority Grade 1, and did not result in discontinuation)

	Avapritinib 25 mg QD (N=141)	Placebo (N=71)
Any AEs[a,b], n (%)	128 (90.8)	66 (93.0)
Grade 1–2 AEs	98 (69.5)	51 (71.8)
Grade 1–2 related AEs	74 (52.5)	30 (42.3)
Grade ≥3 AEs	30 (21.3)	15 (21.1)
Grade ≥3 related AEs	3 (2.1)	2 (2.8)
SAEs, n (%)	7 (5.0)	8 (11.3)
Any grade TRAEs	77 (54.6)	32 (45.1)
Most frequently reported TRAEs (≥5% of patients)		
Headache	11 (7.8)	7 (9.9)
Nausea	9 (6.4)	6 (8.5)
Peripheral edema	9 (6.4)	1 (1.4)
Periorbital edema	9 (6.4)	2 (2.8)
Dizziness	4 (2.8)	5 (7.0)
TRAEs leading to discontinuation	2 (1.4)	1 (1.4)

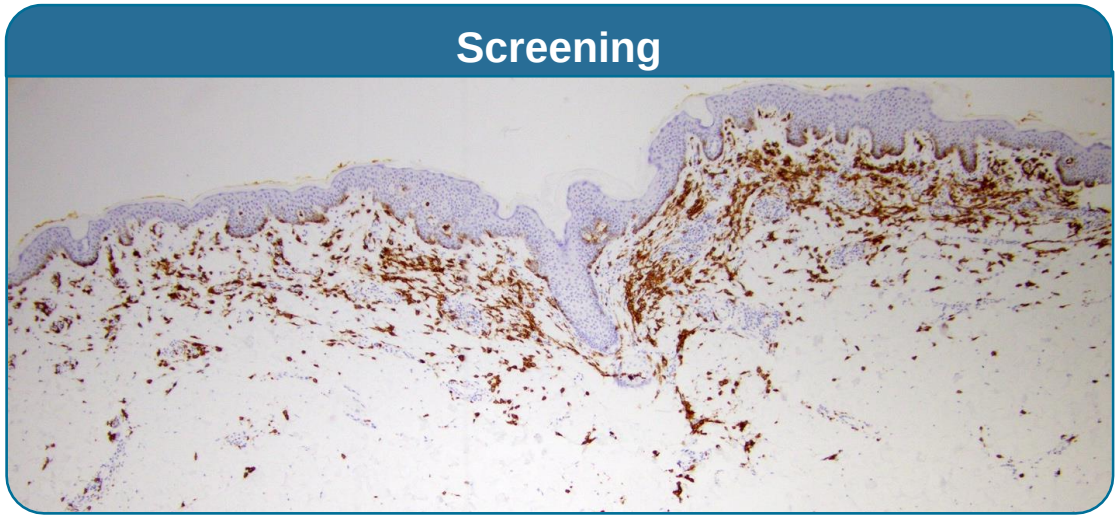
[a]AEs reported occurred between day 1 of Part 2 through to a day prior to day 1 of Part 3 if the patient crossed over to Part 3; if the patient did not crossover, then through 30 days after the last dose of study drug. Treatment-emergent AEs were defined as any AE that occurred between day 1 of Part 2 through to a day prior to day 1 of Part 3 if the patient crossed over to Part 3; if the patient did not crossover, then through 30 days after the last dose of study drug.
[b]There were too few events (≤5 per group) to assess the impact of avapritinib on anaphylaxis.
AEs, adverse events; SAEs, serious adverse events; TRAEs, treatment-related adverse events.

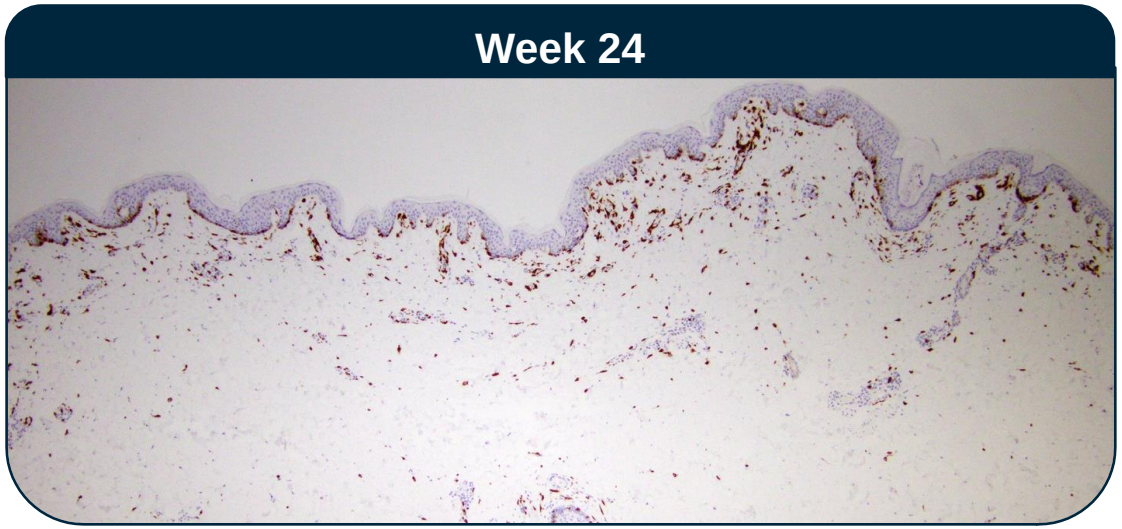
Case study

BSC: **fexofenadine**, **montelukast**, **famotidine**, **omalizumab** (all ongoing)

levocetirizine, **hydroxyzine** (discontinued after ~3 months)

	% change from baseline to Week 24
ISM-SAF TSS	**–23.3**
Skin domain score	–44.4
MC-QoL total score	**–54.7**
Skin domain score	–77.3
Serum tryptase	**–26.3**
***KIT* D816V**	**Central lab:** –63.2
BM mast cells	**No sample collected at Week 24**



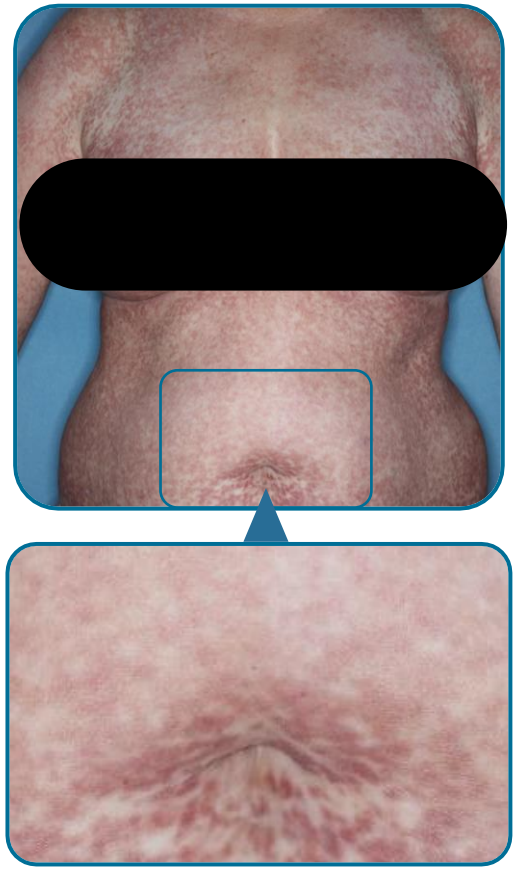


Brown staining indicated CD117 positivity.

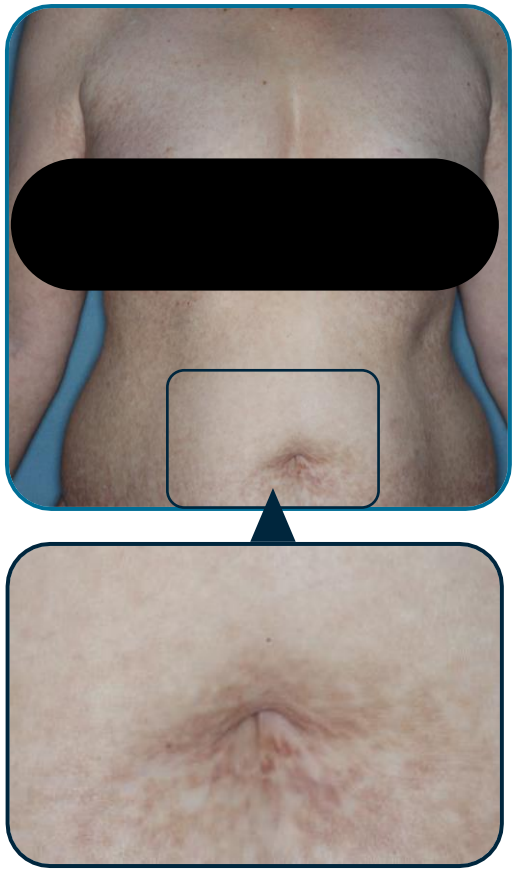
Case study: Area and color of skin lesions improved at Week 24 with avapritinib treatment

Front torso

Baseline

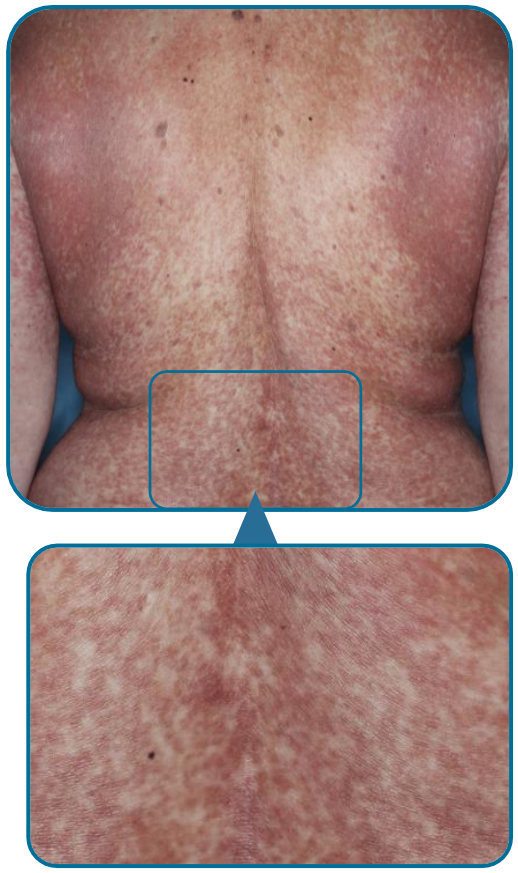


Week 24

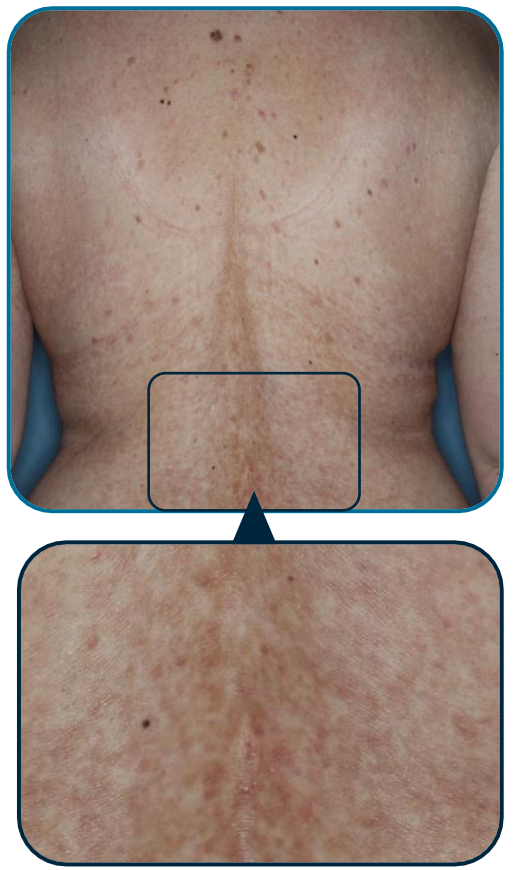


Back torso

Baseline



Week 24



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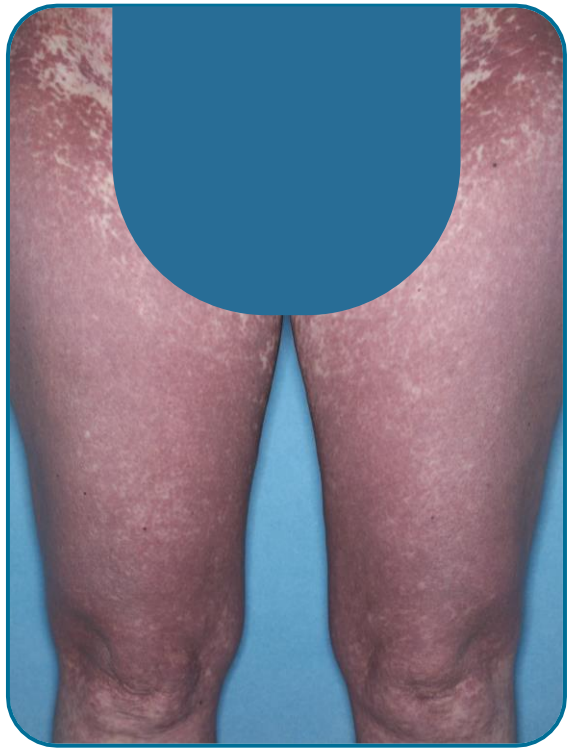
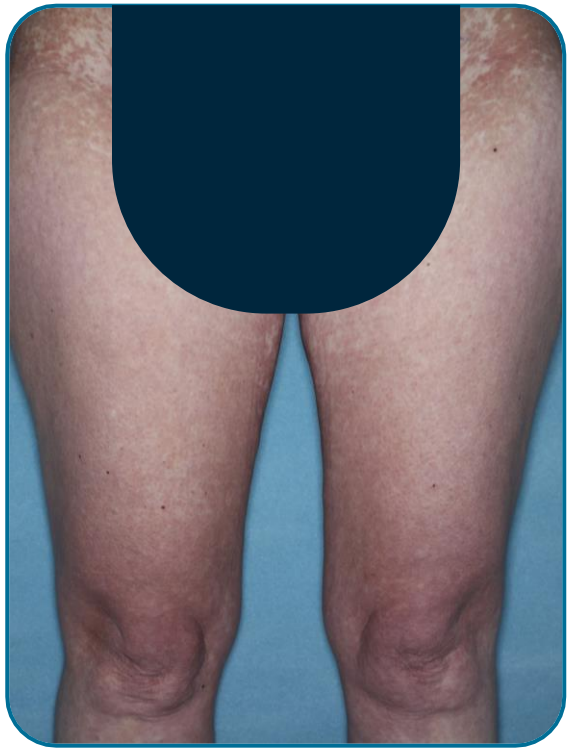
Case study: Area and color of skin lesions improved at Week 24 with avapritinib treatment

Front thigh

Baseline

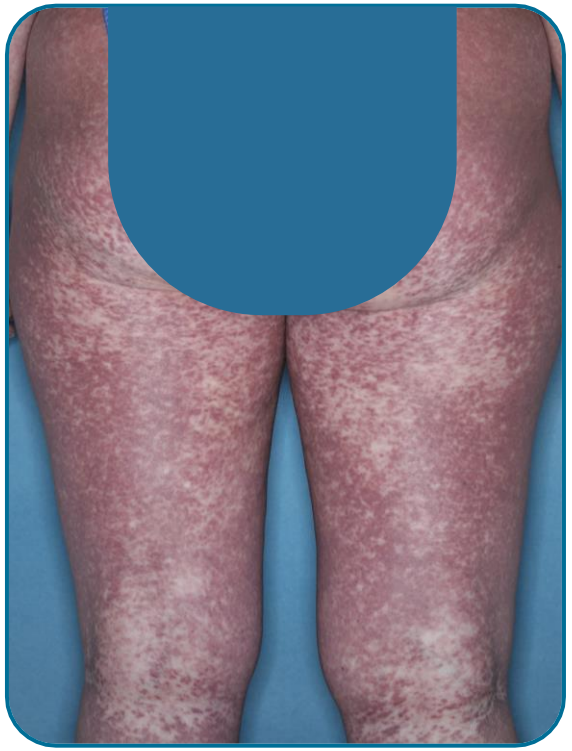


Week 24

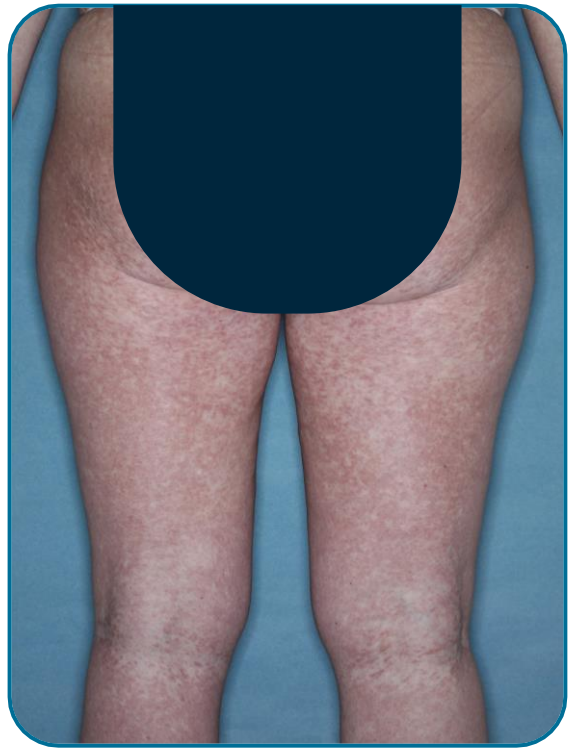


Back thigh

Baseline



Week 24



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Summary

- Avapritinib demonstrated statistically significant and clinically meaningful improvement versus placebo in symptoms in the primary analysis, as measured with the TSS and biomarkers of mast cell burden
  - Of the patients with skin involvement, those treated with avapritinib experienced marked reductions in skin symptoms, skin color, surface area of skin lesions, and pathologic mast cell burden
  - Results confirmed the findings from Part 1, CD30 may be the most relevant biomarker of aberrant mast cells in skin lesions and further research is warranted
  - Improvements in skin symptoms were correlated with improvement in QoL
- Avapritinib was well tolerated and demonstrated a similar safety profile to placebo

Conclusion

- Avapritinib selectively targets KIT D816V, the underlying driver of disease
- Avapritinib substantially impacted ISM-related skin symptoms and skin lesion area and color in addition to providing overall disease improvement in mast cell burden, symptoms, and QoL for patients with ISM

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