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Avapritinib Improved Symptoms and Quality of Life in Patients with Indolent Systemic Mastocytosis in the PIONEER Study

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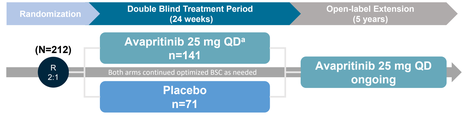
Rationale

- Indolent Systemic Mastocytosis (ISM) is a clonal mast cell disease driven by the *KIT* D816V mutation in approximately 95% of cases[1–3]
- Patients with ISM can have lifelong debilitating symptoms across multiple organ systems which result in impaired daily functioning, ability to work, and quality of life (QoL)[4–7]
- Many patients rely on polypharmacy with best supportive care (BSC) medications; symptoms are not controlled with best supportive care medications in many patients with ISM.[8,9]
- Currently, there are no approved therapies that target the KIT D816V-mutated tyrosine kinase in ISM.
- Avapritinib is a potent and selective inhibitor of the D816V KIT mutation.

Methods

- PIONEER, a randomized placebo-controlled trial, evaluated the safety, efficacy and quality of life of ISM patients receiving avapritinib + BSC (avapritinib) compared to patients receiving placebo + BSC (placebo). ISM patients with uncontrolled moderate-to-severe symptoms, despite treatment with two prior therapies, were eligible for the study.
- The primary efficacy endpoint was mean change in ISM symptoms from baseline to 24-weeks, as measured by a total symptom score (TSS) derived from the ISM Symptom Assessment Form (ISM-SAF), a reliable and validated measure of ISM symptomology.[10]
- Exploratory endpoints included mean and percent change in multiple general and disease-specific patient-reported measures of health status and quality of life scores during the study period (Table 1).

Eligibility
- Age ≥18 years
- ISM confirmed by central pathology review
- Uncontrolled moderate-to-severe (TSS ≥28) symptoms after at least 2 BSC medications



*The recommended dose of avapritinib for Part 2 and Part 3 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)

Symptoms
- Mean change in ISM-SAF Total Symptom Score (**TSS**) from baseline to Week 24 (**primary endpoint**)
- 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
- ≥50% reduction in in bone marrow **mast cell aggregates**

Quality of Life (exploratory endpoints)
- Mean and % change in patient-reported measures of health status & QoL from baseline to Week 24 (Table 1)

Results

- In PIONEER, 141 participants were randomized to avapritinib and 71 to placebo (Table 2).
- Despite use of multiple best supportive care medications, PIONEER patients reported severe ISM symptomology at baseline (Table 2) and worse quality of life than patients with other medical conditions (Figure 1).
- Avapritinib patients experienced improvement in SF-12 physical and mental component summary scores (Figure 2) and all SF-12 health domains (Figure 3)
- Avapritinib patients had significantly greater improvement in quality of life compared to patients receiving placebo, with observed improvement from a nearly 'severe' to mild disease (Figure 4). Significant improvement in symptoms, emotions, and social life/functioning was reported by patients (Figure 5).
- EQ-5D-5L index scores improved in avapritinib patients compared to placebo patients (57.2% versus 15.2%) as did EQ-5D-VAS scores (18.5% versus 4.5%, p=0.048) (Figure 6).
- Patients receiving avapritinib were significantly more likely to have ≥1-point improvement in the PGIS compared to placebo patients (57% versus 39%, p=0.02) (Figure 7).
- At week 24, patients receiving Avapritinib were significantly more likely to report a clinically meaningful improvement than placebo, as reflected by PGIC score ≥3 (80% versus 44%, p<0.0001).

Table 1. Health Status & Quality of Life Measures in PIONEER

Instrument	Domains Assessed	Items	Scoring
Disease-specific Instrument			
Mastocytosis Quality of Life (MC-QoL)[11]	Symptoms, Emotions, Social Life/Functioning, Skin	27	0-100; higher = worse
General Health Status and Quality of Life Instruments			
Short Form 12 (SF-12)[12]	8 Health Domains; Physical & Mental Component Summary Scores	12	0-100; higher = better
EQ-5D-5L[13] Index Score	Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression	5	-0.28-1.0; higher = better
EQ-5D-5L Visual Analogue Scale (EQ-VAS)[14]	General Health State (best health to worst health 'you' can imagine)	1	0-100; higher = better
Patient Global Impression Severity (PGI-S)[15,16]	Symptom Severity (absent, minimal, moderate, severe, very severe)	1	1-5; higher = worse
Patient Global Impression Change (PGI-C)[16,17]	Impression of change/overall improvement	2	1-7; higher = better

Table 2. Baseline Patient Demographics and Characteristics

Baseline Characteristic	Avapritinib 25 mg QD (n=141)	Placebo (n=71)
Age (years), median (range)	50.0 (18–77)	54.0 (26–79)
Female, n (%)	100 (70.9)	54 (76.1)
Total Symptom Score (TSS), mean (SD) [range 0 – 100; TSS ≥28, moderate-to-severe ISM symptoms][10,18]	50.2 (19.1)	52.4 (19.8)
SF-12, mean (SD) (range, 0-100)		
Physical component score (PCS)	33.8 (10.8)	34.1 (10.7)
Mental component score (MCS)	40.6 (10.5)	41.0 (10.7)
EQ-5D-5L, mean (SD)		
Index Score	0.62 (0.28)	0.63 (0.24)
EQ-VAS	57.2 (17.6)	55.9 (17.9)
PGIS, n (%)		
Absent	0 (0%)	0 (0%)
Minimal	9 (7%)	7 (10%)
Moderate	55 (41%)	19 (28%)
Severe	41 (30%)	27 (40%)
Very Severe	30 (22%)	15 (22%)
MC-QoL, mean (SD)	57.5 (16.0)	57.5 (17.2)
Opioid use for SM, n (%)	26 (18.4)	11 (15.5)
Prior cytoreductive therapy, n (%)*	19 (13.5)	7 (9.9)
Prior TKI therapy, n (%)	10 (7.1)	4 (5.6)
Number of best supportive care treatments, median (range)**	3 (0–11)	4 (1–8)

*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.
**All patients had at least two 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.

Figure 1. Baseline SF-12 Scores for ISM Relative to Other Conditions

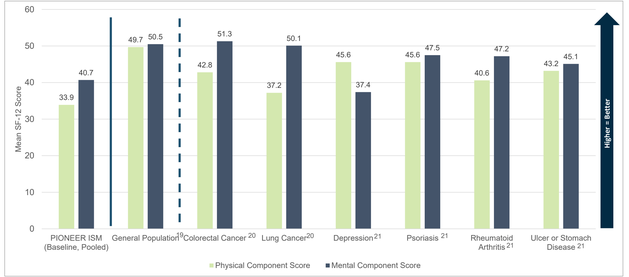


Figure 2. SF-12 PCS and MCS Mean % Change from Baseline at Week 24

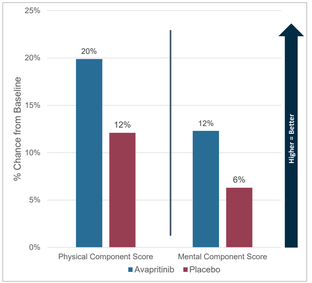


Figure 3. SF-12 Domains Mean % Change from Baseline at Week 24

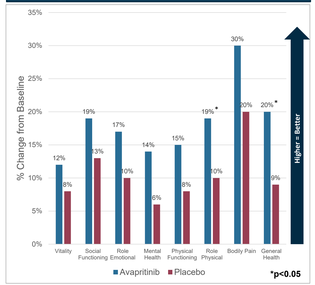


Figure 4. MC-QoL Total Score, Baseline to Week 24

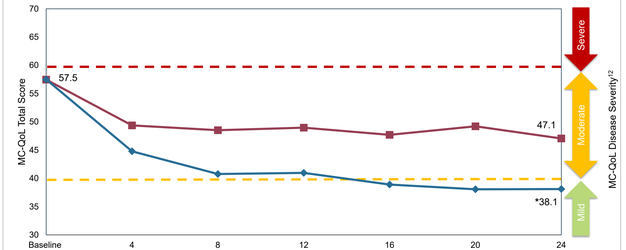


Figure 5. MC-QoL Mean % Change from Baseline by Domain at Week 24

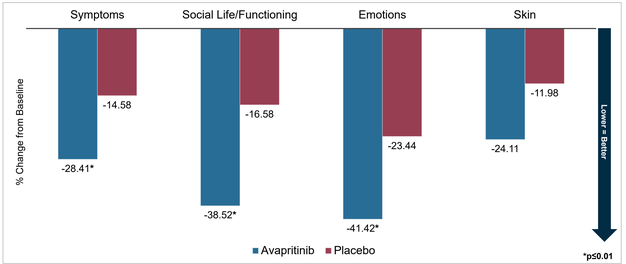
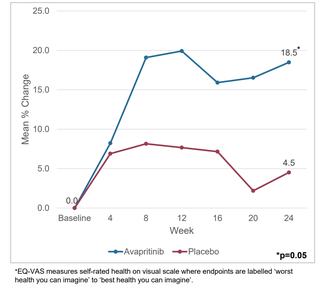
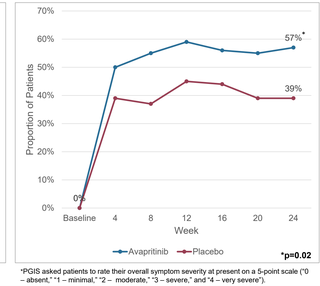


Figure 6. Mean % Change EQ-5D-VAS, Baseline to Week 24



*EQ-VAS measures self-rated health on visual scale where endpoints are labelled 'worst health you can imagine' to 'best health you can imagine'.

Figure 7. Proportion of Patients with ≥1 Point Improvement on PGIS



*PGIS asked patients to rate their overall symptom severity at present on a 5-point scale ("0 – absent," "1 – minimal," "2 – moderate," "3 – severe," and "4 – very severe").

Conclusions

- Despite use of best supportive care medications, ISM patients in PIONEER had severe disease symptomology, poor health status, and impaired quality of life at baseline.
- Patient reported improvement in health status and quality of life measures were observed by week 4 of treatment and sustained through 24 weeks.
- Avapritinib-treated patients experienced significant improvement in symptoms and quality of life.

Abbreviations

QoL, Quality of Life; ISM, Indolent Systemic Mastocytosis; ISM-SAF TSS, Indolent Systemic Mastocytosis Symptom Assessment Form Total Symptom Score; PRO, patient reported outcome; SF-12, 12-Item Short Form Health Survey; PCS, physical component score; MCS, mental component score; MC-QoL, Mastocytosis Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5 Dimension 5 Level; EQ-VAS, EuroQol Visual Analogue Scales; PGI-S, Patient Global Impression of Severity; PGI-C, Patient Global Impression of Change; QD, once daily; TKI, Tyrosine Kinase Inhibitor; BSC, best supportive care; MCFB, mean change from baseline;

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