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SB16 versus reference denosumab in postmenopausal women with osteoporosis: 18-month outcomes of a phase III randomized clinical trial

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ABSTRACT

Purpose: This study evaluated the efficacy, safety, pharmacodynamics (PD), pharmacokinetics (PK), and immunogenicity of SB16 versus reference denosumab (DEN) up to 18 months in postmenopausal osteoporosis (PMO) patients, and assessed outcomes after switching from DEN to SB16 compared to those who continued with DEN or SB16.

Methods: 457 PMO patients were initially randomized, with 407 re-randomized at Month 12 to either continue DEN (DEN+DEN), switch to SB16 (DEN+SB16), or continue SB16 (SB16 + SB16) through Month 18. Efficacy was assessed by the percent change from baseline in bone mineral density (BMD) at the lumbar spine, total hip, and femoral neck. Safety, PD, PK, and immunogenicity were evaluated throughout the study period.

Results: Mean percent changes from baseline in lumbar spine, total hip, and femoral neck BMD at Month 18 were comparable across treatment groups, indicating comparable efficacy between SB16 and DEN. The mean percent change in lumbar spine BMD was 6.8 % (SB16 + SB16), 6.2 % (DEN+SB16), and 6.8 % (DEN+DEN). Total hip BMD increased by 4.4 %, 3.5 %, and 4.0 %, and femoral neck BMD by 3.4 %, 3.1 %, and 2.7 % for SB16 + SB16, DEN+SB16, and DEN+DEN, respectively. Safety profiles were similar among groups, with no new safety concerns identified after switching. Only one patient in the DEN+SB16 group developed non-neutralizing anti-drug antibodies by Month 18, indicating a low immunogenicity risk for SB16.

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Conclusion: Switching from DEN to SB16 demonstrated comparable efficacy, safety, PD, PK, and immunogenicity in PMO patients relative to those who continued DEN. SB16 was well tolerated over 18 months, demonstrating comparable outcomes to DEN.

1. Introduction

Osteoporosis is a widespread bone disease that affects nearly 20 % of the global adult population. It is characterized by a decrease in bone mineral density and structural deterioration of bone tissue [1]. In the US, women with postmenopausal osteoporosis (PMO) represent over two-thirds of all osteoporosis cases [2]; their declining estrogen levels cause an imbalance between bone resorption and bone formation and an increase in the rate of bone remodeling, resulting in accelerated bone loss and significantly increased risk of fractures [3,4].

Anti-RANKL biologics have emerged as a first line treatment for the women with postmenopausal osteoporosis (PMO) with the development of denosumab (Prolia; hereafter referred to as DEN), a fully human monoclonal antibody which selectively binds to RANKL [5,6].

Despite their proven effectiveness, the availability and high cost of originator biologics can limit patient access to vital medications such as DEN [7–9]. Biosimilars are highly similar to an already authorized reference (i.e., the "innovator" or "originator") biological product, with no clinically meaningful differences in terms of quality, safety, or efficacy [10–12]. The motivation for switching to a biosimilar from an originator biologic often stems from the potential for significant cost savings, which can improve patient access and adherence to treatment [13].

SB16 is a proposed DEN biosimilar that has been developed in alignment with these goals. Rigorous analytical evaluations were performed to ensure the biosimilarity of SB16 to DEN, including state-of-the-art analytical methods that were employed to compare the physicochemical, structural, and biological properties. The equivalence in efficacy and comparable safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity between SB16 and DEN up to Month 12 has been previously demonstrated in patients with PMO [14]. This main period study, which spanned 12 months, provided robust evidence supporting the biosimilarity of SB16 to DEN, particularly in terms of its clinical efficacy and safety profile [14].

In many therapeutic areas, emerging data suggest that switching from a reference product to its biosimilar counterpart is as safe and effective as continuing treatment with the reference product [15–17]. A systematic review of over 170 studies showed no significant efficacy, safety, or immunogenicity concerns related to switching from reference biologics to biosimilars, with most data focusing on anti-TNFs [16]. Another systematic review and meta-analysis of 44 switch treatment periods from 31 studies found no significant differences in safety profiles or immunogenicity rates between patients who switched to or from a biosimilar and those who remained on reference biologics [17]. However, uncertainties remain regarding the potential clinical effects of such switching, particularly in relation to biosimilar immunogenicity [18–20].

The current clinical study was designed to address whether switching from DEN to SB16 impacts efficacy, safety, PK, PD, and immunogenicity in patients with PMO. At 12 months, patients originally receiving DEN were re-randomized to either continue DEN or switch to SB16. Herein, we present the results from the switching study, focusing on the clinical outcomes observed over the 18-month study period. In addition to assessing the outcomes of the switching group, this study provides comparative data between patients who continued treatment with SB16 and those who continued with DEN, offering further insights into the sustained efficacy and safety of SB16 over time.

2. Materials and methods

2.1. Study design

This study was a Phase III, randomized, double-blind, parallel-group, multicenter trial designed to evaluate the efficacy, safety, PK, PD, and immunogenicity of SB16 compared to DEN in patients with PMO. The study was conducted across 40 clinical sites in five countries: Czech Republic, Denmark, Lithuania, Poland, and the Republic of Korea.

At Screening, the Interactive Web Response System (IWRS) assigned each patient a unique number to ensure unbiased treatment group assignment, which was concealed from patients, Investigators, and other study personnel. A total of 457 patients were randomized at a 1:1 ratio to receive either SB16 or DEN. SB16 or DEN was administered 60 mg subcutaneously at baseline (Month 0) and again at Month 6 during the main period of the study.

For the switching period, the same patient number used in the main period was conveyed to register the patient using the IWRS. At Month 12, patients receiving DEN were re-randomized at a 1:1 ratio to either continue with 60 mg of DEN (DEN+DEN group) or switch to 60 mg of SB16 (DEN+SB16 group). Patients initially assigned to SB16 continued their treatment with 60 mg of SB16 (SB16 + SB16 group) but underwent the same randomization process at Month 12 to maintain blinding. The switching period concluded at Month 18. Throughout the main period and switching period, all patients received a daily supplement of at least 1 g of elemental calcium and 800 IU of vitamin D to support bone health.

The clinical study protocol, amendments, and informed consent forms were reviewed and approved by an Independent Ethics Committee or Institutional Review Board at each participating site. The study was conducted in accordance with the International Council for Harmonization (ICH) Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Informed consent was obtained from all patients prior to their participation in the study.

2.2. Participants

2.2.1. Key inclusion criteria

Eligible participants for this study were postmenopausal women aged 55 to 80 years. To qualify, participants were required to have a T-score between −2.5 and − 4.0 at either the total hip or lumbar spine as measured during the screening process. Additionally, all participants were required to be naïve to biologic treatments at the time of screening.

2.2.2. Key exclusion criteria

Participants were excluded from the study if they had a history of one severe or more than two moderate vertebral fractures as determined by spinal X-ray. Women with a history of hip fracture or those who had undergone bilateral hip replacement were also excluded. Other exclusion criteria included a serum 25-hydroxyvitamin D level of <20 ng/mL (50 nmol/L), albumin-adjusted serum calcium levels outside the range of 2.1 to 2.62 mmol/L (8.4 to 10.5 mg/dL), and an estimated glomerular filtration rate (eGFR) of <45 mL/min according to the Modification of Diet in Renal Disease (MDRD) formula or those undergoing dialysis. Additionally, participants who had used oral bisphosphonates for osteoporosis treatment for more than three years cumulatively or for three years or less with discontinuation less than one year prior to screening were excluded from the study. The patients with diseases known to cause osteoporosis, such as primary hyperparathyroidism, hyperthyroidism, and Cushing's disease were excluded.

2.3. Assessments and outcomes

The primary and secondary endpoints up to Month 12 of this study have been published previously [14]. The secondary endpoints included in this manuscript are efficacy, safety, PD, PK, and immunogenicity up to Month 18. Efficacy was evaluated by assessing the percent change from baseline in bone mineral density (BMD) at the lumbar spine (L1 to L4), total hip, and femoral neck at Month 18. The BMD measurements were only performed using GE Lunar or Hologic machines, and certified by the central reading center [14]. Safety was monitored through the incidence of adverse events (AEs) and serious adverse events (SAEs) reported throughout the study. A treatment-emergent adverse event (TEAE) was defined as any AE with an onset date on or after the date of the initiation of study drug. AEs which are already present before the initiation of study drug and increase in severity after the initiation of study drug was considered as TEAEs. Abnormalities discovered during laboratory testing, physical examination, vital signs, and/or other safety assessments which were assessed as clinically significant by the investigator were also reported as TEAEs. Adverse events of special interest (AESI) included hypocalcemia, hypersensitivity to IP, osteonecrosis of the jaw, atypical femoral fractures, and skin infections. PD outcomes included the median percent change from baseline in serum C-telopeptide of type I collagen (CTX) and serum procollagen type I N-terminal propeptide (P1NP) concentrations at Month 18. The PK profile was assessed by measuring serum drug concentrations at Month 18. Additionally, immunogenicity was evaluated by determining the incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) at Month 18. The blood samples for PD, PK, and immunogenicity assessment were collected on Month 0, 0.5, 1, 3, 6, 9, 12 (for main period), and Month 18 (for switching period). At time points Month 0, 6 and 12, the blood samples were taken before the SB16 or DEN injection was given.

2.4. Statistical analysis

The sample size calculation, as well as the definitions for the full analysis set (FAS), randomized set (RAN), pharmacokinetic analysis set (PKS), and pharmacodynamics analysis set (PDS), were previously described [10]. The safety analysis set (SAF2) included all patients from the initial safety analysis set (SAF1) who received investigational product (IP) after re-randomization at Month 12.

Secondary efficacy analyses compared the SB16 + SB16, DEN+SB16, and DEN+DEN treatment groups based on available data in the FAS. Safety was assessed during the switching period by comparing these treatment groups in SAF2, with AEs and SAEs coded using MedDRA version 23.0. Each patient was counted once per preferred term (PT) and system organ class (SOC). PK and PD analyses were conducted by comparing the SB16 + SB16, DEN+SB16, and DEN+DEN groups within the PKS and PDS. Immunogenicity was also assessed among these groups during the switching period using SAF2 data.

3. Results

3.1. Patient disposition

Patient disposition up to Month 12 was previously reported [14]. Of the 457 patients randomized, 456 (99.8 %) patients received the IP, and 417 (91.2 %) patients completed the main period (SB16 = 212, DEN = 205). A total of 407 patients were re-randomized (Fig. 1) and entered the switching period, with 206 in the SB16 + SB16 group, 100 in the DEN+SB16 group, and 101 in the DEN+DEN group. During the switching period, three patients withdrew from the study due to consent withdrawal: one from the DEN+SB16 group and two from the DEN+DEN group. 404 patients completed the switching period of the study, with completion rates of 100 % (206 patients) in the SB16 + SB16

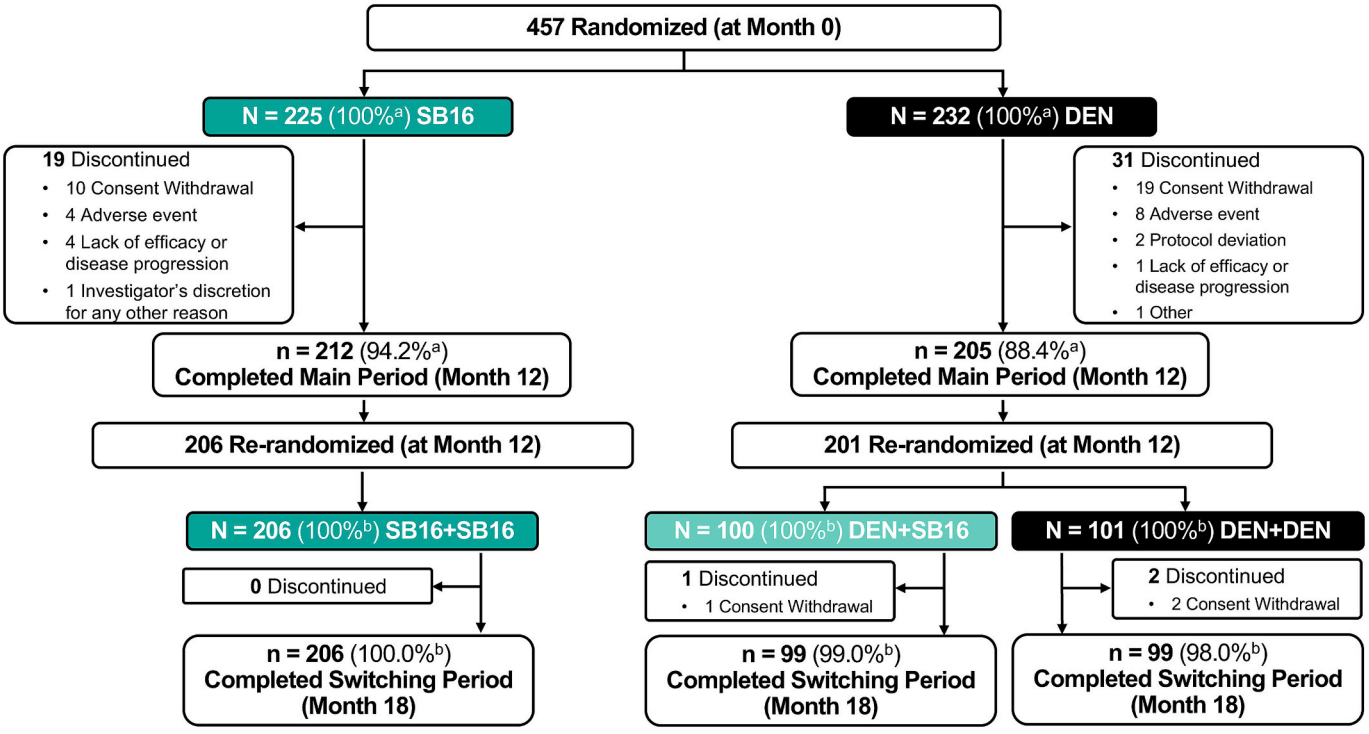

Fig. 1. Patient disposition by treatment group (RAN).
Summary of patient disposition during the study, showing the flow of patients from initial randomization through completion of the switching period, with high completion rates across each treatment group.
Abbreviations: DEN, reference denosumab; RAN, randomized set.
[a] Percentages based on the number of randomized patients at Month 0.
[b] Percentages based on the number of randomized patients at Month 12.

group, 99.0 % (99 patients) in the DEN+SB16 group, and 98.0 % (99 patients) in the DEN+DEN group.

3.2. Patient demographics and disease characteristics

The demographic and disease characteristics of the patients were well-balanced across the treatment groups at baseline and following re-randomization at Month 12 (Table 1).

Table 1
Patient demographics at baseline and disease characteristics at baseline and Month 12 (SAF2)[a].

Category	SB16 + SB16 (*N* = 206)	DEN+SB16 (*N* = 100)	DEN+DEN (*N* = 101)
Demographics at baseline			
Age[b], years; Mean (SD)	66.1 (5.72)	65.8 (5.73)	66.4 (6.05)
Age group ≥65 years; n (%)	120 (58.3)	61 (61.0)	57 (56.4)
Race, n (%)			
Asian	14 (6.8)	10 (10.0)	11 (10.9)
White	192 (93.2)	89 (89.0)	90 (89.1)
Other	0 (0.0)	1 (1.0)	0 (0.0)
BMI (kg/m^2)[c]; Mean (SD)	25.00 (3.72)	24.55 (3.44)	24.95 (3.41)
BMI category[c], n (%) ≥25 kg/m^2	97 (47.1)	40 (40.0)	43 (42.6)
Disease characteristics at baseline			
Years since menopause[d], mean (SD)	16 (7)	15 (7)	17 (8)
Prevalent vertebral fracture, n (%)			
Yes	92 (44.7)	57 (57.0)	49 (48.5)
No	112 (54.4)	43 (43.0)	50 (49.5)
Not assessable	2 (1.0)	0 (0.0)	2 (2.0)
Serum 25-OH-Vitamin D levels (nmol/L), mean (SD)	95.7 (41.4)	93.7 (31.4)	92.9 (39.3)
eGFR using MDRD equation (mL/min/SA), mean (SD)	80.2 (13.7)	79.5 (15.7)	81.9 (15.4)
Serum PTH (pmol/L), mean (SD)	4.2 (1.6)	4.0 (1.6)	4.3 (1.9)
Prior use of oral bisphosphonates, n (%)	40 (19.4)	16 (16.0)	14 (13.9)
T-score, mean (SD)			
Lumbar spine	−3.05 (0.49)	−3.06 (0.53)	−3.07 (0.48)
Total hip	−1.82 (0.78)	−1.88 (0.72)	−1.85 (0.75)
Femoral neck	−2.17 (0.61)	−2.20 (0.57)	−2.17 (0.67)
Serum CTX (ng/mL); Mean (SD)	0.44 (0.21)	0.41 (0.19)	0.46 (0.21)
Disease characteristics at Month 12			
Serum 25-OH-Vitamin D levels (nmol/L), mean (SD)	100.6 (38.3)	100.0 (43.8)	102.2 (49.3)
eGFR using MDRD equation (mL/min/SA), mean (SD)	77.0 (13.4)	75.7 (15.3)	76.8 (14.5)
T-score[e], mean (SD)			
Lumbar spine	−2.71 (0.56)	−2.74 (0.56)	−2.74 (0.55)
Total hip	−1.60 (0.79)	−1.69 (0.75)	−1.65 (0.72)
Femoral neck	−2.01 (0.63)	−2.06 (0.61)	−2.05 (0.68)
Serum CTX (ng/mL)[f]; Mean (SD)	0.14 (0.10)	0.14 (0.09)	0.14 (0.09)

Abbreviations: BMI, body mass index; CTX, C-telopeptide of type I collagen; DEN, denosumab; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; N, number of patients in the SAF2; n, number of patients in each category; PTH, parathyroid hormone; SA, 1.73m^2; SAF2, safety analysis set 2; SD, standard deviation.

[a] Percentages calculated based on available data from the SAF2, which includes patients re-randomized at Month 12.

[b] Age calculated as the difference in years of ICF and birth year obtained.

[c] BMI calculated using baseline weight and height at screening.

[d] Years since menopause = (randomization date - date of last menstruation +1)/365.25.

[e] Instrument quality control (IQC) and cross-calibration (Xcal) corrected BMD measurement value.

[f] Any major protocol deviations impacting results were not included.

At baseline, the mean age of patients was consistent, ranging from 65.8 to 66.4 years across treatment groups, with 40.0 to 47.1 % having a BMI of ≥25 kg/m^2. Other demographics and disease characteristics at baseline including mean T-scores (lumbar spine, total hip, and femoral neck), serum CTX levels, serum 25-OH-Vitamin D levels, and eGFR levels were well-balanced across treatment groups.

At Month 12, the disease characteristics, including T-scores and serum CTX levels, remained well-balanced across the treatment groups, suggesting uniformity in response to treatment.

3.3. Efficacy

At Month 18, the mean percent changes from baseline in BMD for the lumbar spine, total hip, and femoral neck were comparable across treatment groups (between DEN+SB16 and DEN+DEN groups, and between SB16 + SB16 and DEN+DEN groups) (Fig. 2). The mean (SE) percent change in lumbar spine BMD was 6.8 % (0.30) in the SB16 + SB16 group, 6.2 % (0.36) in the DEN+SB16 group, and 6.8 % (0.42) in the DEN+DEN group. For total hip BMD, the mean (SE) percent changes were 4.4 % (0.22), and 3.5 % (0.29), and 4.0 % (0.31) for the SB16 + SB16, DEN+SB16, and DEN+DEN groups, respectively. Femoral neck BMD showed mean (SE) percent changes of 3.4 % (0.28) in the SB16 + SB16 group, 3.1 % (0.35) in the DEN+SB16 group, and 2.7 % (0.35) in the DEN+DEN group.

3.4. Pharmacodynamics and pharmacokinetics

Median percent changes from baseline in serum CTX and P1NP were also comparable across treatment groups (Fig. 3). Serum CTX levels showed a median decrease of at least 50 % compared to baseline at all time points. P1NP levels decreased starting at Month 1, and consistent reductions were observed through Month 18. PK profiles up to Month 18 were comparable between SB16 and DEN treatment groups, both when continuing DEN and when switching from DEN to SB16 (data not shown).

3.5. Safety and Immunogenicity

The mean duration of IP exposure during the overall study period was comparable across treatment groups (518.5 days for the SB16 + SB16 group, 543.4 days for the DEN+SB16 group, and 542.9 days for the DEN+DEN group). TEAEs during the main period were similar between SB16 and DEN groups, as previously reported.

During the switching period, the incidence of TEAEs was also comparable across treatment groups: 35.4 % for the SB16 + SB16 group, 29.0 % for the DEN+SB16 group, and 34.7 % for the DEN+DEN group. Most TEAEs were mild or moderate in intensity (Table 2). AESI were rare during the switching period, with hypocalcemia occurring in 2 of 206 (1.0 %) patients in the SB16 + SB16 group, and no AESI reported in the other treatment groups. Skeletal fractures were reported in 4 of 206 (1.9 %) patients in the SB16 + SB16 group and 3 of 101 (3.0 %) patients in the DEN+DEN group, with none in the DEN+SB16 group. A total of nine SAEs occurred in seven patients (SB16 + SB16: 4 [1.9 %], DEN+SB16: 2 [2.0 %], DEN+DEN: 1 [1.0 %]) across all groups, with none being related to the study drug. No injection site reactions or deaths were reported during the switching period. At Month 18, immunogenicity assessments revealed that only one patient in the DEN+SB16 group developed ADAs; however, NAbs were not detected in this patient (data not shown). No ADAs were detected in the SB16 + SB16 or DEN+DEN treatment groups.

4. Discussion

This study compared the efficacy and safety of SB16 in PMO patients

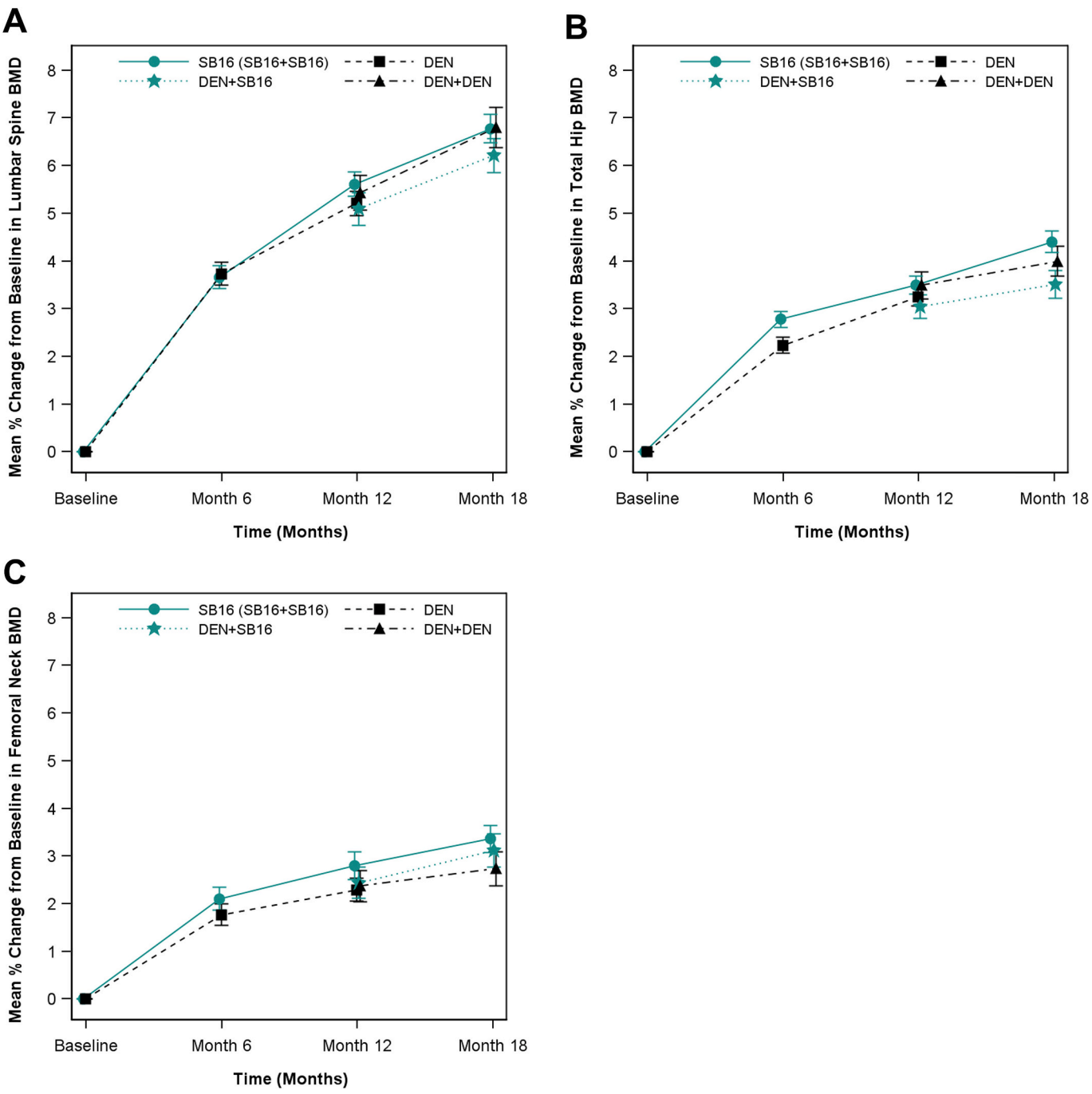

Fig. 2. Mean percent change from baseline in lumbar spine, total hip, and femoral neck BMD (FAS).
Mean percent changes from baseline in BMD up to Month 18 for the lumbar spine (A), total hip (B), and femoral neck (C) were compared between SB16 (SB16 + SB16), DEN+SB16, and DEN+DEN treatment groups. The symbol and error bar represent mean and standard error at each timepoint.
Abbreviations: BMD, bone mineral density; DEN, reference denosumab; FAS, full analysis set.

who switched from DEN to SB16 against those who continued receiving either SB16 or DEN over an 18-month period. The results demonstrated that efficacy was maintained after switching from DEN to SB16, with comparable outcomes observed between the DEN+SB16 and DEN+DEN treatment groups. This study also confirmed that the efficacy of SB16 in PMO patients was comparable and sustained between SB16 + SB16 and DEN+DEN groups up to Month 18. SB16 + SB16, DEN+SB16, and DEN+DEN groups reported the mean percent changes from baseline up to month 18 of 6.2 %–6.8 % in lumbar spine BMD, 3.5 %–4.4 % in total hip BMD, and 2.7 %–3.4 % in femoral neck BMD respectively. The reported values were similar with the results from the FREEDOM study [21] and are consistent with other proposed DEN biosimilar studies involving switching to DEN, including the ROSALIA study and the Phase III CT-P41 study [22,23]. Similarity of efficacy between maintenance and switching groups was sustained up to Month 18 in the ROSALIA study and Phase III CT-P41 study [22,23]. By comparison, in the ROSALIA study, GP2411 + GP2411, DEN+GP2411, and DEN+DEN groups reported the mean percent changes from baseline up to month 18 of 6.4 %–7.1 % in lumbar spine BMD, 3.8 %–4.1 % in total hip BMD, and 2.7 %–3.2 % in femoral neck BMD [22]. In the Phase III CT-P41 study, CT-P41 + CT-P41, DEN+CT-P41, and DEN+DEN groups reported mean percent changes from baseline up to month 18 of 6.6 %–7.1 % in lumbar

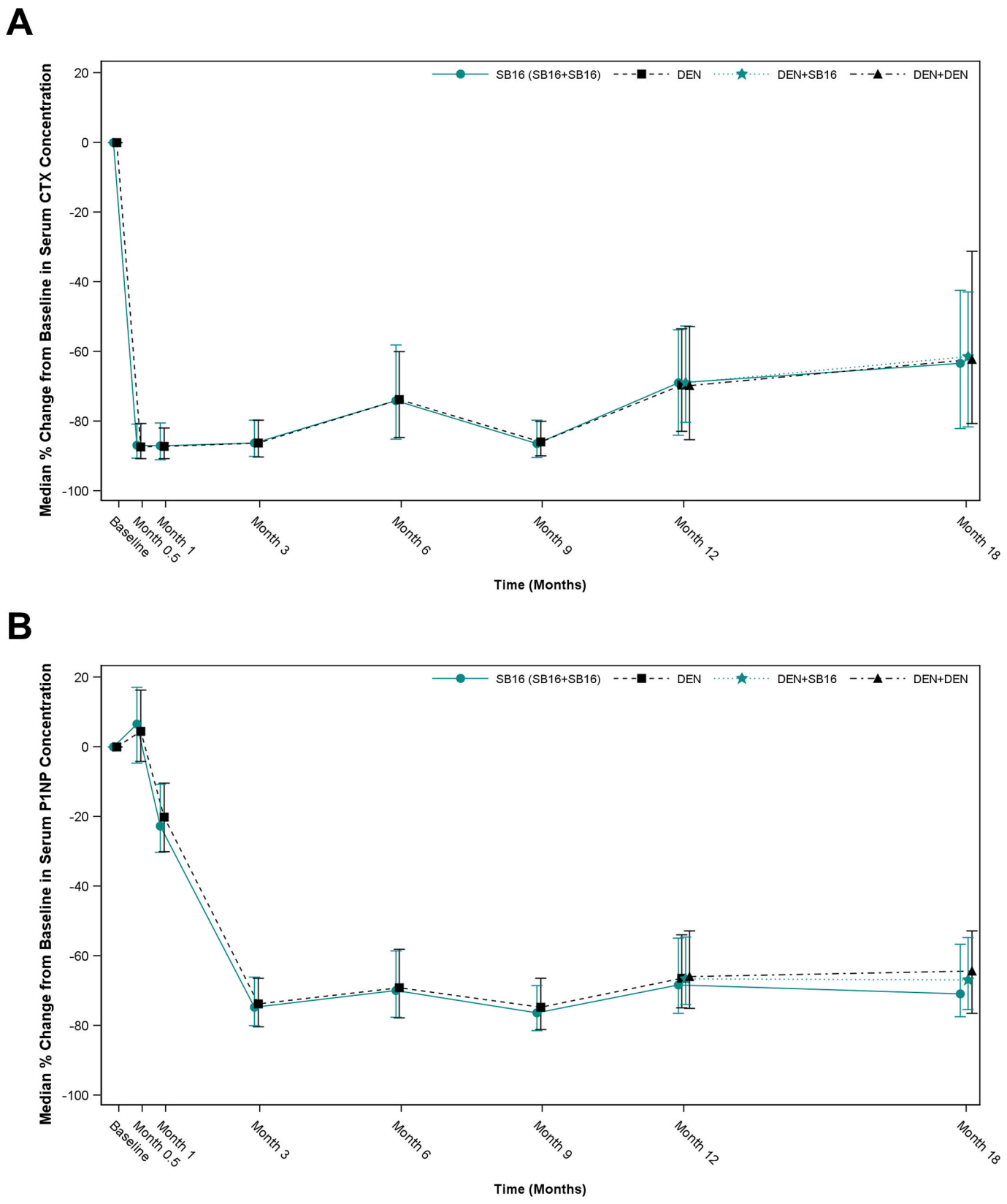

Fig. 3. Median percent changes from baseline in serum CTX and P1NP concentration profiles up to Month 18 (PDS).
Median percent changes from baseline in serum CTX (A) or P1NP (B) concentrations up to Month 18 were compared between SB16 (SB16 + SB16), DEN+SB16, and DEN+DEN treatment groups. Analyses were based on available data from the PDS. The symbol and error bar represent median percent change and interquartile range at each timepoint, respectively.
Abbreviations: BMD, bone mineral density; CTX, C-telopeptide of type I collagen; DEN, reference denosumab; P1NP, procollagen type I N-terminal propeptide; PDS, pharmacodynamics analysis set.

Table 2
Safety profiles during the switching period (SAF2)[a].

Number of subjects experiencing	SB16 + SB16	DEN+SB16	DEN+DEN
	N = 206	N = 100	N = 101
	n (%)	n (%)	n (%)
At least one TEAE	73 (35.4)	29 (29.0)	35 (34.7)
TEAEs related to IP	3 (1.5)	0 (0.0)	0 (0.0)
TEAEs of special interest	2 (1.0)	0 (0.0)	0 (0.0)
Hypocalcemia	2 (1.0)	0 (0.0)	0 (0.0)
At least one serious TEAE	4 (1.9)	2 (2.0)	1 (1.0)
Injection site reactions	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Frequently reported (> 2 %) TEAEs	39 (18.9)	12 (12.0)	15 (14.9)
Arthralgia	7 (3.4)	1 (1.0)	2 (2.0)
Bronchitis	5 (2.4)	1 (1.0)	2 (2.0)
COVID-19	5 (2.4)	1 (1.0)	2 (2.0)
Headache	5 (2.4)	2 (2.0)	2 (2.0)
Hypercholesterolemia	7 (3.4)	1 (1.0)	1 (1.0)
Nasopharyngitis	1 (0.5)	1 (1.0)	4 (4.0)
Upper respiratory tract infection	5 (2.4)	0 (0.0)	0 (0.0)
Vitamin D deficiency	5 (2.4)	5 (5.0)	2 (2.0)

Abbreviations: DEN, denosumab; IP, investigational product; N, number of patients in the SAF2; n, number of patients with event; PTH, parathyroid hormone; SAF2, safety analysis set 2; TEAE, treatment emergent adverse event.

[a] Percentages calculated based on available data from the SAF2, which includes patients re-randomized at Month 12.

spine BMD, 2.8 %–3.5 % in total hip BMD, and 2.4 %- 3.0 % of femoral neck BMD [23]. This further supports SB16 as an effective treatment option, whether as first-line or initiated after DEN treatment, with BMD results aligning closely with those from other biosimilar studies.

PD parameters evaluated in this study included serum CTX and P1NP, which are key indicators of bone resorption and formation. The median percent changes from baseline in CTX levels showed a consistent decrease and maintenance over the study period across all treatment groups, reflecting effective suppression of bone resorption. Similarly, the median percent changes from baseline in serum P1NP levels decreased from the first month and remained stable throughout the study in each treatment group. Comparable PD outcomes in serum CTX and P1NP between SB16 + SB16, DEN+SB16, and DEN+DEN groups confirm that switching from DEN to SB16 does not compromise the therapeutic effects on bone metabolism. These findings are further reinforced by the CTX and P1NP results from the GP-2411 and CT-P41 switching studies which demonstrated maintained suppression of CTX/P1NP after switching from DEN to the respective biosimilar [22,23].

SB16 and DEN exhibited comparable safety profiles during the switching period, with similar incidences and characteristics of TEAEs across the SB16 + SB16, DEN+SB16, and DEN+DEN groups. Most TEAEs were mild or moderate in intensity. Importantly, no injection site reactions were reported. Only two TEAEs of special interest (1.0 %, 2 events of hypocalcemia) were reported in the SB16 + SB16 group, with no TEAEs of special interest reported in the DEN+SB16 or DEN+DEN groups. No deaths or IP-related SAEs were reported, and the incidence of skeletal fractures was comparable among the groups. The immunogenicity assessment in this study revealed a very low ADA incidence consistent with previously reported data from reference DEN (<1 %) [24,25], with only one patient in the DEN+SB16 group testing positive for non-neutralizing ADAs by Month 18. No ADAs were detected in the SB16 + SB16 or DEN+DEN groups. Collectively, these findings suggest that SB16 is well-tolerated, with no significant safety and immunogenicity concerns up to Month 18 including when patients switch from DEN to SB16.

This study does have limitations. Since this study has only 6-month switching period, so the longer-term effect is unknown. This study was not designed to examine the impact of switching on fracture risk; the BMD changes among the groups after switching are similar, so the fracture risk is likely similar. Finally, the effect of denosumab withdrawal on BMD and bone turnover marker (BTM) was not examined. Still, given the similarity of changes in BMD and BTM on treatment, it is likely that the offset effects are similar between SB16 and DEN.

Our study design allowed for direct comparisons between DEN+SB16 and DEN+DEN from Month 12 to Month 18, and between SB16 + SB16 and DEN+DEN up to Month 18. Although not designed to statistically compare equivalence, this switching period study provides valuable data on switching from the reference product to biosimilar. These results support the use of SB16 as a safe and effective alternative to DEN, offering clinicians confidence in transitioning patients to this biosimilar.

5. Conclusions

In conclusion, efficacy, safety, PD, PK, and immunogenicity were comparable between PMO patients who switched to SB16 and those who continued DEN. SB16 was well-tolerated over 18 months, with the safety profile consistent with DEN, and maintained its clinical efficacy, supporting SB16 as an effective and safe alternative in the management of PMO.

Clinical trial registration

ClinicalTrials.gov identifier NCT04664959; EudraCT number 2020–001479-34.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yoon-sok Chung reports a relationship with Amgen that includes: speaking and lecture fees. Yoon-sok Chung reports a relationship with Samsung Bioepis that includes: consulting or advisory and funding

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If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Upon request, and subject to certain criteria, conditions, and exceptions, Samsung Bioepis will provide access to individual de-identified participant data to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply. Proposals should be directed to the corresponding author. For access, data requestors must enter into a data access agreement with Samsung Bioepis.

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