# Avapritinib Improved Gastrointestinal Symptoms in Patients With Indolent Systemic Mastocytosis: Registrational Double-Blind, Placebo-Controlled PIONEER Study

Poster Number P241


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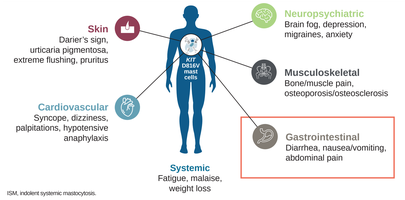
## Background

- Indolent systemic mastocytosis (ISM) is a clonal mast cell disease driven by the *KIT* D816V mutation in ~95% of adult cases[1–4]
- Patients with ISM can have lifelong debilitating symptoms across multiple organ systems[5–9]
  - Gastrointestinal (GI) symptoms are one of the most frequently reported and disabling symptoms in patients with ISM, with diarrhea and abdominal bloating and pain, nausea, vomiting, and gastroesophageal reflux being frequently experienced in and negatively impacting their quality of life (QoL)[7, 10] (**Figure 1**)
- Most patients rely on polypharmacy with best supportive care (BSC) medications, such as H1 and H2 histamine receptor antagonists, ketotifen, and cromolyn sodium, for the management of symptoms. In many patients, these symptoms are not adequately controlled with BSC medications alone[9,11]
- Avapritinib is a potent and highly selective oral therapy targeting KIT D816V, the underlying driver of systemic mastocytosis[1, 2, 4, 12]
- Avapritinib is approved in the USA for adult patients with ISM and advanced systemic mastocytosis and in Europe for adult patients with AdvSM after ≥1 prior systemic therapy; avapritinib is not recommended for patients with platelet counts <50×10⁹/L.[13,14]
- Here, we report on the efficacy of avapritinib on the GI symptoms of patients with ISM, and the subsequent effect on QoL

### Figure 1. ISM Symptoms

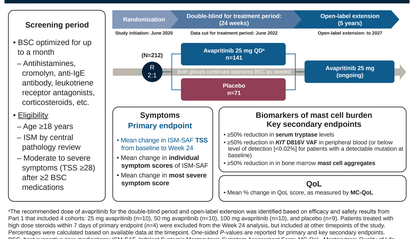



ISM, indolent systemic mastocytosis.

## Methods

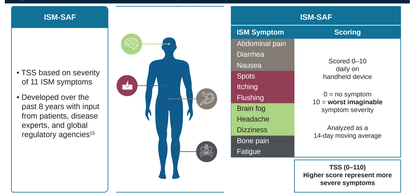
- PIONEER (NCT03731260), a global, randomized, double-blind, placebo-controlled trial, evaluated the safety, efficacy, and QoL in patients with ISM receiving avapritinib + BSC (henceforth termed avapritinib group) compared to patients receiving placebo + BSC (henceforce termed placebo group) (**Figure 2**)
- The ISM Symptom Assessment Form (ISM-SAF ©2017) is a validated symptom assessment tool specifically developed for evaluation of ISM symptomology, including the GI symptoms: diarrhea, abdominal pain, and nausea (**Figure 3**)[15–17]
  - Developed over the past 8 years with input from patients, disease experts, and global regulatory agencies[15]
  - The mean change in Total Symptom Score (TSS) is based on 14-day average of patient-reported severity of 11 ISM symptoms on the ISM-SAF
- Patients completed the Mastocytosis Quality of Life questionnaire (MC-QoL),[18] with a 2-week recall period, once every 4 weeks

### Figure 2. PIONEER study design




*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.
BSC, best supportive care medications; 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.

### Figure 3. ISM-SAF is a validated symptom assessment tool




| ISM-SAF | |
|---|---|
| **ISM Symptom** | **Scoring** |
| Abdominal pain | Scored 0–10 daily on handheld device<br>0 = no symptom<br>10 = worst imaginable symptom severity<br>Analyzed as a 14-day moving average |
| Diarrhea | |
| Nausea | |
| Spots | |
| Itching | |
| Flushing | |
| Brain fog | |
| Headache | |
| Dizziness | |
| Bone pain | |
| Fatigue | |

**TSS (0–110)**
**Higher score represent more severe symptoms**

## Results

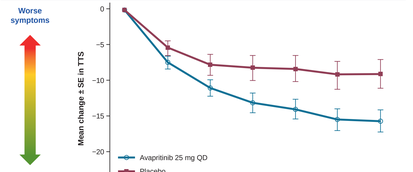
- Baseline patient demographics and characteristics were well balanced across avapritinib and placebo groups (**Table 1**)

### Table 1. Baseline demographic and characteristics

| | ITT population (N=212) | |
|---|---|---|
| **Patient demographic** | **Avapritinib 25 mg QD (n=141)** | **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 score, mean (SD) | 50.2 (19.1) | 52.4 (19.8) |
| Most severe symptom score, mean (SD) | 7.7 (1.7) | 7.9 (1.7) |
| GI TSS score, mean (SD) | | |
| Diarrhea severity | 2.9 (2.4) | 3.1 (2.6) |
| Diarrhea frequency | 1.4 (1.6) | 1.5 (1.5) |
| Abdominal pain | 3.9 (2.3) | 4.0 (2.5) |
| Nausea | 2.9 (2.5) | 3.4 (2.5) |
| **SM therapy** | | |
| Prior cytoreductive therapy, n (%)[a] | 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 (%)[b] | 140 (99) | 71 (100) |
| H1 antihistamines | 137 (97) | 71 (100) |
| H2 antihistamines | 93 (66) | 47 (66) |
| Leukotriene receptor antagonists | 49 (35) | 25 (35) |
| Cromolyn sodium | 43 (30) | 25 (35) |
| Proton pump inhibitors | 22 (16) | 20 (28) |
| Corticosteroids | 17 (12) | 7 (10) |
| Anti-IgE antibody (omalizumab) | 14 (10) | 7 (10) |
| Other | 33 (23) | 19 (27) |

[a]Cytoreductive therapies included dasatinib, imatinib, masitinib, nilotinib, midostaurin, brentuximab vedotin, cladribine, hydroxyurea, rapamycin, and interferon alfa, includes treatments received by patients at baseline; patients may have received BSC treatments previously that had been discontinued at the time of enrollment/baseline. [b]All patients had ≥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.
GI, gastrointestinal; ITT, intent-to-treat; SD, standard deviation; SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor.

### Figure 4. Mean change in TSS over time up to 24 weeks for patients in the avapritinib group *versus* the placebo group

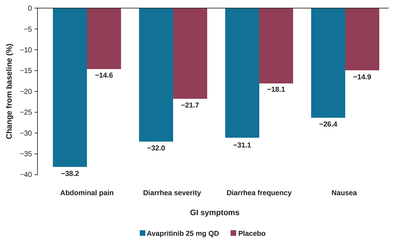



| Number of patients | Baseline | 4 | 8 | 12 | 16 | 20 | 24 |
|---|---|---|---|---|---|---|---|
| Avapritinib | 139 | 137 | 135 | 135 | 135 | 136 | 133 |
| Placebo | 71 | 71 | 71 | 68 | 67 | 66 | 66 |

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

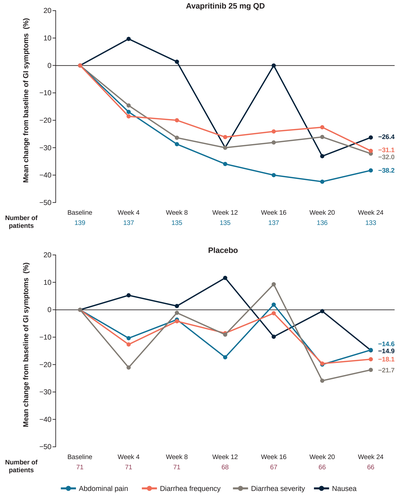
- At 24 weeks, avapritinib demonstrated significant and durable improvement in symptoms *versus* placebo (–15.6 *vs* –9.2, *P*=0.003) in TSS, the primary endpoint of the PIONEER trial[19]

### Figure 5. Mean change in GI symptoms on the ISM-SAF from baseline up to Week 24 by treatment group



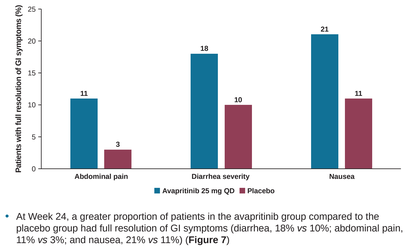

- Patients experienced improvements in the ISM-SAF assessed GI symptoms at Week 24 with avapritinib *versus* placebo (abdominal pain, 38.2% *vs* 14.6%; diarrhea severity, 32.0% *vs* 21.7%; diarrhea frequency, 31.1% *vs* 18.2%; nausea, 26.4% *vs* 14.6%) (**Figure 5**)
- Avapritinib demonstrated durable improvements in GI symptoms *versus* placebo that were sustained through to Week 24

### Figure 6. Mean change from baseline in individual GI symptom scores from ISM-SAF from baseline up to Week 24 over time by treatment group



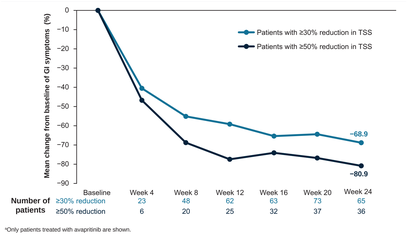

- Improvements were rapid (within the initial 4 weeks) for diarrhea and abdominal pain in the avapritinib group compared to the placebo group (**Figure 6**)

### Figure 7. Proportion of patients who had full resolution of GI specific symptoms at Week 24




- At Week 24, a greater proportion of patients in the avapritinib group compared to the placebo group had full resolution of GI symptoms (diarrhea, 18% *vs* 10%; abdominal pain, 11% *vs* 3%; and nausea, 21% *vs* 11%) (**Figure 7**)

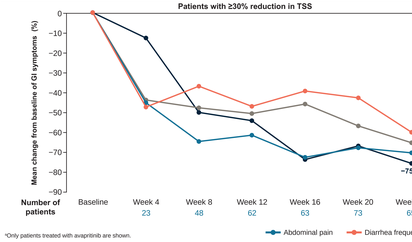
### Figure 8. Mean change from baseline in the GI domain score from ISM-SAF from baseline up to Week 24 in patients in the avapritinib group with a ≥30% or ≥50% reduction in TSS[a]




[a]Only patients treated with avapritinib are shown.

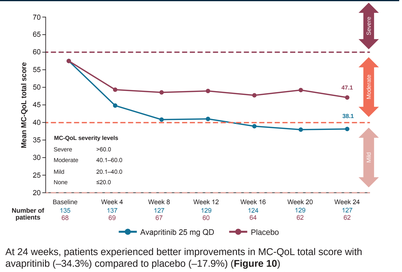
- In patients with a ≥30% and ≥50% reduction in TSS, improvements from baseline in the GI domain score were –68.9% and –80.9%, respectively (**Figure 8**)
- In patients with a ≥30% and ≥50% reduction in TSS, improvements from baseline in abdominal pain (–70.2% and –85.3%), diarrhea severity (–64.9% and –70.8%), diarrhea count (–59.4% and –65.0%), and nausea (–75.2% and –62.5%) at Week 24 were observed (**Figure 9**)
- Baseline MC-QoL total scores correlated with baseline ISM-SAF GI domain scores (R=0.56)

### Figure 9. Mean change from baseline in individual GI symptom scores from ISM-SAF from baseline up to Week 24 in patients in the avapritinib group with a ≥30% or ≥50% reduction in TSS[a]




[a]Only patients treated with avapritinib are shown.

### Figure 10. Mean MC-QoL total score up to 24 weeks by treatment group




- At 24 weeks, patients experienced better improvements in MC-QoL total score with avapritinib (–34.3%) compared to placebo (–17.9%) (**Figure 10**)
- At 24 Weeks, reduction in cromolyn use was observed in 9 out of 43 patients in the avapritinib group compared to 0 out of 25 patients in the placebo group

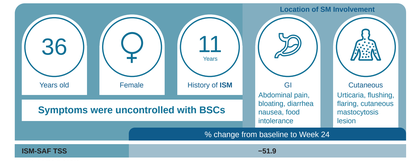
### Table 2. Summary of AEs

| | Avapritinib 25 mg QD (n=141) | Placebo (n=71) |
|---|---|---|
| Any AEs,[a,b] n (%) | 128 (91) | 66 (93) |
| Grade 1–2 AEs | 98 (70) | 51 (72) |
| Grade 1–2 related AEs | 74 (52) | 30 (42) |
| Grade ≥3 AEs | 30 (21) | 15 (21) |
| Grade ≥3 related AEs | 3 (2) | 2 (3) |
| SAEs, n (%) | 7 (5) | 8 (11) |
| Any grade TRAEs | 77 (55) | 32 (45) |
| Most frequently reported TRAEs (≥5% of patients) | | |
| Headache | 11 (8) | 7 (10) |
| Nausea | 9 (6) | 6 (8) |
| Peripheral edema | 9 (6) | 1 (1) |
| Periorbital edema | 9 (6) | 2 (3) |
| Dizziness | 4 (3) | 5 (7) |
| TRAEs leading to discontinuation | 2 (1) | 1 (1) |

[a]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 crossover, then through 30days after the last dose of study drug. [b]There were no 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 as assessed by investigators.

- Avapritinib 25 mg QD was well tolerated, with a similar safety profile to placebo
- The majority of AEs were Grade 1 or 2 with a low rate of discontinuation (**Table 2**)
- SAEs were reported more frequently in the placebo group however there were no treatment-related SAEs in either group
- Reporting of edema events was higher in the avapritinib group (majority Grade 1, and did not result in discontinuation)

### Figure 11. Case study




| | % change from baseline to Week 24 |
|---|---|
| ISM-SAF TSS | −51.9 |
| GI domain score | −59.4 |
| MC-QoL total score | −80.0 |
| Serum tryptase | −81.0 |
| *KIT* D816V | −100.0 |
| BM mast cells[a] | −70.0 |

[a]BM mast cells percentage change from baseline was calculated from measurements taken at baseline and 12 weeks as this was the primary endpoint during part 1 of the PIONEER study.

- After 3 months of avapritinib treatment the patient reported improved GI symptoms, and after 7 months the patient reported minimal GI symptoms and was able to tolerate reintroduced foods
- The patient has continued to take avapritinib 25 mg QD for over 4 years and has reported significant improvement in her QoL with minimal GI symptoms and no cutaneous mastocytosis lesions
- The patient had a basal serum tryptase level of 95.1 mg/mL, and after continued avapritinib treatment, this dropped to 13.5 ng/mL

## Conclusions

- PIONEER is the first randomized, double-blind, placebo-controlled trial of a highly selective KIT D816V-targeting agent in patients with ISM
- Patients treated with avapritinib showed rapid, durable, and clinically meaningful improvements in mast cell burden, symptoms, and QoL compared to patients treated with placebo at 24 weeks of treatment
- At 24 weeks, patients who were treated with avapritinib showed meaningful improvements in GI symptoms assessed by ISM-SAF *versus* placebo
- At 24 weeks, patients treated with avapritinib showed improvements in MC-QoL total scores compared to the placebo group
- A reduction in cromolyn use was observed at 24 weeks in patients who were treated with avapritinib
- Avapritinib was well tolerated with a similar safety profile to placebo

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## Disclosures

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