Evaluation of Bone Formation Marker Changes in Summit, a Trial Assessing Bezuclastinib in Adults with Non-Advanced Systemic Mastocytosis : An Exploratory Analysis

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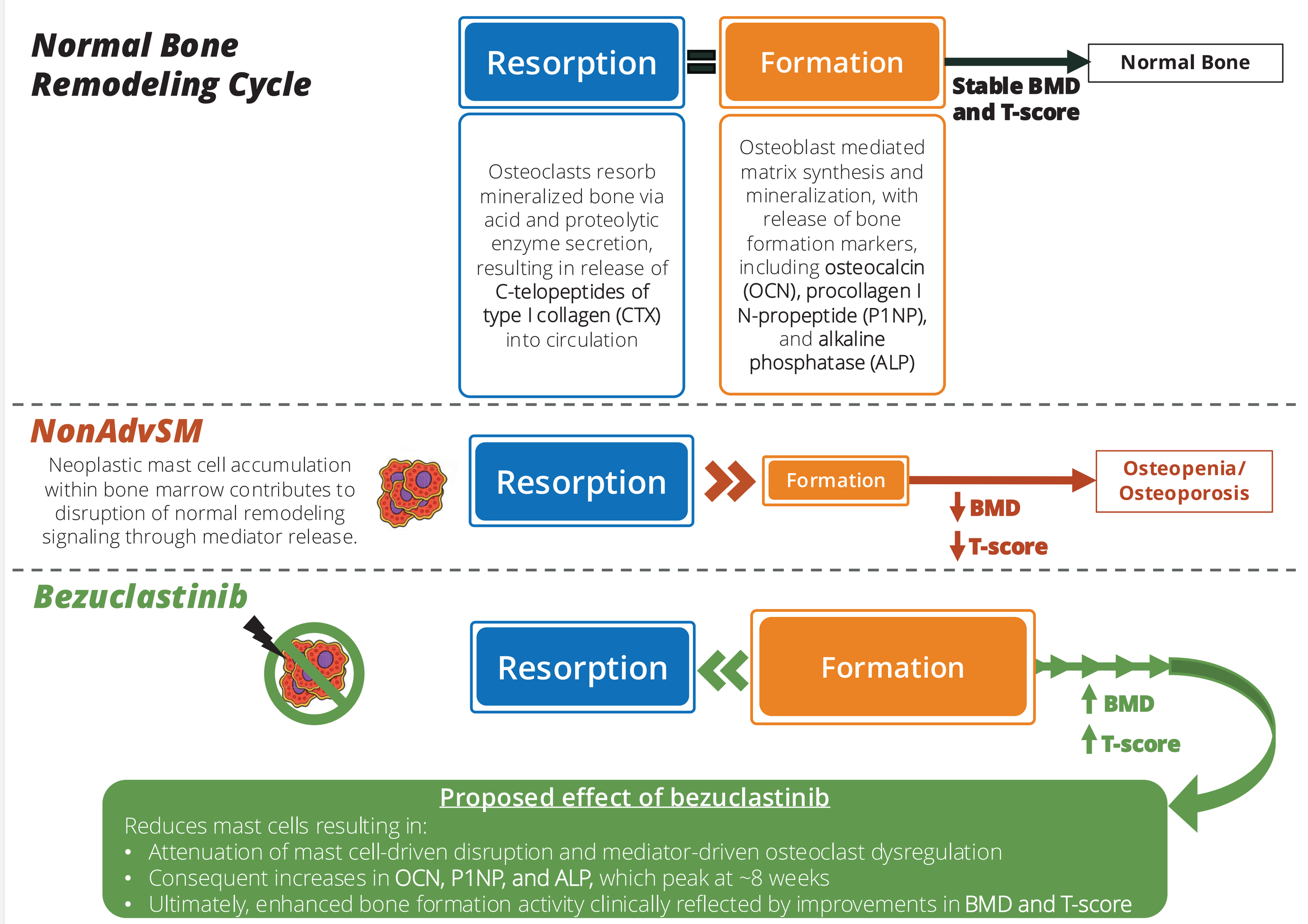
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INTRODUCTION

Bezuclastinib (CGT9486) is an oral, potent, and selective type 1 TKI that reduces symptoms of nonadvanced systemic mastocytosis[1-3]

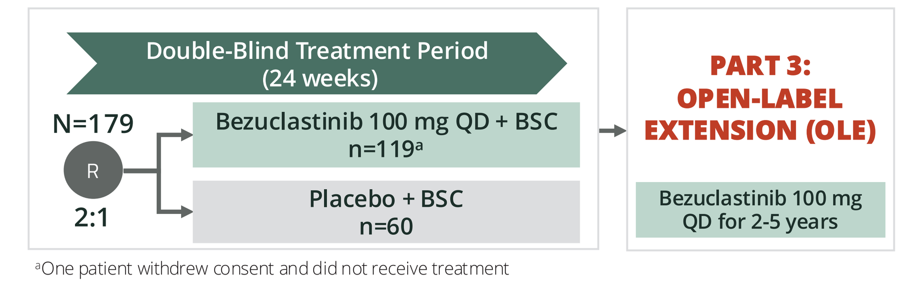
- Mast cells play a critical role in bone turnover, metabolism, and homeostasis[4]
- Nonadvanced SM (NonAdvSM) is characterized by mast cell accumulation and activation, which can lead to musculoskeletal impacts including[5-9]:
 - — Changes in bone remodeling markers
 - — Skeletal complications such as osteolysis, osteopenia, and osteoporosis
 - — Increased risk of fragility fractures
- The *KIT* c.2447 A>T (p.D816V) mutation is found in ~95% of patients with NonAdvSM[10]
- Bezuclastinib is highly active against KIT D816V, has minimal brain penetration, and spares closely related kinases, which minimizes off-target toxicities, such as bleeding, cognitive impairment, edema, and pleural effusion[1-3, 11]
- In the Summit trial, which evaluated bezuclastinib in patients with NonAdvSM, clinically meaningful symptom improvement and significant reductions in objective disease markers were demonstrated along with a favorable safety profile[3]
- Here we report the effect of bezuclastinib on bone formation markers, bone mineral density, and T-score

Bone remodeling cycle in NonAdvSM[4-9] and proposed effect of bezuclastinib


Normal Bone Remodeling Cycle
Resorption
Formation
Normal Bone
Stable BMD and T-score
Osteoclasts resorb mineralized bone via acid and proteolytic enzyme secretion, resulting in release of C-telopeptides of type I collagen (CTX) into circulation
Osteoblast mediated matrix synthesis and mineralization, with release of bone formation markers, including osteocalcin (OCN), procollagen I N-propeptide (P1NP), and alkaline phosphatase (ALP)
NonAdvSM
Neoplastic mast cell accumulation within bone marrow contributes to disruption of normal remodeling signaling through mediator release.
Resorption
Formation
↓BMD
↓T-score
Osteopenia/ Osteoporosis
Bezuclastinib
Resorption
Formation
↑BMD
↑T-score
Proposed effect of bezuclastinib
Reduces mast cells resulting in:
• Attenuation of mast cell-driven disruption and mediator-driven osteoclast dysregulation
• Consequent increases in OCN, P1NP, and ALP, which peak at ~8 weeks
• Ultimately, enhanced bone formation activity clinically reflected by improvements in BMD and T-score

METHODS

Summit (NCT05186753): Pivotal phase 2, multicenter, randomized, double-blind, placebo-controlled study evaluating bezuclastinib in NonAdvSM


SUMMIT PART 2 | Primary Objective: Determine the efficacy of bezuclastinib
Double-Blind Treatment Period (24 weeks)
N=179
R
2:1
Bezuclastinib 100 mg QD + BSC n=119ᵃ
Placebo + BSC n=60
PART 3: OPEN-LABEL EXTENSION (OLE)
Bezuclastinib 100 mg QD for 2-5 years

ᵃOne patient withdrew consent and did not receive treatment

- Effect of bezuclastinib on bone was evaluated as exploratory assessments during Summit Part 2
 - — Bone formation markers, including serum P1NP and osteocalcin, were assessed
 - — Bone density was evaluated from optional dual-energy X-ray absorptiometry (DXA) scans

RESULTS

Bone health characteristics in patients with DXA scans

Parameter	Overall (N=179)	Bezuclastinib (N=119)	Placebo (N=60)
Patients with DXA scan, n (%)	79 (44.1%)	59 (49.6%)	20 (33.3%)
Normal BMD (T-score ≥ −1.0), n (%)	39 (49.4%)	27 (45.8%)	12 (60%)
Osteopenia, n (%)	31 (39.2%)	29 (49.2%)	2 (10%)
Osteoporosis, n (%)	9 (11.4%)	3 (5.1%)	6 (30%)

	Normal Bone Mineral Densityᵃ (N=39)	Osteopeniaᵃ (N=31)	Osteoporosisᵃ (N=9)
Age, years – median (range)	50 (24–73)	55 (29–71)	55 (36-66)
Female, n (%)	27 (69)	20 (65)	6 (67)
BMI, kg/m² – median (range)	31.0 (19.1–46.4)	27.7 (19.1–38.7)	27.3 (16.1-42.1)
Medical history of bone fracture, n (%)ᵇ	5 (13%)	7 (23%)	2 (22%)
Patients taking concomitant bone health medications, n (%)			
Calcium	10 (26%)	11 (35%)	4 (44)
Vitamin D	22 (56%)	19 (61%)	8 (89)
Bisphosphonates	0 (0)	4 (13%)	2 (22)
Denosumab	1 (3%)	1 (3%)	2 (22)
T-score on DXA scan, mean (SD) [n]			
Lumbar spine	−0.04 (0.87) [34]	−1.35 (0.93) [27]	-2.94 (0.29) [9]
Femoral neck	0.08 (0.83) [27]	−1.07 (0.71) [24]	-1.51 (0.67) [5]
Pelvis	0.47 (0.88) [19]	−0.72 (0.73) [17]	-0.57 (1.18) [3]

- A significant proportion of patients enrolled in Summit with DXA scans had compromised bone health, including 39% with osteopenia and 11% with osteoporosis
- Characteristics were generally balanced between placebo and bezuclastinib arms

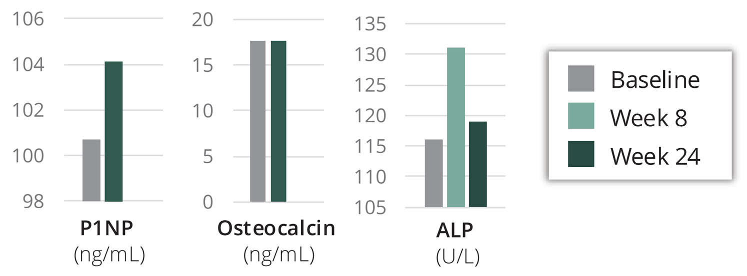
ᵃBone mineral density categories are based on lowest T-score (Normal ≥ −1.0; Osteopenia −2.5 to < −1.0; Osteoporosis < −2.5).
ᵇMedical history depends on what is reported and may be incomplete regarding fracture history.

Patient cases demonstrate improvement in T-score as early as 24 weeks after bezuclastinib treatment

Patient Case 1

- 43-year-old male with ISM and low BMD, including lumbar spine T-score in the Grade 1 osteoporotic range and Z-score below age-expected norms
- No prior ISM-directed therapy; received concomitant vitamin D3 and calcium citrate throughout study
- Randomized to bezuclastinib 100 mg on 7 Oct 2024

	BMD		T-score		Z-score	
	BL	Wk 24	BL	Wk 24	BL	Wk 24
Neck	0.93	0.96	0	0.2	0.6	0.8
Spine	0.83	0.90	-2.4	-1.7	-2.2	-1.5
Pelvis	0.98	1.0	-0.3	-0.2	-0.1	0


P1NP (ng/mL)
Osteocalcin (ng/mL)
ALP (U/L)
Baseline
Week 8
Week 24

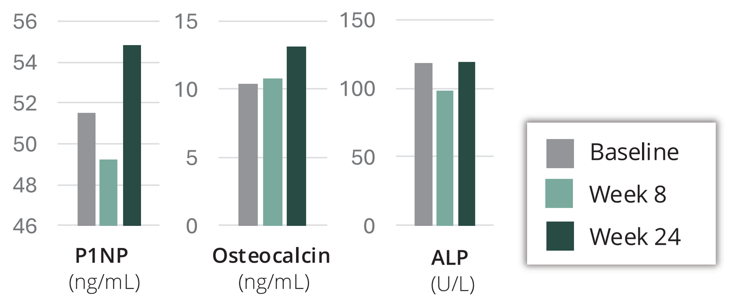
Biomarkers	BL	Wk 24	Wk 24 %CFB
MC Burden	10	2	-80
KIT	0.07	0	-100
Tryptase	22.5	3.6	-84

Early rise or stabilization of bone formation markers, coupled with measurable BMD gains by Week 24 of bezuclastinib treatment, collectively suggest an emerging bone-anabolic treatment effect in this patient.

Patient Case 2

- 63-year-old male with ISM and baseline Grade 1 osteopenia, with mild neck and low back pain
- No prior ISM-directed or bone-targeted therapies
- Randomized to bezuclastinib 100 mg on 4 Nov 2024

	BMD		T-score		Z-score	
	BL	Wk 24	BL	Wk 24	BL	Wk 24
Neck	1.05	ND	-0.2	1.2	1.1	0
Spine	0.96	ND	-2.2	0.1	-1.4	-0.7


P1NP (ng/mL)
Osteocalcin (ng/mL)
ALP (U/L)
Baseline
Week 8
Week 24

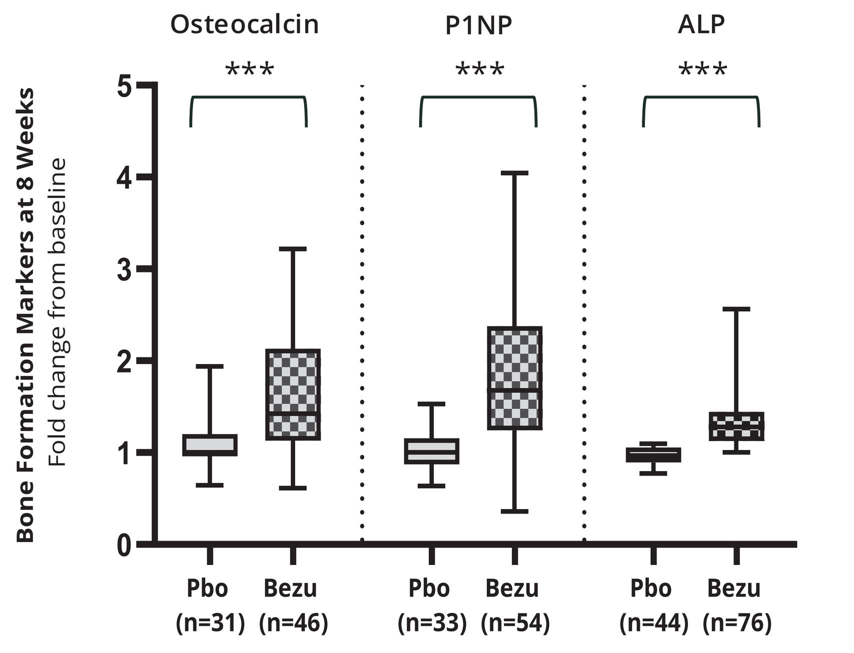
Biomarkers	BL	Wk 24	Wk 24 %CFB
MC Burden	10	2	-80
KIT	0.04	0	-100
Tryptase	20.6	5.7	-72.33

Marked improvements in both lumbar spine and femoral neck T-scores, and supportive improvement in spine Z-score, by Week 24 of bezuclastinib treatment suggest an early, favorable effect on bone density, particularly at the lumbar spine, which is a clinically relevant site for fracture risk in patients with ISM.

Bezuclastinib improves bone formation markers, bone mineral density, and T-scores by Week 24, demonstrating evidence of early bone-anabolic response

Bone formation markers increase 8 weeks after initiating bezuclastinib, indicating that treatment has activated the bone remodeling process

- Osteocalcin, P1NP and ALP all show increases at 8 weeks in bezu patients compared to no increase in placebo patients
 - — This increase at 8 weeks corresponds to the bone formation phase, which should occur 6-12 weeks following activation of the bone remodeling process

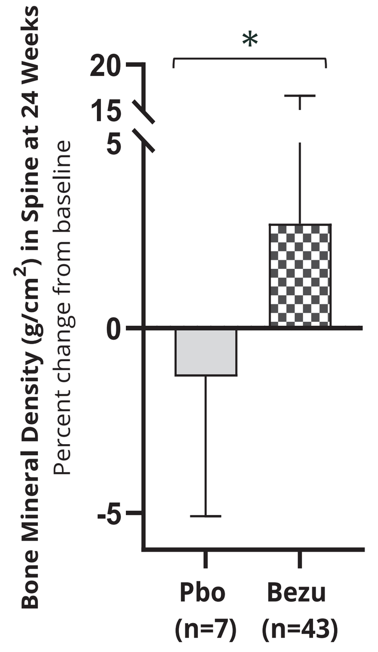

Bone Formation Markers at 8 Weeks
Fold change from baseline
Osteocalcin
P1NP
ALP

Pbo (n=31)
Bezu (n=46)
Pbo (n=33)
Bezu (n=54)
Pbo (n=44)
Bezu (n=76)

Significant improvement in bone mineral density at 24 weeks, demonstrating clinical impact of bone remodeling after treatment

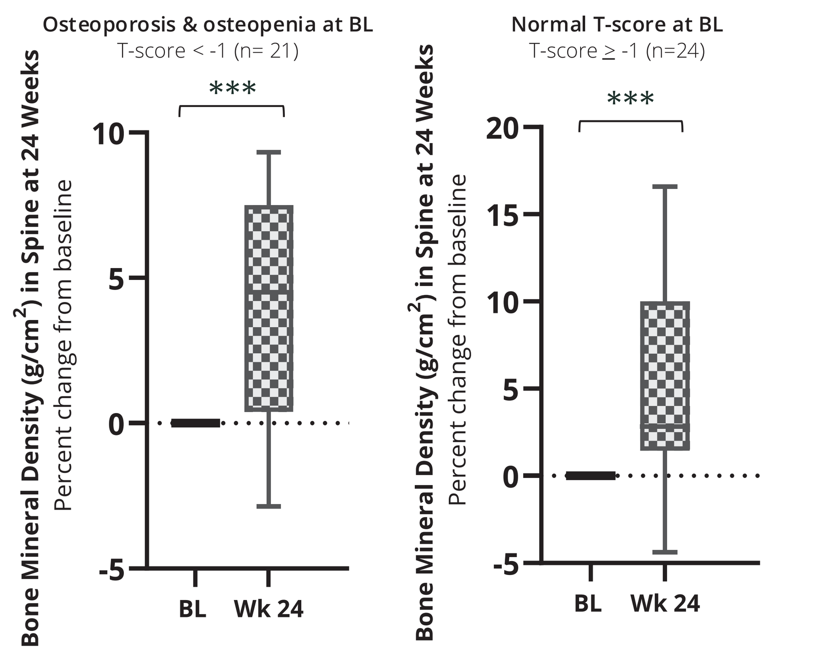
Comparison to placeboᵃ

- Mean lumbar spine BMD increased at Week 24 with bezuclastinib, whereas patients on placebo experienced a decline over the same period


Bone Mineral Density (g/cm²) in Spine at 24 Weeks
Percent change from baseline
*
Pbo (n=7)
Bezu (n=43)

Comparison to baseline in patients receiving bezuclastinibᵃ

- Improvement in mean BMD were observed across baseline bone health categories in bezuclastinib-treated patients, indicating a treatment-related gain in bone density

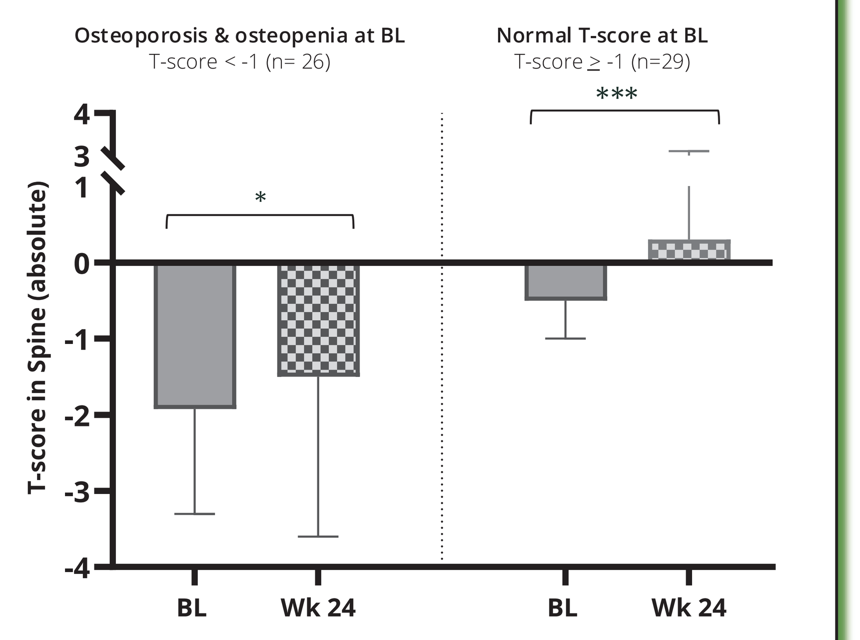

Osteoporosis & osteopenia at BL
T-score < -1 (n= 21)
Normal T-score at BL
T-score ≥ -1 (n=24)
Bone Mineral Density (g/cm²) in Spine at 24 Weeks
Percent change from baseline

BL
Wk 24

Significant improvement in spine T-scores at 24 weeks, demonstrating the clinical impact of bone remodeling after treatment initiation

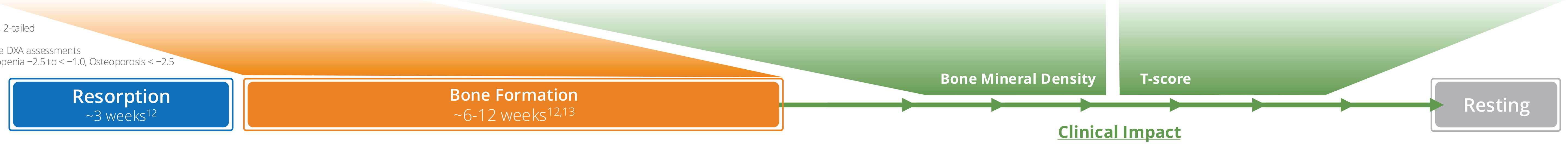
Comparison to baseline in patients receiving bezuclastinibᵃ

- Improvements in mean BMD corroborated by improvements in mean spine T-score compared with baseline
- T-score improvements observed across baseline bone health categories, including:
 - — Patients with baseline osteopenia or osteoporosis (T-score < –1)
 - — Patients with normal baseline T-scores (≥ –1)


Osteoporosis & osteopenia at BL
T-score < -1 (n= 26)
Normal T-score at BL
T-score ≥ -1 (n=29)
T-score in Spine (absolute)
*

BL
Wk 24

T-test: Mann-Whitney test, unpaired, nonparametric test, 2-tailed
* = p<0.01; *** = p<0.0001
ᵃAmong patients with available DXA assessments
T-score: Normal ≥ −1.0, Osteopenia −2.5 to < −1.0, Osteoporosis < −2.5


Resorption
~3 weeks[12]
Bone Formation
~6-12 weeks[12,13]
Bone Mineral Density
T-score
Resting
Clinical Impact

CONCLUSIONS

Evidence of disease modification with bezuclastinib based on improved bone formation markers, BMD, and T-scores by week 24

- A substantial proportion of Summit patients with DXA assessments showed baseline bone involvement, with 39% presenting with osteopenia and 11% with osteoporosis
 - — This distribution reflects abnormal bone loss commonly observed in patients with NonAdvSM and highlights the relevance of evaluating bone density and bone remodeling outcomes in this population
- Bezuclastinib treatment was associated with early activation of bone remodeling, reflected by increases in bone formation markers (osteocalcin, P1NP, ALP) at 8 weeks, peaking during the expected bone formation phase (6–12 weeks)
- Clinically meaningful improvements in BMD were observed at Week 24, particularly at the lumbar spine, a key fracture-risk site in patients with NonAdvSM
 - — Patients receiving bezuclastinib demonstrated increased spine BMD at Week 24, while those receiving placebo showed no improvement or a decrease
 - — BMD gains were seen regardless of baseline bone health, including patients with normal T-scores (≥ –1) and those with baseline osteopenia or osteoporosis (T-score < –1)
- Case summaries across age groups (<50 and >50 years) reinforced a consistent pattern, suggesting an emerging anabolic effect on bone with bezuclastinib treatment in patients with NonAdvSM:
 - — Early increases in bone formation markers,
 - — Measurable improvements in spine BMD
 - — Favorable shifts in T- and Z-scores

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ALP, alkaline phosphatase; BL, baseline; BM, bone marrow; BMD, bone mineral density; BMM, bone marrow mastocytosis; BSC, best supportive care; H1RA, histamine receptor type 1 antagonist; HR2A, histamine receptor type 2 antagonist; ISM, indolent SM; LTRA, leukotriene receptor antagonists; MC, mast cell; MS2D2, mastocytosis symptom severity daily diary; NonAdvSM, non-advanced systemic mastocytosis; OCN, osteocalcin; P1NP, procollagen type I N-terminal propeptide; PPI, proton pump inhibitors; QD, once daily; R, randomized; SSM, smoldering SM; TSS, total symptom score; VAF, variant allele frequency; Wk, week; WHO, World Health Organization.

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