# Changes in Long-Term Bone Health in Patients Receiving Avapritinib for the Treatment of Indolent Systemic Mastocytosis in the PIONEER Study

Poster Number 5582

Mariana Castells,[1] Vishnu Sundaresh,[2] Jason Gotlib,[3] Tsewang Tashi,[4] Vito Sabato,[5] Cristina Bulai Livideanu,[6] Cem Akin,[7] Deepti H. Radia,[8] Frank Siebenhaar,[9,10] Daniel J. DeAngelo,[11] Tracy I. George,[4,12] Hui-Min Lin,[13] Ashley Doyle,[13] Janet Hong,[13] Guang Yang,[13] Rachel L. Erlich,[13] Kate Newberry,[13] Benjamin Lampson,[13] Ivan Alvarez-Twose[14]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]University of Utah School of Medicine, Salt Lake City, UT, USA; [3]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, USA; [4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [5]Department of Immunology, Allergology and Rheumatology, University of Antwerp, and Antwerp University Hospital, Antwerp, Belgium; [6]Département de dermatologie, CEREMAST CHU de Toulouse, Toulouse, France; [7]University of Michigan, Ann Arbor, MI, USA; [8]Guy's & St Thomas' NHS Foundation Trust, London, UK; [9]Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [10]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [11]Department of Medical Oncology, Dana–Farber Cancer Institute, Boston, MA, USA; [12]ARUP Laboratories, Department of Pathology, University of Utah, Salt Lake City, UT, USA [13]Blueprint Medicines Corporation, Cambridge, MA, USA; [14]Institute of Mastocytosis Studies of Castilla-La Mancha, Toledo, Spain.

## Introduction

- Indolent systemic mastocytosis (ISM) is a clonal mast cell disease driven by the *KIT* D816V mutation in ~95% of patients and is associated with symptoms of mast cell activation and tissue infiltration that can be debilitating[1–4]
- Approximately 40–60% of patients with ISM have abnormal bone loss,[5,6] which is associated with an increased risk of skeletal complications such as osteoporosis (~25% of patients), osteopenia (~30%), and fragility fractures (~30% lifetime risk)[7–9]
  - Decreased bone density may reflect increased mast cell-derived cytokines that promote bone resorption and decreased bone formation[10]
  - Medications that increase bone density may prevent skeletal complications; this is supported by evidence showing an increase in bone mineral density (BMD) of 1.4–3.2% reduces the fracture risk in primary osteoporosis[11]
- Avapritinib is an oral, potent, selective KIT D816V inhibitor; it is the first and only approved targeted therapy for adults with ISM in the USA and for those with moderate to severe symptoms in the EU[12,13]
- In the placebo-controlled portion of PIONEER (NCT03731260), patients with ISM treated with avapritinib 25 mg plus best supportive care (BSC) demonstrated superiority to placebo plus BSC at 24 weeks; avapritinib-treated patients experienced reductions in symptoms (as measured by the ISM-Symptom Assessment Form[9,14] [ISM-SAF] total symptom score [TSS]) and biomarkers of disease burden; after 6 months of blinded therapy, the safety profile of avapritinib was comparable to placebo, with the exception of higher rates of low-grade edema, flushing and insomnia[15–17]
- 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 BMD[18]
- Here, we expanded upon the prior subset analysis to more comprehensively analyze the following changes for avapritinib-treated patients
  - BMD across all PIONEER patients who underwent optional dual-energy X-ray absorptiometry (DXA) scans
  - Tartrate-resistant acid phosphatase 5b (TRAcP-5b) levels to comprehensively assess bone health in patients with ISM receiving avapritinib; TRAcP-5b is a bone turnover biomarker and is associated with osteoclast activity[19]



## Methods

- PIONEER is an ongoing study evaluating avapritinib plus BSC in patients with ISM (**Figure 1**)
  - Patients with centrally confirmed ISM with uncontrolled moderate to severe symptoms (ISM-SAF TSS of ≥28 at screening), despite treatment with ≥2 BSC, were eligible for enrollment
  - Upon completion of Part 1 (the dose-finding portion) or Part 2 (the randomized, placebo-controlled, double-blind portion) of PIONEER, patients were eligible to receive open-label avapritinib for up to 5 years in Part 3

**Figure 1. Pioneer Study design**


QD, once daily; RP2D, recommended Part 2 dose.

- Physician-reported history of osteoporosis, osteopenia, prior fracture history, and use of medications supporting bone health were collected at enrollment
- DXA scans, optional per the study protocol and performed in a subset of study participants, assessed BMD at screening, at 6 months in Part 2, and at 12 months and annually thereafter in Part 3
  - The BMD analyses were performed retrospectively on patients who had been on avapritinib between 6–12 months (Year 1), 18–24 months (Year 2), and 26–37 months (Year 3)
  - We also compared BMD in patients with and without concomitant use of anti-osteoporosis therapies (bisphosphonates, denosumab, or parathyroid hormone analogs) during avapritinib treatment
- TRAcP-5b was 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 TRAcP-5b at baseline and 48 weeks of avapritinib treatment, and Welch's t-test was used for comparing baseline TRAcP-5b in patients *versus* HDs

## Results

- In PIONEER, 246 patients received avapritinib in Parts 1, 2, or 3, of whom 48 (20%) had a medical history of osteopenia and 56 (23%) had a medical history of osteoporosis
  - Among avapritinib-treated patients, medications supporting bone health at baseline included calcium (24% of patients), vitamin D (39%), bisphosphonates (10%), parathyroid hormone analog (1%), and denosumab (3%; **Table 1**)
- 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

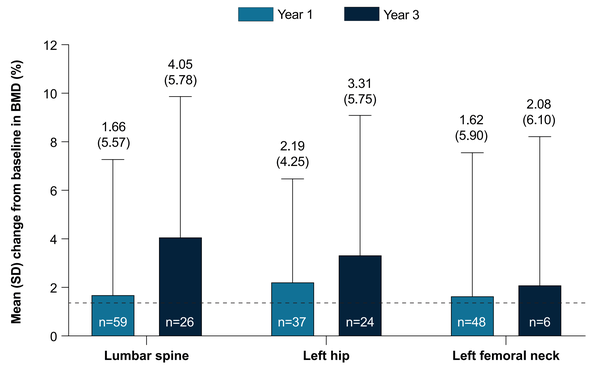
**Table 1. Baseline demographics in patients with ISM at the time of initiating avapritinib treatment, and who had baseline and ≥1 post-baseline DXA scans, and with or without concomitant anti-osteoporosis medications**

| | All patients who received avapritinib (N=246) | Patients with paired DXA scans available (N=79) | Patients with paired DXA scans available and without concomitant anti-osteoporosis medications (N=66) | Patients with paired DXA scans available and with concomitant anti-osteoporosis medications (N=13) |
|---|---|---|---|---|
| **Age, median years (range)** | 51 (18–79) | 51 (22–73) | 51 (22–73) | 56 (46–73) |
| **Female, n (%)** | 179 (73) | 59 (75) | 47 (71) | 12 (92) |
| **Concomitant medications supporting bone health at baseline, n (%)** | | | | |
| Calcium | 60 (24) | 19 (24) | 12 (18) | 7 (54) |
| Vitamin D | 96 (39) | 30 (38) | 21 (32) | 9 (70) |
| Bisphosphonates | 24 (10) | 6 (8) | 0 | 6 (46) |
| Parathyroid hormone analogs | 1 (1) | 1 (1) | 0 | 1 (8) |
| Denosumab | 8 (3) | 4 (5) | 0 | 4 (31) |
| **Medical history of bone fracture, n (%)** | 28 (11) | 6 (8) | 3 (5) | 3 (23) |
| **BMI, median kg/m² (range; n)** | 28.2 (17.6–51.4; 242) | 27.8 (19.4–51.4; 78) | 27.8 (19.4–51.4; 66) | 28.1 (19.4–38.6; 12) |
| **Bone mineral density, g/cm², mean (SD; n)** | | | | |
| Lumbar spine | NA | 1.02 (0.78; 77) | 1.04 (0.16; 65) | 0.91 (0.21; 12) |
| Left hip | NA | 0.93 (0.14; 60) | 0.96 (0.14; 49) | 0.83 (0.09; 11) |
| Left femoral neck | NA | 0.84 (0.16; 64) | 0.87 (0.16; 52) | 0.73 (0.11; 12) |

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

- 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

**Figure 2. Percent change from baseline in BMD for the lumbar spine, left hip, and left femoral neck for patients with ISM treated with avapritinib who had baseline and ≥1 post-baseline DXA scans**




Dashed line indicates a BMD change of +1.4%, which has been associated with a reduction in fractures in primary osteoporosis.[11]
BMD, bone mineral density.

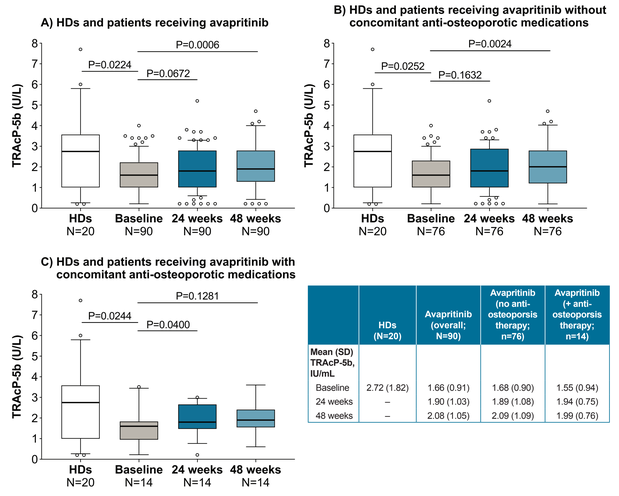
- TRAcP-5b was measured in 20 HDs and 131 patients with ISM (median [range] age: 52 [22–79] years; 75% female; **Table 2**)

**Table 2. Baseline demographics at the time of initiating avapritinib in patients with ISM with bone turnover biomarkers measured**

| | Patients with bone turnover biomarkers measured at baseline (N=131) |
|---|---|
| **Age, median years (range)** | 50 (22–79) |
| **Female, n (%)** | 98 (75) |
| **Bone health, n (%)** | |
| Osteopenia | 24 (18) |
| Osteoporosis | 30 (23) |
| **Concomitant medications supporting bone health (%)** | |
| Calcium | 29 (22) |
| Vitamin D | 55 (42) |
| Bisphosphonates | 14 (11) |
| Parathyroid hormone analogs | 1 (1) |
| Denosumab | 2 (2) |
| **Medical history of bone fracture, n (%)** | 15 (11) |
| **BMI, median kg/m² (range; n)** | 28.2 (17.6–42.2; 129) |
| **BMD, g/cm², mean (SD; n)** | |
| Lumbar spine | 1.03 (0.18; 68) |
| Left hip | 0.93 (0.15; 51) |
| Left femoral neck | 0.84 (0.16; 57) |

- In total, 90 patients had paired baseline and avapritinib treatment samples tested (**Figure 3**)
  - Baseline TRAcP-5b concentration was significantly lower in patients with ISM compared with HDs (P=0.0224)
  - By Week 48, TRAcP-5b concentration significantly increased above baseline (P=0.0006) toward the normal range in patients receiving avapritinib
  - This pattern of change was observed in those with and without concomitant anti-osteoporosis therapy

**Figure 3. Median (interquartile range) of TRAcP-5b levels in HDs (baseline only) and patients with ISM at baseline and after 24 weeks and 48 weeks of avapritinib treatment**




| | HDs (N=20) | Avapritinib (overall; N=90) | Avapritinib (no anti-osteoporosis therapy; n=76) | Avapritinib (+ anti-osteoporosis therapy; n=14) |
|---|---|---|---|---|
| **Mean (SD) TRAcP-5b, IU/mL** | | | | |
| Baseline | 2.72 (1.82) | 1.66 (0.91) | 1.68 (0.90) | 1.55 (0.94) |
| 24 weeks | – | 1.90 (1.03) | 1.89 (1.08) | 1.94 (0.75) |
| 48 weeks | – | 2.08 (1.05) | 2.09 (1.09) | 1.99 (0.76) |

HDs, healthy donors; TRAcP-5b, tartrate-resistant acid phosphatase 5b.

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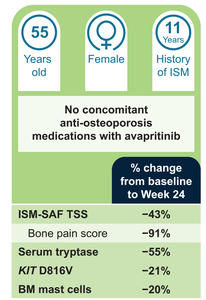
### Conflicts of interest/disclosures

Dr Castells has served as a consultant for Blueprint Medicines Corporation 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.

## Case examples

- **Case example 1:** a 55-year-old woman with an 11-year history of ISM and who did not take concomitant anti-osteoporotic medications during avapritinib treatment had improved ISM-SAF total symptom score (–43%), bone pain score (–91%), tryptase (–55%), *KIT* D816V variant allele frequency (–21%), and bone marrow mast cells (–20%) at Week 24 of avapritinib treatment
  - From screening to 1 year of avapritinib treatment, her lumbar spine BMD increased, and her T- and Z-scores increased, suggesting an overall improvement in her bone health
- **Case example 2:** a 28-year-old woman with a 2-year history of ISM and who also did not take concomitant anti-osteoporotic medications during avapritinib treatment, had improved symptom score and objective measures of disease burden at Week 24, increased lumbar spine BMD, and T- and Z-scores at 1 year, and increased TRAcP-5b toward the normal range

**Case example 1**

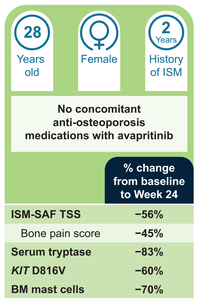



| | % change from baseline to Week 24 |
|---|---|
| **ISM-SAF TSS** | **–43%** |
| Bone pain score | **–91%** |
| **Serum tryptase** | **–55%** |
| ***KIT* D816V** | **–21%** |
| **BM mast cells** | **–20%** |

| | Screening | 1 year |
|---|---|---|
| **BMD lumbar spine** | **0.799 g/cm²** | **0.907 g/cm²** |
| **T-score lumbar spine** | **–2.3** | **–1.3** |
| **Z-score lumbar spine** | **–1.1** | **–0.1** |

| | Screening | 1 year |
|---|---|---|
| **TRAcP-5b, U/L** | **1.30** | **Not tested** |

**Case example 2**




| | % change from baseline to Week 24 |
|---|---|
| **ISM-SAF TSS** | **–56%** |
| Bone pain score | **–45%** |
| **Serum tryptase** | **–83%** |
| ***KIT* D816V** | **–60%** |
| **BM mast cells** | **–70%** |

| | Screening | 1 year |
|---|---|---|
| **BMD lumbar spine** | **0.745 g/cm²** | **0.824 g/cm²** |
| **T-score lumbar spine** | **–3.6** | **–3.0** |
| **Z-score lumbar spine** | **–3.8** | **–3.1** |

| | Screening | Week 24 |
|---|---|---|
| **TRAcP-5b, U/L** | **1.40** | **2.30** |

BM, bone marrow; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; TSS, total symptom score.

## Conclusions

- Improvements in BMD were seen over time during long-term treatment (~3 years) in patients receiving avapritinib. Prior literature has shown that increases in BMD of 1.4–3.2% are associated with a reduction in fracture risk in individuals with osteoporosis[11]
- These favorable changes were observed regardless of the concomitant use of other medications known to increase bone density
- TRAcP-5b is typically elevated in primary osteoporosis,[20] but interestingly, TRAcP-5b was lower at baseline in patients with ISM from PIONEER compared with HDs
  - An increase in TRAcP-5b toward HD levels was observed while on avapritinib, suggesting the mechanism of bone loss and elevated TRAcP-5b levels in mastocytosis is not well understood
- By targeting the underlying *KIT* D816V driver mutation in ISM, benefits with avapritinib may extend beyond symptom and quality of life improvements to include addressing other health consequences of ISM
- 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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