

Disease Modifying Effects of Avapritinib in Patients With Advanced Systemic Mastocytosis: Impact on Bone Turnover Markers (BTMs) and Bone Disease

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Introduction

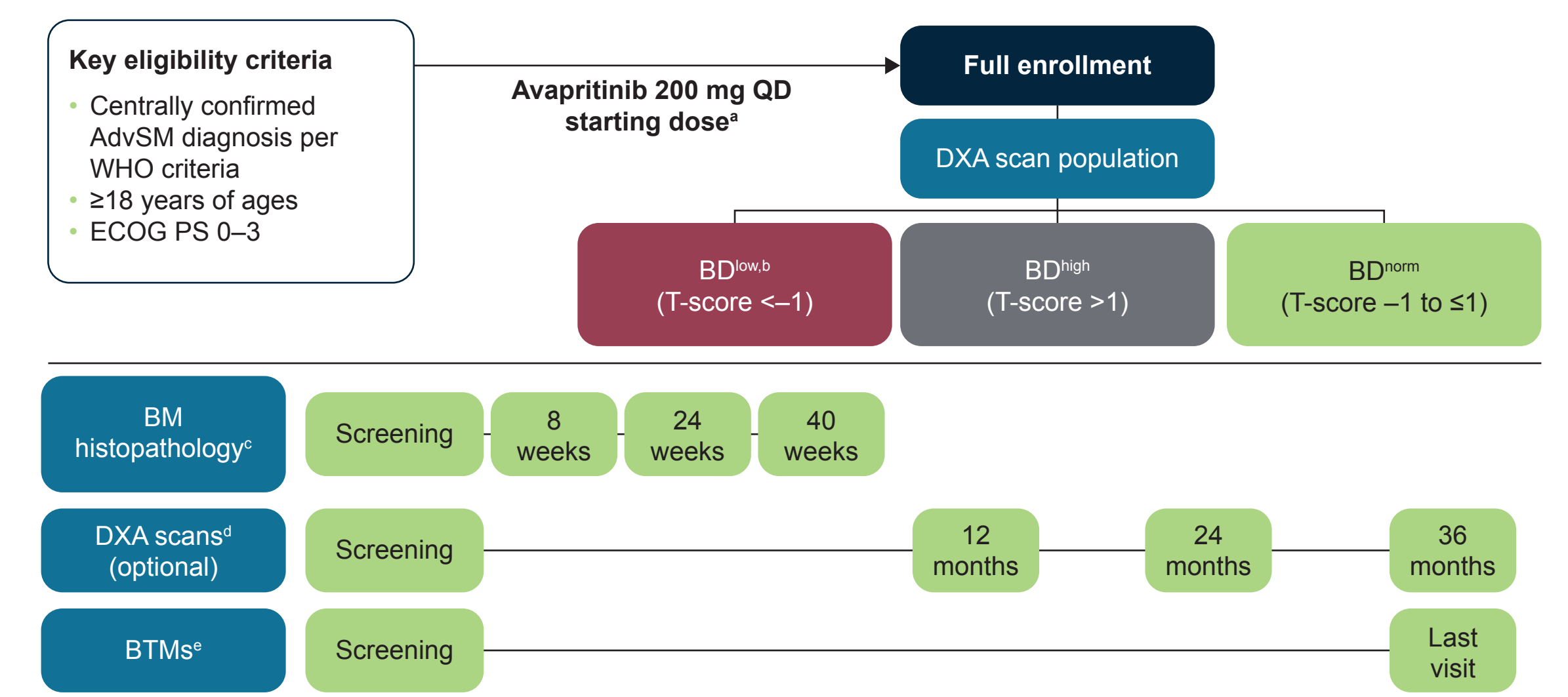
- Systemic mastocytosis (SM) is a clonal mast cell (MC) disease driven by the *KIT* D816V mutation in ~95% of cases,¹⁻⁴ and has a prevalence estimated to affect up to 1 in 5000 people⁵
- SM is a spectrum of diseases including indolent SM (ISM) and advanced SM (AdvSM)
 - AdvSM is a hematologic neoplasm that includes aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and MC leukemia (MCL)⁴
- Patients with AdvSM can have evidence of bone disease, such as osteosclerosis (~50% of patients), osteolytic lesions, osteopenia/osteoporosis, and bone marrow MC (BM MC) infiltration^{6,7}
- Bone disease can be assessed by several complementary methods, including:
 - bone density (BD), static bone mass measurement via dual-energy X-ray absorptiometry (DXA)⁸; 2) bone turnover markers (BTMs), dynamic bone-remodeling assessment that includes intact procollagen I N-propeptide (intact PINP; bone formation marker) and tartrate-resistant acid phosphatase type 5b (TRAcP-5b; bone resorption marker)^{9,10}; and 3) bone histopathology assessment¹¹
- Avapritinib, an oral, potent, selective inhibitor of *KIT* D816V, is approved in the United States regardless of prior therapy and in the European Union after ≥1 prior therapy for adults with AdvSM^{12,13} based on results from the phase 1 EXPLORER (NCT02561988) and phase 2 PATHFINDER (NCT03580655) clinical studies^{14,15}

- Improvements in BD during avapritinib treatment have been reported in patients with ISM and in patients with AdvSM with low BD^{16,17}
- We report long-term effects of avapritinib on BD, BTMs, and bone histopathology in patients with AdvSM from the PATHFINDER study (NCT03580655)

Methods

- PATHFINDER was an international, multicenter, open-label, single-arm, phase 2 study designed to assess the efficacy and safety of avapritinib in adult patients with a centrally confirmed AdvSM diagnosis
- A *post hoc* analysis was performed among patients who underwent optional DXA scans according to local procedures at each study center to assess BD at baseline and had ≥2 serial DXA scans during avapritinib treatment (Figure 1)
- BD according to lumbar T-score was categorized as normal (BD^{norm} T-score -1 to ≤1), low (BD^{low} T-score less than -1), and high (BD^{high} T-score >1), and the difference between groups was assessed using paired t-tests comparing baseline and follow-up measurements
 - Improvement in BD was defined as a change in T-score ≥0.5 toward the normal range, stability was defined as a change in T-score <0.5, and worsening was defined as a change in T-score ≥0.5 away from the normal range
- Plasma intact PINP and TRAcP-5b levels were measured in a subset of patients with serial DXA scans and healthy volunteers (HVs) using the IDS-iSYS intact PINP assay and TRAcP-5b assay measured by BioAgilytix Labs
 - Baseline BTM levels were compared between patients and HVs using Welch's t-test and matching the reference values for post-menopausal females and males over 45 years of age
 - Within-patient changes in BTM levels from baseline to post-avapritinib treatment were assessed using the Wilcoxon signed-rank test
- Serum tryptase levels and *KIT* D816V variant allele frequency in peripheral blood were centrally assessed as objective markers of MC disease burden as previously described¹⁸
- BM biopsies for histopathology were collected at screening and after 8, 24, and 40 weeks
 - Specimen handling, processing, staining, and histopathology assessments, including BM cellularity, grade of BM fibrosis, and grade of BM osteosclerosis, were performed according to standard published procedures^{19,20}
 - Student's t-tests were used to compare baseline and last-visit values for all histopathology assessments

Figure 1. PATHFINDER study design and bone health assessments



Data cut-off: March 13, 2025. *Two patients initiated 100 mg QD avapritinib, all others initiated at 200 mg QD. †Four patients in the BD^{low} group had a medical history of relevant bone fractures before entering the study, and one of those experienced an additional fracture on study. ‡Assessments included cellularity, grade of BM fibrosis, and grade of BM osteosclerosis. §These were planned timepoints and each patient did not have all evaluations and/or at these timepoints. ¶Plasma BTM levels were measured at baseline and post-avapritinib treatment at last visit in a subset of patients with serial DXA scans. AdvSM, advanced systemic mastocytosis; BD, bone density; BD^{low}, lumbar T-score >1; BD^{norm}, lumbar T-score less than -1; BD^{high}, lumbar T-score -1 to ≤1; BM, bone marrow; BTM, bone turnover marker; DXA, dual-energy X-ray absorptiometry; ECOG PS, Eastern Cooperative Oncology Group Performance Status; QD, once daily; WHO, World Health Organization.

Results

- Of the 107 patients in the PATHFINDER study, 56 (52%) had optional DXA scans at baseline and ≥2 follow-up visits (median visits: 3; range 2–6), and 47 of the 56 had paired baseline and last-visit measurements of intact PINP and TRAcP-5b levels and bone histopathology assessments (Table 1)
- At baseline, low BD was observed in 21% (12/56) of patients and high BD was observed in 38% (21/56) of patients
- Baseline characteristics were comparable across groups (Table 1)

Table 1. Baseline characteristics of patients with bone assessments and all patients from the PATHFINDER study

	Overall population (N=107)	Patients with serial DXA scans (n=56)	BD ^{low} (n=12) ^a	BD ^{norm} (n=23)	BD ^{high} (n=21)	Patients with paired BTM levels (n=47)
Age, years, median (range)	68 (31–88)	69 (52–88)	70 (55–88)	68 (52–80)	69 (52–85)	69 (52–88)
Female, n (%)	45 (42)	27 (48)	6 (50)	12 (52)	9 (43)	22 (47)
Postmenopausal ^b	41 (91)	25 (93)	6 (100)	12 (100)	7 (78)	20 (91)
AdvSM subtype per central assessment, n (%)						
ASM	21 (20)	9 (16)	2 (17)	6 (26)	1 (5)	8 (17)
SM-AHN	71 (66)	41 (73)	9 (75)	15 (65)	17 (81)	33 (70)
MCL ^c	15 (14)	6 (11)	1 (8)	2 (9)	3 (14)	6 (13)
BM MC burden, median % (range)	40 (1–95)	50 (10–95)	20 (10–75)	50 (10–90)	40 (10–95)	50 (10–95)
Serum tryptase, ng/mL, median (range)	262 (24–1600)	196 (33–1336)	177 (60–1208)	316 (77–564)	169 (33–1336)	238 (37–1336)
<i>KIT</i> D816V VAF in PB, median % (range)	15.8 (ND–47.5)	23.0 (0.02–46.7)	12.7 (0.16–45.4)	25.1 (1.6–46.7)	22.2 (0.02–45.3)	22.2 (0.02–46.7)

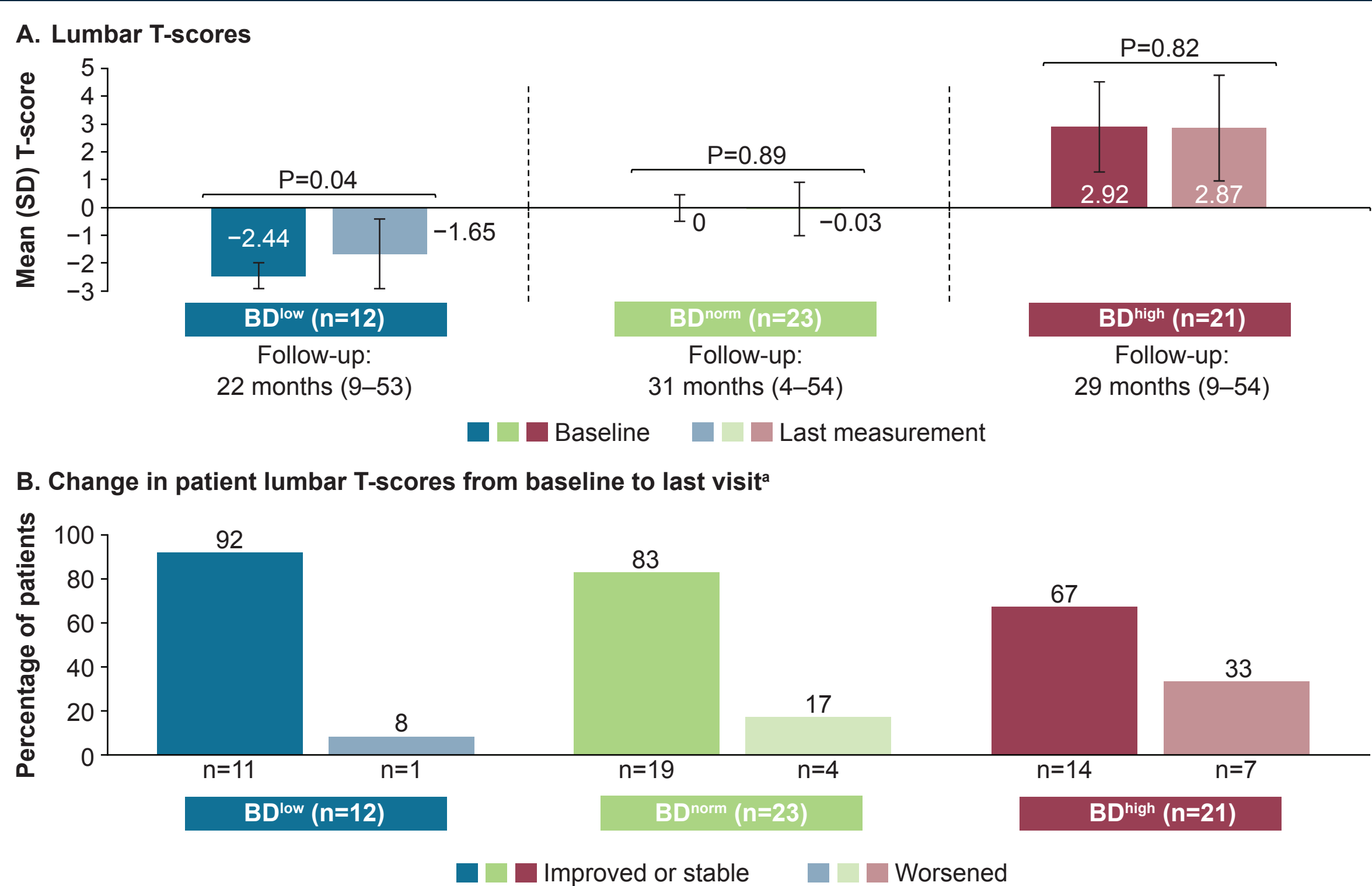
^aFour patients in the BD^{low} group had a medical history of relevant bone fractures before entering the study, and one of those experienced an additional fracture on study. ^bPercentage calculated from the number of women in the group. ^cIncluding four MCL-AHN. ASM, aggressive systemic mastocytosis; BM MC, bone marrow mast cell; MCL, mast cell leukemia; MCL-AHN, mast cell leukemia with an associated hematologic neoplasm; ND, not detected; PB, peripheral blood; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; VAF, variant allele frequency.

- BD (T-scores) significantly improved in the BD^{low} group and stabilized in the other two BD groups during avapritinib treatment (Figure 2A); the majority of patients in each BD group had improved or stable BD from baseline to the last visit (Figure 2B)

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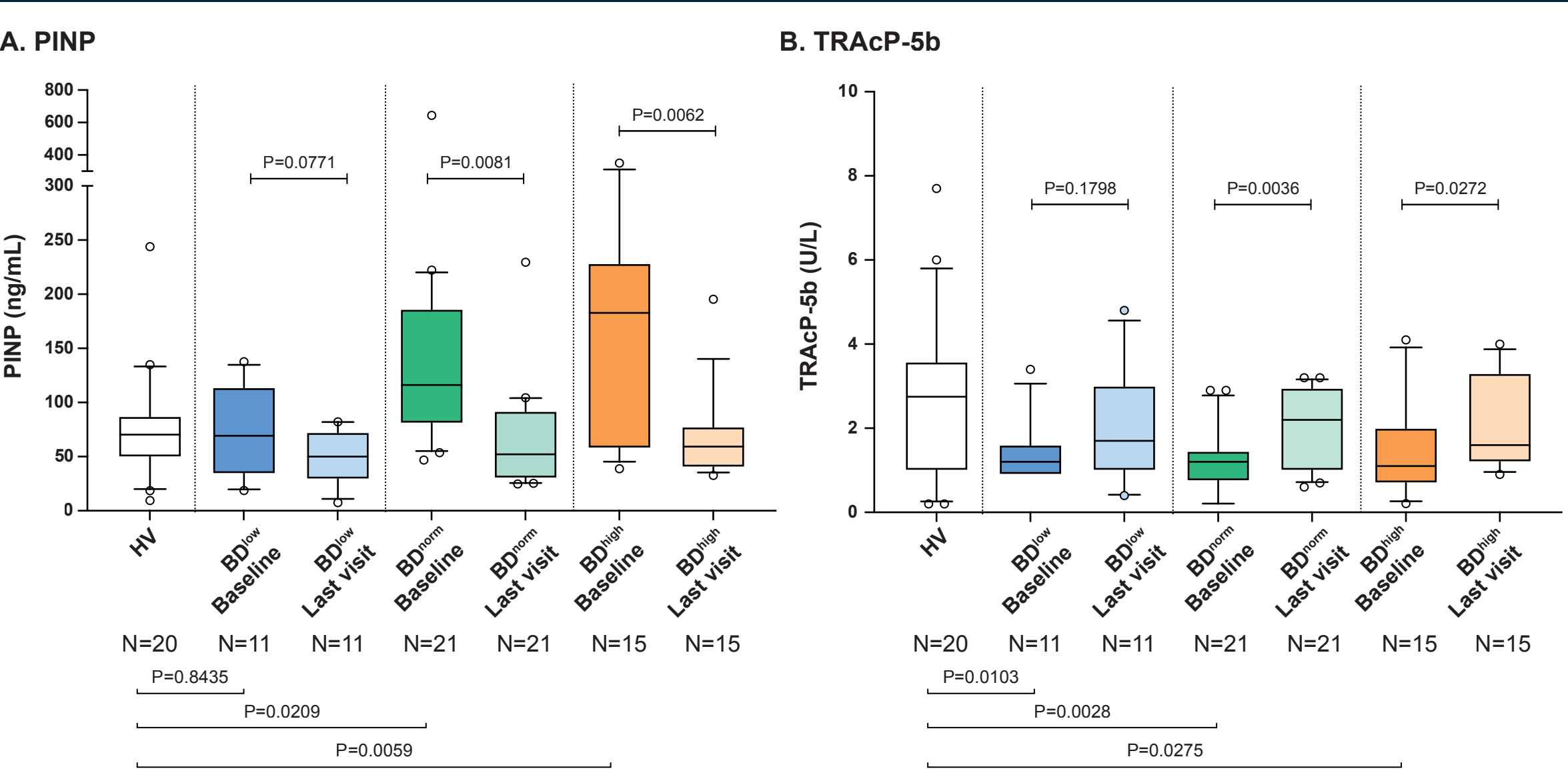
Figure 2. BD^{low} patients had significant improvements in mean T-scores at the last visit (A), and most patients in each BD group had improved or stable T-scores (B)



*Improved defined as change in T-score ≥0.5 toward normal range; stable defined as change in T-score <0.5; worsened defined as change in T-score ≥0.5 away from normal range. SD, standard deviation.

- Baseline intact PINP was significantly higher in BD^{high} and BD^{norm} patients than HVs and returned to the normal range during avapritinib treatment (Figure 3A)
- Baseline TRAcP-5b was significantly lower than HVs in all three BD subgroups and returned to the normal range in BD^{high} and BD^{norm} patients following avapritinib treatment (Figure 3b)

Figure 3. (A) Baseline intact PINP was significantly higher in BD^{high} and BD^{norm} subgroups than HVs and normalized during avapritinib treatment; (B) Baseline TRAcP-5b was significantly lower than HVs in all three BD subgroups and normalized in the BD^{high} and BD^{norm} subgroups during avapritinib treatment



HV, healthy volunteer; PINP, procollagen I N-propeptide; TRAcP-5b, tartrate-resistant acid phosphatase type 5b.

- Significant improvements in indices of BM disease based on bone histopathology were observed during avapritinib treatment (Figure 4)

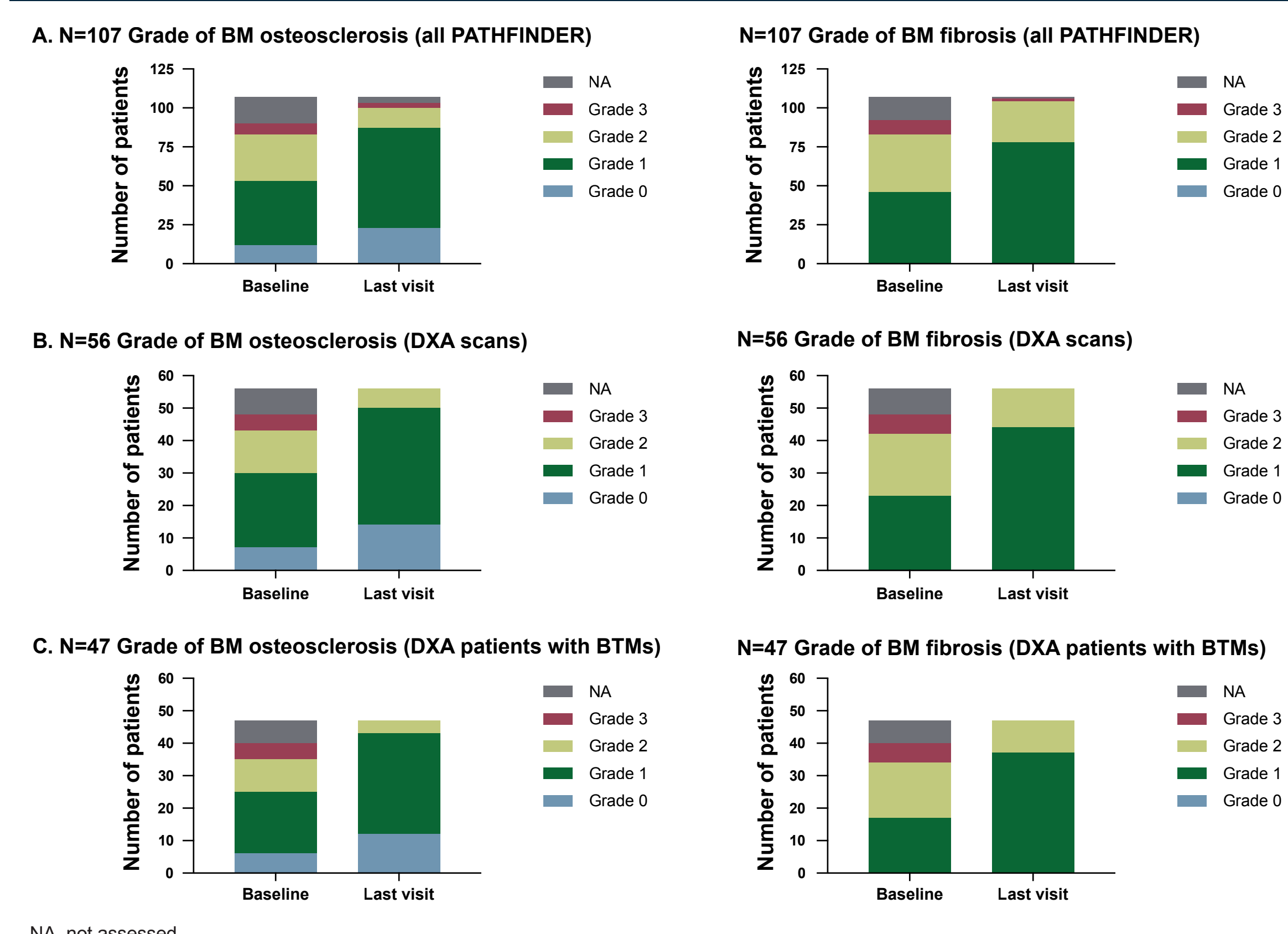
Acknowledgements

The authors thank the patients, their families, all other investigators, and all investigational site members involved in this study. This study was funded by Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi. Medical writing support was provided by Francis John Golder, BVSc, PhD, CMPP, and editorial support was provided by Travis Taylor, BA, of the Prime Group of Companies (Knutsford, UK) and was funded by Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi. Responsibility for all opinions, conclusions, and data interpretation lies with the authors.

Conflicts of interest/disclosures

Dr Lübke has received honoraria from Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi.

Figure 4. Grade of BM fibrosis and grade of BM osteosclerosis significantly improved in patients with AdvSM during treatment with avapritinib



- Changes in BD, BTMs, and histopathology for two representative patients are depicted in Figure 5

Figure 5. Representative cases demonstrating improvements in bone disease parameters during avapritinib treatment, one with high BD (A) and one with low BD (B) at screening

	A. BD ^{high} patient		B. BD ^{low} patient	
	Screening	22 months	Screening	22 months
69 Years old			55 Years old	
Female			Male	
SM-AHN ^a			SM-AHN ^b	
High BD subgroup			Low BD subgroup	
BM MC, %	75	10	70	1
Serum tryptase, ng/mL	604.0	194	173.0	2.8
<i>KIT</i> D816V VAF, %	35.43	9.91	1.12	Undetectable
T-score lumbar spine	1.2	0.1	-3.5	-1.8
PINP, ng/mL	266.9	50.0	34.3	82.1
TRAcP-5b, U/L	2.0	2.1	0.9	1.1
BM cellularity, %	100	90	95	50
Grade of BM fibrosis	2	2	2	1
Grade of BM osteosclerosis	3	2	2	0

^aAssociated hematologic neoplasm was CMML. ^bAssociated hematologic neoplasm was an unclassifiable myeloid neoplasm. CMML, chronic myelomonocytic leukemia.

Conclusions

- Avapritinib treatment improved bone density in the low bone density group, stabilized bone density in the normal and high bone density groups, and resulted in normalization of the bone turnover markers, intact PINP and TRAcP-5b
- Avapritinib was associated with improvements in bone marrow histopathology (cellularity, fibrosis, and osteosclerosis)
- These encouraging exploratory results support further evaluation of the effects of avapritinib on bone disease in systemic mastocytosis