Avapritinib Benefit in Patients With Moderate Symptoms of Indolent Systemic Mastocytosis: Subgroup Analysis From PIONEER

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Introduction

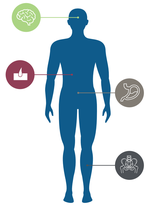
- Systemic mastocytosis (SM), including indolent SM (ISM), is a clonal mast cell disease driven by the *KIT* D816V mutation in 95% of cases[1-3]
- ISM is characterized by chronic heterogeneous, debilitating symptoms across multiple organ systems that negatively impact quality of life (QoL)[4-7]
- Avapritinib is a potent, oral, tyrosine kinase inhibitor that selectively targets the *KIT* D816V mutation[8]
- In PIONEER (NCT03731260), avapritinib significantly improved ISM-Symptom Assessment Form[a] (ISM-SAF) total symptom scores (TSS), biomarkers of disease burden, and QoL with a well-tolerated safety profile, leading to approval for adults with ISM in the USA and Europe[8,9]
- Patients who enrolled on PIONEER could have either moderate (TSS 28–42) or severe (TSS ≥42) symptoms despite the use of symptom-directed best supportive care (BSC; including H1 and H2 antihistamines, leukotriene inhibitors, cromolyn sodium, protein pump inhibitors, corticosteroids, and anti-immunoglobulin E antibodies)
- Prior analyses have focused on the benefit of avapritinib treatment to the study population as a whole. Here, we report a subgroup analysis to determine the effects of avapritinib treatment on patients with moderate symptoms and patients with severe symptoms at baseline

[a]ISM-SAF © 2018 Blueprint Medicines Corporation.

Figure 2. The ISM-SAF is a validated symptom assessment tool

ISM-SAF

- TSS based on severity of 11 ISM symtoms
- Developed over the past 8 years with input from patients, disease experts, and global regulatory agencies[19]



ISM-SAF	
ISM Symptom	**Scoring**
Abdominal pain Diarrhea Nausea	Scored 0–10 daily on handheld device
Spots Itching Flushing	0 = no symptom 10 = **worst imaginable** symptom
Brain fog Headache Dizziness	Analyzed as a 14-day moving average
Bone pain Fatigue	
	TSS (0–110) **Mild symptoms TSS <28** **Moderate symtoms TSS 28-42** **Severe symptoms TSS ≥42**

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 compared with patients receiving placebo plus BSC
- Adult patients with centrally confirmed ISM with uncontrolled moderate (TSS 28–42) to severe (TSS ≥42) symptoms at screening, despite treatment with ≥2 BSC, were eligible for the study
- In Part 2, 212 patients were randomly assigned to receive avapritinib 25 mg orally once daily (QD) plus BSC (avapritinib; n=141) or placebo plus BSC (placebo; n=71) for 24 weeks. After 24 weeks of treatment, patients were eligible to receive open-label avapritinib 25 mg QD for up to 5 years in Part 3 (**Figure 1**)
- The ISM-SAF is a validated symptom assessment tool specifically developed for evaluation of ISM symptomology[10–12] (**Figure 2**)
  - TSS is based on self-reported severity of 11 ISM symptoms
  - The ISM-SAF was developed over 8 years with input from patients, disease experts, and global regulatory agencies[9]
- The primary endpoint of PIONEER was the change in ISM-SAF TSS from baseline to Week 24 in avapritinib-treated patients compared to placebo-treated patients and secondary endpoints included change in biomarkers of disease burden
  - In these analyses the mean percentage change was stratified by the baseline disease severity (moderate and severe)
  - Data from the completed Part 2 of the ongoing PIONEER study (as of June 23, 2022) are presented

Figure 1. Study design

Screening period

- 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

Randomization (Study initiation: June 2020) → **Double-blind for treatment period: (24 weeks)** (Data cut for treatment period: June 2022) → **Open-label extension (5 years)** (Open-label extension: to 2027)

(N=212) → R 2:1

- **Avapritinib 25 mg QD[a] n=141**
- **Placebo n=71**

Both groups continued optimized BSC as needed

→ **Avapritinib 25 mg (ongoing)**

Symptoms
Primary endpoint
- Mean change in ISM-SAF **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**

QoL
- Mean % change in QoL score, as measured by **MC-QoL**

[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 four 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.
BSC, best supportive care; IgE, immunoglobulin E; ISM, indolent systemic mastocytosis; 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.

Results

- At baseline, 52 avapritinib-treated patients and 26 placebo-treated patients had moderate symptoms, and 87 avapritinib-treated patients and 45 placebo -treated patients had severe symptoms, all despite optimized use of symptom-directed therapies. Baseline characteristics in these groups are presented in **Table 1**

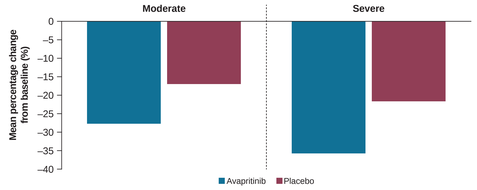
Table 1. Baseline characteristics

	Moderate symptoms (TSS 28–42)		Severe symptoms (TSS ≥42)	
	Avapritinib 25 mg (n=52)[b]	**Placebo (n=26)**	**Avapritinib 25 mg (n=87)[b]**	**Placebo (n=45)**
Age (years), median (range)	51 (22–77)	58 (30–79)	49 (18–73)	53 (26–73)
Female, n (%)	31 (60)	18 (69)	67 (77)	36 (80)
ISM symptom burden				
TSS score, mean (SD)[a]	31.7 (7.0)	33.6 (6.9)	61.2 (15.2)	63.3 (16.4)
Disease burden markers				
Median serum tryptase (central), ng/mL (range)	34.75 (3.6–248.8)	44.15 (6.1–501.6)	38.40 (5.5–256.0)	43.50 (5.7–159.0)
Median bone marrow biopsy mast cells (central), % (range)	6.0 (1.0–50.0)	8.5 (1.0–70.0)	7.0 (1.0–50.0)	7.0 (2.0–40.0)
Median *KIT* D816V VAF in peripheral blood[a], % (range)	0.29 (undetectable–29.12)	0.50 (undetectable–25.69)	0.42 (undetectable–41.29)	0.23 (undetectable–36.74)
Quality of life				
MC-QoL, mean (SD)	47.2 (12.8)	48.2 (15.7)	63.5 (14.8)	62.5 (16.0)

[a]A *KIT* D816V VAF in peripheral blood of less than the limit of detection, 0.022%, is considered undetectable. [b]A total of two patients in the avapritinib group had missing TSS values; therefore, the denominator was on the basis of patients with available data (n=139). SD, standard deviation.

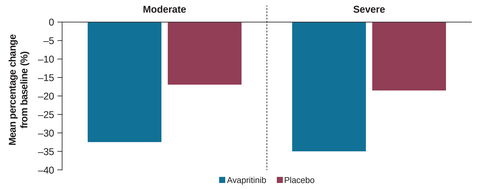
- From baseline to Week 24, avapritinib-treated patients had a mean change from baseline of −15.6 points (95% confidence interval; −18.6 to −12.6) in TSS compared to −9.2 points (−13.1 to −5.2) in the placebo group ($P<0.003$)[13]
- After 24 weeks of therapy, numerical improvements were seen for avapritinib *versus* placebo in mean percentage change from baseline in TSS for patients with both moderate (–27.7% *vs* –16.9%) and severe (–35.8% *vs* –21.6%) symptoms at baseline (**Figure 3**)

Figure 3. Mean percentage change from baseline in TSS at Week 24 for patients with baseline moderate and severe symptoms



- Patients with both moderate and severe symptoms at baseline had numerical improvements in MC-QoL responses at 24 weeks compared to placebo (**Figure 4**)

Figure 4. Mean percentage change from baseline in MC-QoL questionnaire responses at Week 24 for patients with baseline moderate and severe symptoms at baseline



- Avapritinib showed benefit in the disease burden measures serum tryptase (**Figure 5**) and *KIT* D816V VAF (**Figure 6**) for patients with moderate and severe symptoms at baseline *versus* placebo

Figure 5. Mean percentage change from baseline in serum tryptase at 24 weeks for patients with baseline moderate and severe symptoms

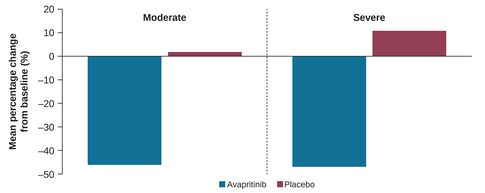
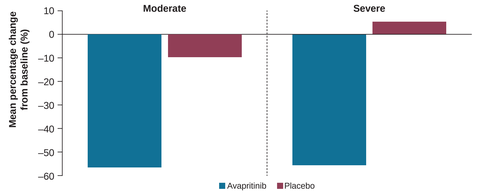


Figure 6. Mean percentage change from baseline in *KIT* D816V VAF at 24 weeks for patients with baseline moderate and severe symptoms



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Placebo-controlled evaluation of safety

- At Week 24, the incidence of anaphylaxis (as a reported adverse event [AE]) was low in both the group with moderate symptoms (2% of avapritinib-treated *vs* 8% of placebo-treated patients) and the group with severe symptoms (3% *vs* 2%)
- AEs after 24 weeks of therapy were similar in avapritinib-treated and placebo-treated patients, regardless of whether baseline symptoms were moderate or severe (**Table 2**)

Table 2. Summary of AEs

	Moderate symptoms (TSS 28–42)		Severe symptoms (TSS ≥42)	
	Avapritinib 25 mg n=52	**Placebo n=26**	**Avapritinib 25 mg n=87**	**Placebo n=45**
Any AEs[a,b], n (%)	46 (88)	25 (96)	81 (93)	41 (91)
Grade ≥3 AEs	11 (21)	6 (23)	19 (22)	9 (20)
Grade ≥3 related AEs	2 (4)	1 (4)	1 (1)	1 (2)
SAEs, n (%)	1 (2)	3 (12)	6 (7)	5 (11)
Any grade TRAEs, n (%)	23 (44)	12 (46)	53 (61)	20 (44)
Most frequently reported TRAEs (≥5% in avapritinib or placebo arm overall)				
Headache	2 (4)	4 (15)	9 (10)	3 (7)
Nausea	3 (6)	4 (15)	6 (7)	2 (4)
Peripheral edema	5 (10)	0 (0)	4 (5)	1 (2)
Periorbital edema	1 (2)	1 (4)	8 (9)	1 (2)
Dizziness	1 (2)	1 (4)	3 (3)	4 (9)
TRAEs leading to discontinuation, n (%)	1 (2)	1 (4)	1 (1)	0 (0)

AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event.

Conclusions

- ISM is a disease driven by *KIT* D816V–mutant mast cells that can be targeted by avapritinib
- Avapritinib-treated patients showed rapid and clinically meaningful improvements in disease-related symptoms compared to placebo-treated patients at 24 weeks of treatment, regardless of whether symptoms were moderate or severe at baseline
- Avapritinib-treated patients showed numerical improvements in the disease burden markers serum tryptase and *KIT* D816V VAF at 24 weeks, regardless of symptom severity at baseline
- Avapritinib was well tolerated in patients with moderate and patients with severe symptoms, with a similar safety profile in each of the two subgroups
- Further research is needed to understand the impact of avapritinib on anaphylaxis in the ISM population
- Avapritinib is effective across the clinical spectrum of ISM. Avapritinib should be considered in patients with moderate symptoms, as well as patients with severe symptoms, when such symptoms are present despite the use of symptom-directed therapies

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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.

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