Long-Term Bone Health Outcomes in Patients Treated with Avapritinib for Indolent Systemic Mastocytosis: Findings from the PIONEER study

Poster Number 530

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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 and associated with symptoms of mast cell activation and tissue infiltration[1–4]
- Approximately 40–60% of patients with ISM have abnormal bone loss,[5] which is associated with an increased risk of skeletal complications, such as secondary osteoporosis (~25% of patients), osteopenia (~30%), and fragility fractures (~30% lifetime risk)[6–8]
  - Decreased bone density may reflect increased mast cell-derived cytokines that promote bone resorption and decreased bone formation[9]
  - Medications used to treat primary osteoporosis increase bone mineral density and ultimately prevent skeletal complications. In secondary osteoporosis, management is often focused at treating the underlying disease causing the decreased bone density[10]
- Bone turnover markers are useful to investigate the effects of anti-osteoporosis therapies on bone
  - Tartrate-resistant acid phosphatase 5b (TRAcP5b) is a bone turnover biomarker associated with osteoclast activity and bone resorption[11,12]
  - Procollagen type 1 N-terminal propeptide (PINP) is a bone turnover marker associated with osteoblast activity and bone formation[13]
  - Increases in bone resorption and bone formation biomarkers are seen with parathyroid hormone receptor agonists used to improve bone density in primary osteoporosis[14,15]
- Avapritinib is an oral, potent, selective KIT D816V inhibitor that was approved for adults with ISM in the USA and for those with moderate-to-severe symptoms in the EU, based on the findings from the randomized, double-blind, placebo-controlled PIONEER study (NCT03731260)[16,17]
- In a previous subset analysis of data from a single site (n=15) from the PIONEER study, patients with ISM treated with avapritinib had improvements in bone mineral density (BMD)[18]
- Here, we expanded upon the prior subset analysis to more comprehensively analyze changes in BMD and bone turnover biomarkers (TRAcP5b and PINP) in avapritinib-treated patients

Methods

Figure 1. PIONEER study design

BSC, best supportive care; QD, once daily; RP2D, recommended Part 2 dose.

- PIONEER is an ongoing study evaluating avapritinib plus best supportive care (BSC) in patients with ISM (**Figure 1**)
  - Patients with centrally confirmed ISM with uncontrolled moderate to severe symptoms (total symptom score of ≥28 at screening; ISM-Symptom Assessment Form[a,19]), despite treatment with ≥2 BSC, were eligible for enrollment
  - We report outcomes from a data cut-off of February 21, 2025
- Physician-reported history of osteoporosis, osteopenia, prior fracture history, and use of medications supporting bone health were collected at enrollment
- Dual-energy X-ray absorptiometry (DXA) scans, optional per the study protocol and performed in a subset of study participants, assessed BMD at screening, and at 12 months and annually thereafter in Part 3
  - The BMD analyses were performed retrospectively only on patients who had been on avapritinib between 6–12 months (Year 1) and 26–37 months (Year 3)
- TRAcP5b and PINP were retrospectively measured in age- and sex-matched healthy donors (HDs) and in the subgroup of patients with banked plasma samples at baseline and while on therapy
- Paired t-test was used for comparing TRAcP5b and PINP at baseline and 24 weeks of avapritinib treatment, and Welch's t-test was used for comparing baseline values in patients *versus* HDs

Results

Baseline demographics

- In PIONEER, 246 patients received avapritinib in Parts 1, 2 or 3, with a median duration of treatment of 40 months (~3 years)
  - Of these, 48 (20%) had a medical history of osteopenia and 56 (23%) had a medical history of osteoporosis
- In total, 79 patients (median [range] age 51.0 [22–73] years; 75% female) receiving avapritinib had baseline and ≥1 post-baseline DXA scans (**Table 1**)
  - Of these, 13 patients (16%) used anti-osteoporotic therapy (bisphosphonates, denosumab or parathyroid hormone analogues) while receiving avapritinib

Changes in BMD following treatment with avapritinib

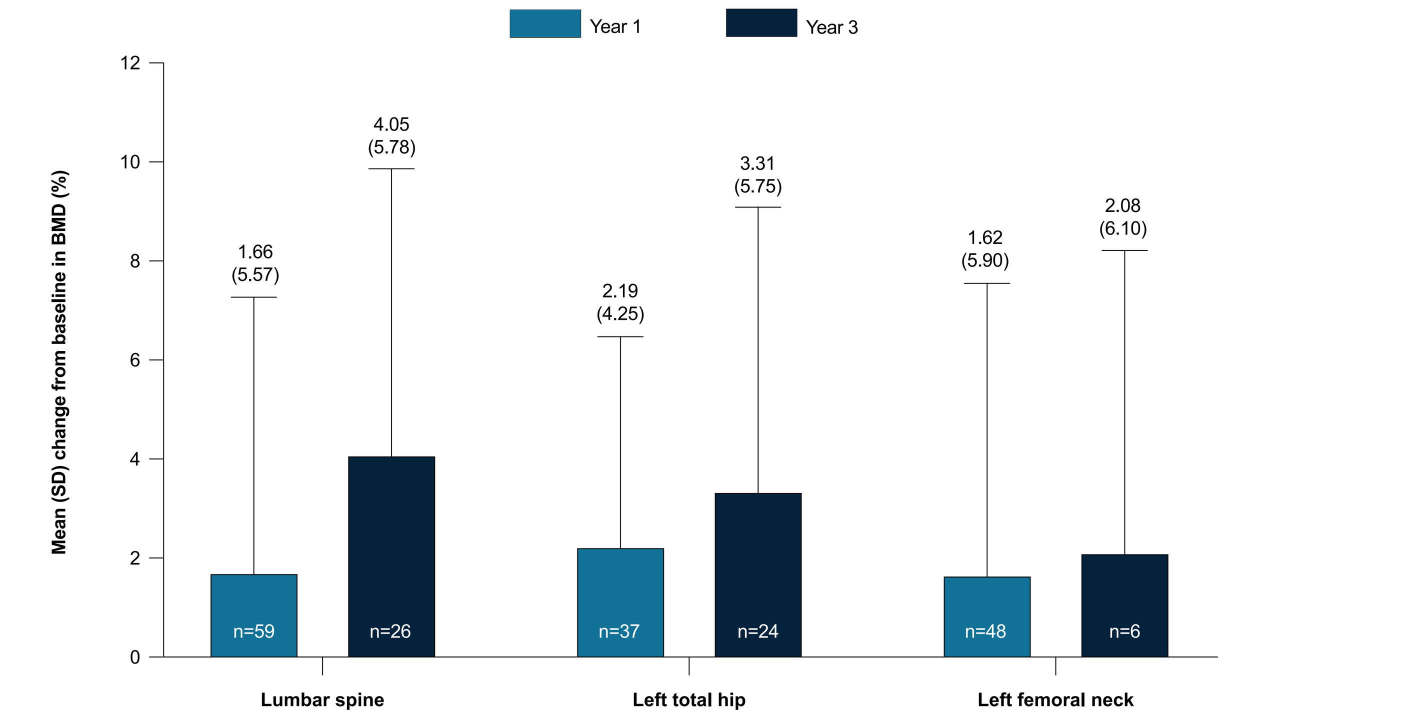
- In avapritinib-treated patients, an increase from baseline in mean BMD at 1 year and 3 years of treatment was observed in the lumbar spine (Year 1: 1.66%; Year 3: 4.05%), left total hip (Year 1: 2.19%; Year 3: 3.31%), and left femoral neck (Year 1: 1.62%; Year 3: 2.08%; **Figure 2**)
  - This pattern of increased mean BMD was also generally observed for patients receiving and not receiving anti-osteoporosis therapy concomitantly with avapritinib
  - For context, a change in BMD in the total hip of 1.42% is the threshold at which fracture risk reduction may be seen[20]
  - In the absence of any therapy, white women in the peri-menopausal period have an average rate of decline in BMD of –2.5% per year in the lumbar spine and –1.8% per year in the femoral neck[21]

Table 1. Baseline demographics in patients with ISM at the time of initiating avapritinib treatment

	All patients who received avapritinib (N=246)	Patients with paired DXA scans available (N=79)	Patients with bone turnover biomarkers measured at baseline (N=131)
Age, median years (range)	51 (18–79)	51 (22–73)	52 (22–79)
Female, n (%)	179 (73)	59 (75)	98 (75)
Concomitant medications supporting bone health at baseline, n (%)			
Calcium	60 (24)	19 (24)	29 (22)
Vitamin D	96 (39)	30 (38)	55 (42)
Bisphosphonates	24 (10)	6 (8)	14 (11)
Denosumab	8 (3)	4 (5)	2 (2)
Parathyroid hormone analogs	1 (<1)	1 (<1)	1 (<1)
Medical history of fractures, n (%)	28 (11)	6 (8)	15 (11)
BMI, median kg/m² (range; n)	28.2 (17.6–51.4; 242)	27.8 (19.4–51.4; 78)	28.2 (17.6–42.2; 129)
Bone mineral density, g/cm², mean (SD; n)			
Lumbar spine	NA	1.021 (0.177; 77)	1.029 (0.177; 68)
Left total hip	NA	0.934 (0.139; 60)	0.931 (0.152; 51)
Left femoral neck	NA	0.845 (0.158; 64)	0.835 (0.158; 57)

BMI, body mass index; DXA, dual-energy X-ray absorptiometry; NA, not available; SD, standard deviation.

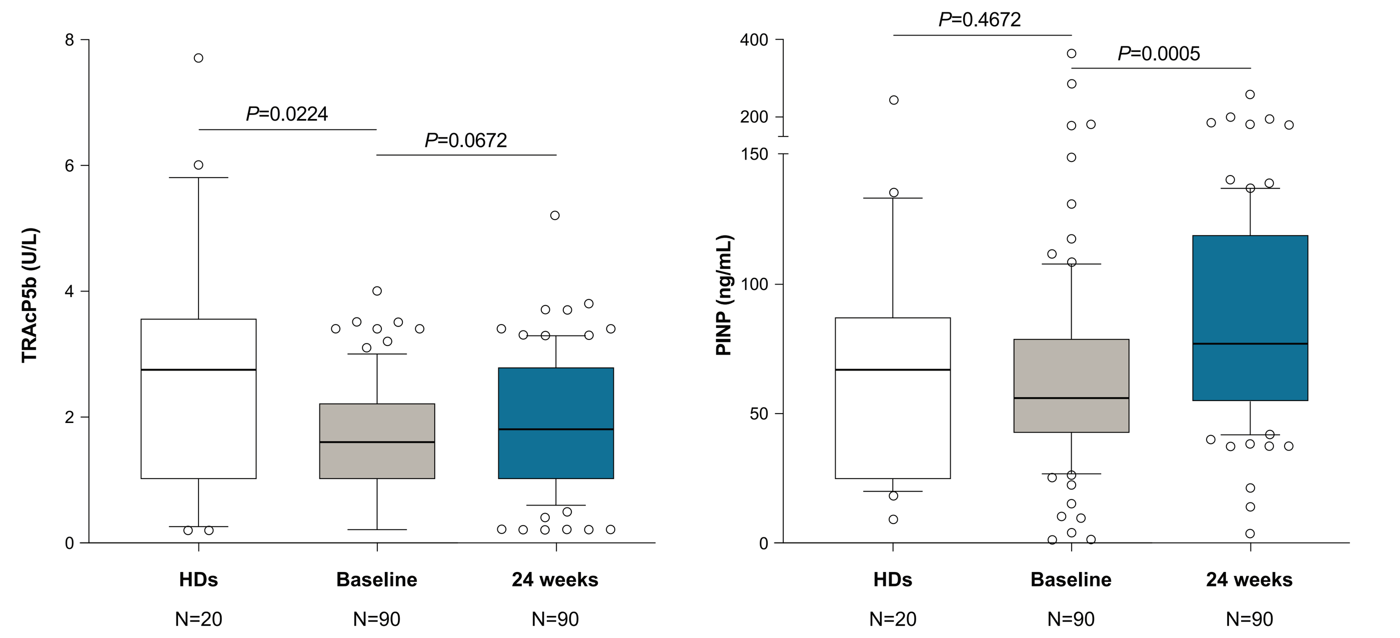
Figure 2. Percent change from baseline in BMD for patients with ISM treated with avapritinib who had baseline and ≥1 post-baseline DXA scans



BMD, bone mineral density; ISM, indolent systemic mastocytosis; SD, standard deviation.

- Ninety patients had paired baseline and avapritinib treatment samples tested (**Figure 3**)
  - Baseline TRAcP5b were lower in patients compared to HDs (P=0.0224), while PINP concentrations were similar (P=0.4672)
  - By Week 24, PINP concentrations increased above baseline (P=0.0005) toward the normal range in patients receiving avapritinib, with a similar directional trend in TRAcP5b (P=0.0672)

Figure 3. Median (interquartile range) of TRAcP5b and PINP levels in HDs (baseline only) and patients with ISM at baseline and after 24 weeks



HD, healthy donor; ISM, indolent systemic mastocytosis; PINP, procollagen type 1 N-terminal propeptide; TRAcP5b, tartrate-resistant acid phosphatase 5b.

- TRAcP5b and PINP were measured in 20 HDs and 131 patients with ISM (median [range] age: 52 [22–79] years; 75% female) (Table 1)

Case examples

- Case example 1: a 64-year-old woman with a 5-year history of ISM had improved symptom score and objective measures of disease burden at Week 24, increased lumbar BMD and T- and Z-scores at 1 year, and increased TRAcP5b and PINP levels toward the normal ranges
- Case example 2: a 28-year-old woman with a 2-year history of ISM also had improved symptom score and objective measures of disease burden at Week 24, increased lumbar BMD and T- and Z-scores at 1 year, and increased TRAcP5b and PINP levels toward the normal ranges

Case example 1

64 Years old | Female | 5 Years History of ISM

No concomitant anti-osteoporosis medications with avapritinib

	% change from baseline to Week 24
ISM-SAF TSS	−45%
Serum tryptase	−50%
KIT D816V	−56%
BM mast cells	−53%

	Screening	1 year
BMD lumbar spine	0.937 g/cm²	0.981 g/cm²
T-score lumbar spine	−1.9	−1.5

	Screening	Week 24
TRAcP5b, U/L	1.60	3.30
PINP, ng/mL	61.80	95.40

Case example 2

28 Years old | Female | 2 Years History of ISM

No concomitant anti-osteoporosis medications with avapritinib

	% change from baseline to Week 24
ISM-SAF TSS	−56%
Serum tryptase	−83%
KIT D816V	−60%
BM mast cells	−70%

	Screening	1 year
BMD lumbar spine	0.745 g/cm²	0.824 g/cm²
Z-score lumbar spine	−3.8	−3.1

	Screening	Week 24
TRAcP5b, U/L	1.40	2.30
PINP, ng/mL	34.30	60.80

BM, bone marrow; BMD, bone mineral density; ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PINP, procollagen type 1 N-terminal propeptide; TRAcP5b, tartrate-resistant acid phosphatase 5b; TSS, total symptom score.

Conclusions

- Improvements in BMD were seen over time during long-term treatment (~3 years) in patients receiving avapritinib with or without concomitant anti-osteoporosis medication use; prior literature has shown increases in BMD are associated with a reduction in fracture risk in individuals with osteoporosis[20]
- Supporting the BMD results, increases in PINP towards levels seen in HDs were observed in ISM patients while on avapritinib
- By targeting the underlying *KIT* D816V driver mutation in ISM, benefits with avapritinib may extend beyond symptom and QoL improvements, including potential disease-modifying effects on bone health
- These results provide an impetus for pursuing longitudinal follow-up studies assessing BMD changes with *KIT* D816V-targeted therapy in larger cohorts of patients with ISM

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Conflicts of interest/disclosures

Dr Castells has served as a consultant for Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi. and is a principal investigator 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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