Avapritinib Led to Reductions in Symptom Burden and Polypharmacy in Patients With Indolent Systemic Mastocytosis (ISM)

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Introduction

- Indolent systemic mastocytosis (ISM) is a clonal mast cell disease driven by the *KIT* D816V mutation in ~95% of patients[1–3]
- Patients with ISM may experience life-long debilitating symptoms including life-threatening anaphylaxis and poor quality of life (QoL) with significant morbidity[4–8]
- For the management of these symptoms, most patients rely on polypharmacy with best supportive care (BSC) medications, but no controlled trials of BSC medications exist to provide evidence of clinical benefits[1,9]
  - Furthermore, such polypharmacy can have negative consequences for patients, including increased adverse drug events, harmful drug–drug interactions, and decreased medication adherence[9]
- Avapritinib is a potent, oral, tyrosine kinase inhibitor that selectively targets the *KIT* D816V mutation[10,11]
- In the PIONEER trial (NCT03731260), avapritinib plus BSC has been shown to improve symptoms, improve QoL, and reduce biomarkers of mast cell burden *versus* placebo plus BSC in patients with moderate to severe ISM[12]
  - Patients experienced an improvement in all ISM symptoms per the ISM Symptom Assessment Form (ISM-SAF®)[12]
- Avapritinib is approved in the USA and Europe for adult patients with ISM based on the outcomes of the PIONEER trial[10–12]
- Here, we report longer-term findings on symptom burden and examine the changes in polypharmacy following avapritinib treatment in patients with ISM enrolled in PIONEER

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Methods

- PIONEER, a global, randomized, double-blind, placebo-controlled trial, evaluated the safety, efficacy, and QoL in adult patients with ISM receiving avapritinib plus BSC (**avapritinib**) compared with patients receiving placebo plus BSC (**placebo**)
- Eligibility criteria included adult patients experiencing moderate to severe ISM symptoms (total symptom score [TSS] of ≥28 at screening) despite treatment with ≥2 BSC (including H1 and H2 antihistamines, leukotriene receptor antagonists, cromolyn sodium, proton pump inhibitors, corticosteroids, and omalizumab)
- Upon completion of Part 1 (the dose-finding portion) or Part 2 (the randomized, double-blind, placebo-controlled portion) of the PIONEER study, patients were eligible to receive open-label avapritinib for up to 5 years (Part 3, ongoing; **Figure 1**)

Figure 1. PIONEER study design

Overall, 226 patients were exposed to avapritinib 25 mg QD across Parts 1, 2, and 3

Part 1 (24 weeks; complete)[a] Determination of RP2D

Part 2 (24 weeks; complete) Randomized, placebo-controlled, double-blind treatment period

- Avapritinib 25 mg QD n=141
- Placebo n=71

Part 3 (ongoing)[b] Open-label extension (up to 5 years)

Primary objectives
- Long-term safety and efficacy of avapritinib in patients with ISM

Secondary objectives
- Changes in TSS per the ISM-SAF at 1 year of treatment with avapritinib
- Changes in objective measures of disease burden
- Changes in BSC usage
- Changes in QoL measures

[a]The recommended Part 2 dose of avapritinib was identified based on efficacy and safety results from Part 1 that included four blinded, randomized cohorts: 25 mg avapritinib (n=10), 50 mg avapritinib (n=10), 100 mg avapritinib (n=10), and placebo (n=9). [b]Part 3 includes 135 patients who received avapritinib in Part 2 and 66 patients who received placebo in Part 2, as well as patients from Part 1.
BSC, best supportive care; ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; QD, once daily; QoL, quality of life; RP2D, recommended Part 2 dose; TSS, total symptom score.

- The ISM-SAF is a validated symptom assessment tool specifically developed for evaluation of ISM symptomology[13–15]
  - TSS is based on the self-reported severity of 11 ISM symptoms
  - The ISM-SAF was developed over the past 8 years with input from patients, disease experts, and global regulatory agencies[14]
- The primary endpoint of PIONEER Part 2 was the mean change in ISM-SAF TSS from baseline to Week 24 in avapritinib-treated patients compared to placebo, and in Part 3 the primary endpoint is to assess the long-term clinical experience of avapritinib
- Changes in BSC usage (overall and by drug class) for the management of ISM symptoms were also assessed
- Data from the completed Part 2 are presented at a data cut-off of June 23, 2022. Part 3 data at Week 48 are presented at a cut-off of April 7, 2023

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Disclosures

Dr Castells has served as a consultant for Blueprint Medicines Corporation and is a PI on several clinical trials for Blueprint Medicines Corporation. She has received author fees from UpToDate and the Editorial Board for *Annals of Allergy, Asthma & Immunology*. For all author disclosures, please contact: medinfo@blueprintmedicines.com

Results

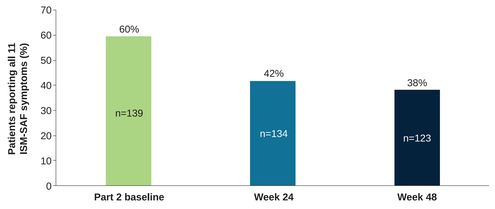
Table 1. Baseline characteristics

Patient demographic	Randomized-controlled Part 2: Avapritinib 25 mg QD (n=141)	Randomized-controlled Part 2: Placebo (n=71)
Age (years), median (range)	50.0 (18–77)	54.0 (26–79)
Female, n (%)	100 (71)	54 (76)
ISM symptom burden		
TSS, mean (SD)	50.2 (19.1)	52.4 (19.8)
Most severe symptom score, mean (SD)	7.7 (1.7)	7.9 (1.7)
Mast cell burden		
Median serum tryptase (central), ng/mL (range)	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)
Mast cell aggregates present, n (%)	106 (75)	57 (80)
Median *KIT* D816V VAF in peripheral blood, % (range)[a]	0.4 (0.0–41.3)	0.3 (0.0–36.7)
KIT D816V positivity, n (%)	131 (93)	69 (97)
SM therapy		
Prior cytoreductive therapy, n (%)	19 (13)	7 (10)
Prior TKI therapy, n (%)	10 (7)	4 (6)
BSC use		
Number of BSC treatments, median (range)	3 (0–11)	4 (1–8)
BSC use at baseline, n (%)	140 (99)	71 (100)
H1 antihistamines	137 (97)	71 (100)
H2 antihistamines	93 (66)	47 (66)
Leukotriene inhibitors	49 (35)	25 (35)
Cromolyn sodium	43 (30)	25 (35)
Proton pump inhibitors	22 (16)	20 (28)
Corticosteroids	17 (12)	7 (10)
Omalizumab	14 (10)	7 (10)
Other[b]	33 (23)	19 (27)

[a]By digital droplet polymerase chain reaction; limit of detection 0.02%. [b]Other includes acetaminophen, acetylsalicylic acid, duloxetine, gabapentin, carbasalate, sumatriptan, topical/inhaled steroids, nasal decongestants, bronchodilators, bisphosphonates, antiemetics, antacids, and vitamin/mineral supplements
SD, standard deviation; SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor; VAF, variant allele fraction.

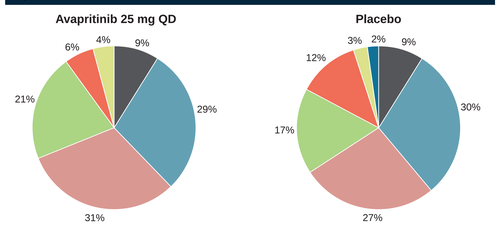
- In Part 2, baseline characteristics and demographics were balanced between avapritinib and placebo groups (**Table 1**)
- BSC use at baseline for all patients who received avapritinib 25 mg once daily (QD) during the study are shown in **Table 1**
- Avapritinib demonstrated a significant and durable improvement in symptoms *versus* placebo at Week 24, as shown by the decrease in TSS, maintained up to Week 48 (**Figure 2A**)
- In each symptom domain, all three individual symptoms (Gastrointestinal [abdominal pain, diarrhea, nausea], **Figure 2B**; Neurocognitive [brain fog, headache, dizziness], **Figure 2C**; Skin [spots, itching, flushing], **Figure 2D**) improved with avapritinib treatment at 24 and 48 weeks and contributed to the decrease in the domain symptom score
- With avapritinib treatment, patients who reported all 11 ISM-SAF symptoms at baseline (60%) reduced at Week 24 (42%) and further improved at Week 48 (38%; **Figure 3**)

Figure 3. Proportion of patients reporting all 11 ISM-SAF symptoms (avapritinib patients only)



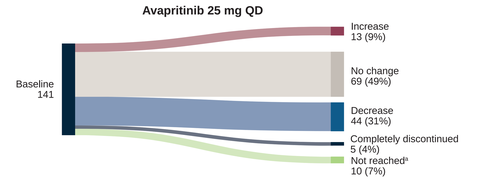
- At baseline, the majority of patients in the PIONEER trial were using three or more BSC classes (**Figure 4**)
  - The number of BSC classes used at baseline was balanced between avapritinib 25 mg QD and placebo treatment groups (**Figure 4**)

Figure 4. Number of BSC classes used at baseline



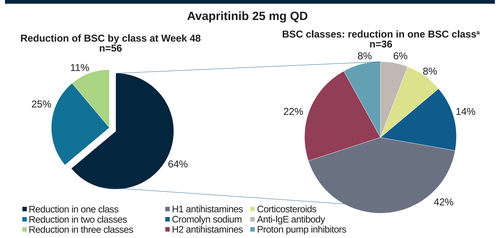
- By Week 24, in patients treated with avapritinib 25 mg QD, 21% (30/141) had decreased BSC *versus* 13% (9/71) of patients with placebo
  - With avapritinib treatment, 3% (4/141) were able to completely discontinue BSC *versus* 0% with placebo
- After 48 weeks of avapritinib 25 mg QD treatment, 31% (44/141) of patients had decreased BSC and 4% (5/141) were able to completely discontinue BSC (**Figure 5**)
- At Week 48, 64% (36/56) of patients experienced a reduction in one class of BSC (**Figure 6, left**)
- Of the patients who experienced a reduction in one class of BSC, the most reductions were seen in H1 antihistamines (42%), H2 antihistamines (22%), and cromolyn sodium (14%; **Figure 6, right**)

Figure 5. Decrease in BSC use at Week 48



[a]Includes patients who had not yet reached 48 weeks of treatment or had discontinued treatment.

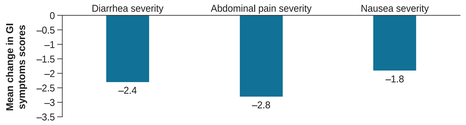
Figure 6. Decreases in individual BSC classes at Week 48



[a]At Week 48, there were no patients reporting one class improvement of leukotriene inhibitors.
IgE, immunoglobulin E.

- After 48 weeks of treatment with avapritinib 25 mg QD, the BSC classes with the largest proportion of patients who decreased or discontinued use were cromolyn sodium (17/67; 25%), H1 antihistamines (42/193; 22%), H2 antihistamines (30/139; 22%), and proton pump inhibitors (6/41; 15%)
- Patients who reduced or discontinued cromolyn sodium (n=14) after 48 weeks on avapritinib had significant improvements in their gastrointestinal symptoms (**Figure 7**)

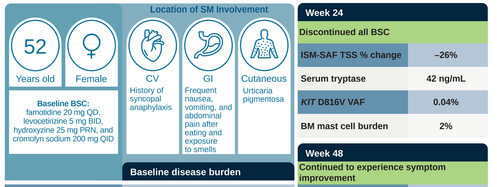
Figure 7. Reduction in cromolyn sodium use at Week 48 aligns with improvements[a] in GI symptoms



GI, gastrointestinal.

- A 52-year-old female diagnosed with ISM in 2015 had symptoms that severely restricted her QoL (**Figure 8**)
- She was randomized to avapritinib 25 mg QD in Part 2 of the PIONEER study
- After 24 weeks on avapritinib, she experienced improvements in symptoms and measures of disease burden and was able to stop all BSC medications
- After 48 weeks on avapritinib, she continued to experience improvement in symptom and disease burden

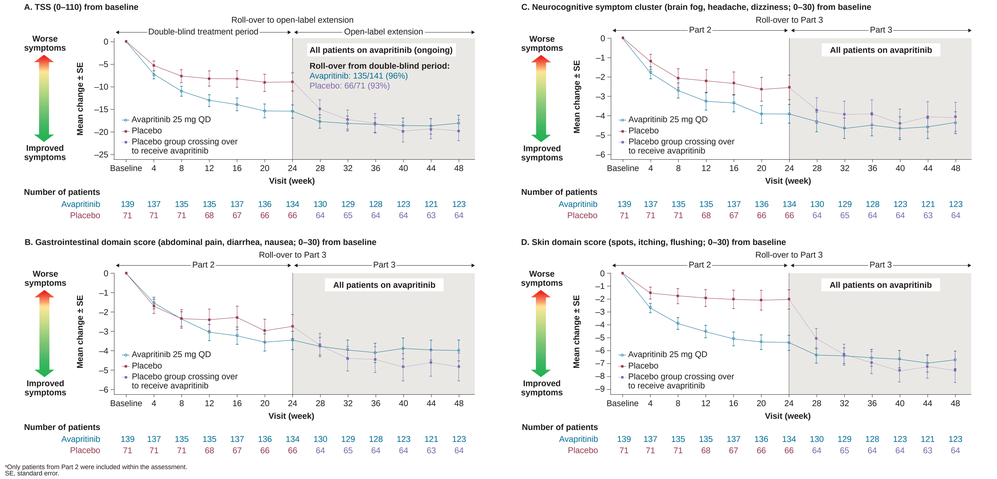
Figure 8. Clinical vignette



Baseline disease burden		Week 24: Discontinued all BSC	
ISM-SAF TSS (0–110)	55.4	ISM-SAF TSS % change	–26%
Serum tryptase	113 ng/mL	Serum tryptase	42 ng/mL
KIT D816V VAF	0.17%	*KIT* D816V VAF	0.04%
BM mast cell burden	5%	BM mast cell burden	2%
		Week 48: Continued to experience symptom improvement	
		ISM-SAF TSS (0–110)	–58%
		Serum tryptase	28 ng/mL
		KIT D816V VAF	0.06%
		BM mast cell burden	NR

BID, twice daily; BM, bone marrow; CV, cardiovascular; NR, not reported; PRN, as needed; QID, four times daily.

Figure 2. Mean change in ISM-SAF TSS and symptom domains over time[a]



[a]Only patients from Part 2 were included within the assessment.
SE, standard error.

Safety results

Table 2. Summary of AEs

	Randomized-controlled Part 2: Avapritinib 25 mg QD (n=141)	Randomized-controlled Part 2: Placebo (n=71)	All patients who received avapritinib 25 mg QD during Parts 1, 2, or 3 (n=226)[a]
Any AEs, n (%)	128 (91)[b]	66 (93)[b]	223 (99)
Grade ≥3 AEs	30 (21)[b]	15 (21)[b]	86 (38)
Any grade TRAEs, n (%)	77 (55)	32 (45)	151 (67)
Grade ≥3 TRAEs	3 (2)	2 (3)	11 (5)
SAEs, n (%)	7 (5)	8 (11)	31 (14)
Most frequently reported TRAEs (≥5% of patients)			
Headache	11 (8)	7 (10)	20 (9)
Nausea	9 (6)	6 (8)	17 (8)
Peripheral edema	9 (6)	1 (1)	23 (10)
Periorbital edema	9 (6)	2 (3)	18 (8)
Dizziness	4 (3)	5 (7)	9 (4)
TRAEs leading to discontinuation	2 (1)	1 (1)	6 (3)

[a]This includes patients from Part 1 who 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 QD. [b]AEs refer to treatment-emergent AEs, 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 cross over, then through 30 days after the last dose of study drug.
AEs, adverse events; SAEs, serious adverse events; TRAEs, treatment-related adverse events.

Placebo-controlled (Part 2) evaluation

- Avapritinib 25 mg QD was generally well tolerated, with a similar safety profile to placebo during the blinded, randomized Part 2 (median follow-up of 5.5 months; **Table 2**)
- The majority of adverse events (AEs) were Grade 1 or 2 with a low rate of discontinuation
- Serious AEs (SAEs) were reported more frequently in the placebo group (no treatment-related SAEs in either group)
- Edema AEs were higher in the avapritinib group (majority Grade 1), and did not result in discontinuation
- AEs of special interest include intracranial hemorrhage (ICH) and cognitive effects. No ICHs were observed. The rate of cognitive effects in patients treated with avapritinib (3%) and placebo (4%) were similar

Longer-term open-label evaluation

- The Part 3 open-label extension of PIONEER allowed for the assessment of longer-term safety of avapritinib at 25 mg QD in 226 patients
- Median total follow-up across all parts of the study for avapritinib 25 mg QD was 18.0 months (range 0.7–46.1 months)
- No new safety concerns were observed with longer follow-up; the most common treatment-related AEs (TRAEs; ≥5% of patients) remained consistent to those reported during Part 2 (**Table 2**)
- No ICHs were observed. The rate of cognitive effects remained low
- The number of TRAEs leading to discontinuation remained low
- Drug interruptions were predominantly for non-TRAE and other reasons

Conclusions

- Avapritinib-treated patients showed rapid and clinically meaningful improvements in disease-related symptoms compared with patients on placebo (both with BSC) at 24 weeks of treatment
  - Durable benefit was seen at 48 weeks of therapy, with continued symptom improvement seen across all three symptom domains (gastrointestinal, neurocognitive, and skin)
  - Patients eliminated more symptoms on avapritinib *versus* placebo (both with BSC) after 24 weeks of treatment, and this continued to improve at Week 48
- At baseline, patients enrolled in PIONEER had moderate to severe disease symptoms as assessed by TSS, despite taking at least two BSC medications
  - Treatment with avapritinib reduced the use of BSC medications in patients with ISM, with further reductions seen with longer-term use at Week 48
  - Classes of BSC medications with the greatest reductions in use were cromolyn sodium, proton pump inhibitors, H1 antihistamines, and H2 antihistamines
  - Patients who reduced cromolyn sodium use continued to have markedly improved GI symptoms
- Avapritinib was generally well tolerated, with a similar safety profile to placebo and no new safety concerns observed with a median treatment duration of 18 months

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