ORIGINAL ARTICLE

A Prospective, Active-controlled, Randomized, Double-blind, Multicenter, Phase III Study to Compare the Safety and Efficacy of Biosimilar Denosumab vs Reference Denosumab in the Treatment of Postmenopausal Osteoporosis

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Abstract

Objective: Denosumab, a human monoclonal antibody that exhibits strong affinity and specificity for the receptor activator of nuclear factor-kappa B ligand (RANK-L), is essential in regulating bone turnover. Its inhibition of RANK-L decreases bone resorption by preventing the development, function, and survival of osteoclasts.

The objective of the study was to evaluate and compare the efficacy and safety of biosimilar denosumab with the reference product, Prolia (denosumab), in Indian women suffering from postmenopausal osteoporosis.

Methods: This phase III study was a prospective, active-controlled, randomized, double-blind trial that included postmenopausal women diagnosed with osteoporosis. Participants were randomly allocated in a 2:1 ratio to receive either the biosimilar denosumab (Treatment A) or the reference denosumab (Prolia®; Treatment B). All participants also received daily supplementation of 500 international units (IU) of vitamin D3 and 1000 mg calcium. The primary outcomes measured were the bone mineral density (BMD) percentage change at the lumbar spine and the neck of femur, while the secondary endpoint assessed changes in biomarkers from baseline at months 6 and 12.

Results: The lumbar spine BMD percentage change for group A vs group B from baseline to month 6 was 5.69 ± 0.88 ($p < 0.0001$) vs 5.08 ± 1.19 ($p < 0.0001$), and at 12 months was 7.26 ± 1.05 ($p < 0.0001$) vs 7.31 ± 1.40 ($p < 0.0001$), demonstrating equivalent efficacy. Both treatment groups showed statistically significant improvement in femoral neck BMD at 12 months. No statistically significant difference was noted in the ln-transformed primary pharmacokinetic parameters, including C-max, AUC0-120d, and AUC0-∞.

Conclusion: Biosimilar denosumab was comparable to reference denosumab with respect to its efficacy, safety, pharmacokinetics (PK), pharmacodynamics, and immunogenicity in women with postmenopausal osteoporosis. Thus, biosimilar denosumab is expected to improve the quality of life in osteoporotic patients at affordable prices.

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Introduction

Osteoporosis is associated with diminished bone mineral density (BMD) and changes in bone microstructure, which heighten the risk of fractures from low-impact injuries. These osteoporotic fractures significantly impair quality of life and contribute to elevated rates of morbidity, mortality, and disability.[1] While osteoporosis can affect individuals of any age and both genders, women are at greater likelihood of developing the condition and experiencing fractures compared to men. Osteoporosis-related fractures are particularly common in postmenopausal women, occurring more frequently than stroke, myocardial infarction, and breast cancer combined.[2]

Osteoporotic fractures affect one out of every three women over the age of 50 worldwide. There are >100 million women in India who are above the age of 50. According to research conducted in Delhi, 42.5% of women over the age of 50 have osteoporosis.[3]

The discovery and comprehension of the critical role played by the receptor activator of nuclear factor-kappa B ligand (RANK-L) pathway in controlling osteoclast activity have revealed novel therapeutic targets for osteoporosis. As a complete human IgG2 monoclonal antibody, denosumab binds specifically to RANK-L with notable specificity and affinity, having a crucial function in managing bone turnover. By inhibiting RANK-L, it decreases resorption of bone by impairing osteoclast development, function, and survival.[4,5]

Over a period of 36 months, the phase III FREEDOM trial assessed the role of denosumab in minimizing the likelihood of developing fractures in postmenopausal women diagnosed with osteoporosis. The results showed that denosumab led to a 68% decreased probability of incurring new vertebral fractures ($p < 0.001$) when assessed against the placebo. Additionally, at 6 and 12 months, the denosumab group exhibited a relative improvement in BMD of 3.9 and 5.5%, respectively, as opposed to the placebo group.[6]

Denosumab was the first RANK-L inhibitor to receive approval for the treatment of osteoporosis. This phase III clinical trial was conducted to assess and compare the efficacy and safety of biosimilar denosumab (developed by Alkem Laboratories Ltd/Enzene Biosciences Ltd) with the reference drug, Prolia (denosumab), in Indian women with postmenopausal osteoporosis.

Methods

Study Design and Patient Selection

This prospective, active-controlled, double-blind, randomized phase III study, carried out across multiple locations, involved osteoporotic postmenopausal women aged between 50 and 80 years. The study adhered to the principles and requirements of the Declaration of Helsinki (2013), ICH-GCP (E6-R2, Step 4) guidelines, and local regulatory standards, including Good Clinical Practices (GCP) for Clinical Research in India (2004), Indian Council of Medical Research (ICMR) guidelines for Biomedical Research on Human Subjects (2017), and the New Drugs and Clinical Trial Rules, 2019. It was conducted following approvals from the relevant Institutional Ethics Committee.

After providing informed consent, participants were screened 7 days prior to the baseline visit to determine their eligibility based on the study criteria. Eligible participants needed to be a minimum of 5 years postmenopause and must have osteoporosis verified through an evaluation of bone density *via* Dual-energy X-ray absorptiometry (DXA). This was defined as BMD of T-scores ≤ –2.5 standard deviations (SD) at either the lumbar spine (L1–L4) or the neck of femur. They also needed to give consent in writing, voluntarily, after a thorough explanation to participate in the study.

Participants with vertebral abnormalities at L1–L4 that may interfere with the assessment by DXA, vitamin D deficiency, thyroid dysfunction, hypocalcemia or hypercalcemia, rheumatoid arthritis, abnormal laboratory findings, positive serology for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), or Human Immunodeficiency Virus (HIV), any presence of metabolic bone disease other than osteoporosis, any malignancy, identified hypersensitivity to denosumab or any of its excipients, any oral/dental conditions, malabsorption syndrome, or any gastrointestinal disorders associated with malabsorption, active or chronic infection, or history of hip replacement surgery at screening, participants on any previous treatment with bisphosphonates within 12 months before the screening process, any other drug affecting bone metabolism within 3 months before the screening process, or immunosuppressive therapy, and participants who were not inclined or capable of meeting the protocol stipulations, or had participated in any other clinical study in the last 30 days were omitted from the present trial.

Treatment Plan

Throughout the treatment phase, participants were randomly assigned using an Interactive Web Response System (IWRS) in a ratio of 2:1 to receive either the biosimilar denosumab group (Alkem Laboratories Ltd/Enzene Biosciences Limited; Treatment A) or the reference denosumab group (Prolia®; Treatment B). Participants also received vitamin D3 500 international units (IU) and calcium 1000 mg once daily as supplements and were dispensed at baseline, days 14, 30, 60, 90, 180, and 270.

Biosimilar denosumab 60 mg injection or reference denosumab 60 mg injection was administered subcutaneously once every 6 months during the study visit, that is, baseline and day 180. Each participant was scheduled for a total of 10 site visits: visit 1 for initial screening, visit 2 for baseline assessment, visit 3 scheduled on day 14 ± 1, visit 4 at 1 month, visit 5 at 2 months, visit 6 at 3 months, visit 7 at 6 months, visit 8 at 9 months, visit 9 at 12 months, and visit 10 at the end of the study in month 13. Visits from month 1–12 had a window period of ± 2 days.

The pharmacokinetics (PK) assessments were also performed on a subset of participants who voluntarily consented to take part in the PK sub-study in addition to the main study. Blood samples were collected at predose (30 minutes before dosing), on days 7, 10, 14, 30, 60, 90, and 120 post the investigational product administration. All the PK parameters were calculated using the actual time of the sample collected. The PK samples were analyzed for plasma concentrations of denosumab in both test and reference products, and Cmax, AUC0–120 days, AUC0–∞, and Tmax were assessed.

Efficacy and Safety Variables

The primary endpoint was the percentage change in BMD at the lumbar spine and femoral neck from baseline to months 6 and 12 of treatment. The secondary efficacy endpoint assessed changes in biomarkers from baseline, specifically serum type 1 C-telopeptide (CTX) at months 6 and 12. Safety endpoints included the development of both serious and non-serious treatment-emergent adverse events (AEs), variations in clinical lab parameters from baseline to the conclusion of treatment, and the assessment of antidenosumab antibodies. Throughout the study, data were gathered on both primary and secondary endpoints. BMD was measured using a DXA scanner for efficacy evaluation, and laboratory samples were collected to assess both efficacy and safety.

Statistical Analysis

The analysis of covariance (ANCOVA) models for the primary endpoint were adjusted for the baseline as well as the randomization stratification factor as covariates.

The efficacy analysis was conducted on all participants in both the modified intention-to-treat (mITT) and the per-protocol (PP) populations. To evaluate changes from baseline to 6 and 12 months, a regression model was used with the percent change from baseline as the response variable. This model included the stratification variable from randomization to treatment as independent variables to compare the mean difference in percent change between the two treatments. The results were reported as adjusted least squares mean (LSM) with standard error, along with *p*-values and 95% confidence intervals for the differences. For safety analyses, AEs were categorized based on the Medical Dictionary for Regulatory Activities (MedDRA) coding system and organized by system organ class for summarization.

The sample size was calculated using clinical difference (10%), standard deviation (29), noninferiority margin (15%), alpha (5%), power (90%), and allocation ratio (2:1). Considering a 20% dropout rate, the overall participant

requirement for the trial was 177 (innovator denosumab = 59 and biosimilar denosumab = 118). According to the calculations, the trial is expected to have over 90% power to establish the noninferiority of the biosimilar test product in relation to the reference product.

Results

Patient Population and Demographic

After screening 637 participants, 177 were randomized (116 assigned to Treatment A/biosimilar denosumab and 61 assigned to Treatment B/reference denosumab). Of these, 155 patients (87.6%) completed the study, with 102 (87.9%) from Treatment A and 53 (86.9%) from Treatment B. Patient disposition is detailed in Figure 1. The baseline characteristics did not differ significantly between the two treatment groups (Table 1).

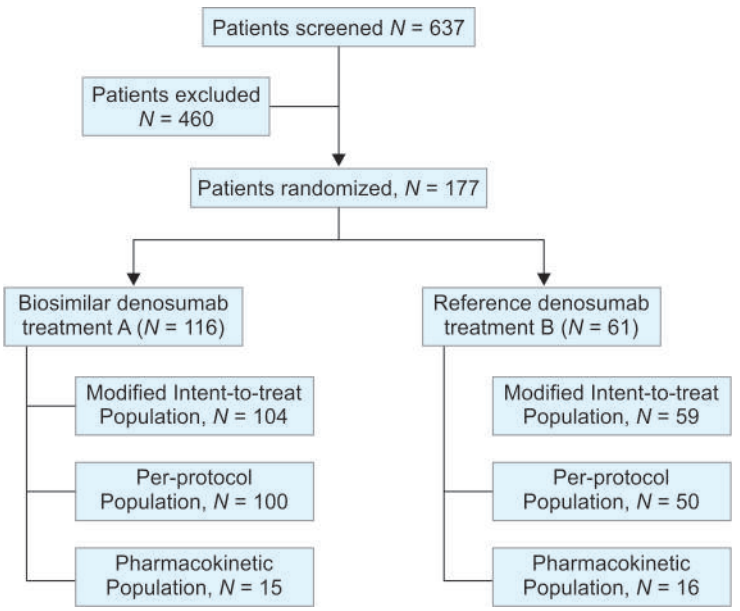

Fig. 1: Patient disposition

Lumbar Spine Bone Mineral Density Improvement at Month-6 and 12 (mITT and PP Populations)

In both treatment groups, a statistically significant improvement was observed concerning the percentage change from baseline to 6 and 12 months in the mITT and PP populations. The difference was not statistically significant in LSM percentage change across the treatment groups, indicating noninferiority of Treatments A to B (Table 2, Figs 2 and 3).

Femoral Neck Bone Mineral Density Improvement at Month-6 and 12 (mITT and PP Populations)

In both treatment groups, there was an improvement in BMD. However, a statistically significant improvement was observed only with Treatment A at 6 months, and with both treatment groups at 12 months. The difference was not statistically significant in LSM percentage change across the two treatment groups, indicating noninferiority of Treatments A to B (Table 3, Figs 2 and 3).

Biomarkers associated with bone turnover were assessed, and there was no significant difference in the mean change in serum CTX levels from baseline to months 6 and 12 across Treatment groups A and B (Table 4).

Pharmacokinetic Comparison

This sub-study involved 31 participants. The differences between the ln-transformed primary pharmacokinetic parameters, including Cmax, AUC0–120d, and AUC0–∞, were statistically insignificant. The geometric LSM for biosimilar denosumab (T) and reference denosumab (R), along with their ratios (T/R)%, derived from the analysis of these ln-transformed parameters, are summarized in Table 5.

Table 1: Baseline demographic characteristics of patients

Baseline characteristics	*Treatment A (biosimilar denosumab) (n = 116)*	*Treatment B (reference denosumab) (n = 61)*	*Total (n = 177)*
Age (years), mean (SD)	63.28 (7.53)	63.69 (7.58)	63.42 (7.53)
Height (cm), mean (SD)	149.1 (6.59)	148.1 (6.28)	148.8 (6.49)
Weight (kg), mean (SD)	55.20 (11.56)	55.18 (10.78)	55.19 (11.27)
Baseline BMD lumbar spine, mean (SD)	0.7375 (0.120)	0.7461 (0.0963)	–
Baseline BMD femoral neck, mean (SD)	0.662 (0.105)	0.663 (0.112)	–

Table 2: Percentage change in Lumbar spine BMD from baseline to months 6 and 12 (mITT and PP population)

	mITT population			*PP population*		
	Treatment A (biosimilar denosumab)	*Treatment B (reference denosumab)*	*LSM percent change difference (test–reference) ± SE (p-value)*	*Treatment A (biosimilar denosumab)*	*Treatment B (reference denosumab)*	*LSM percent change difference (test–reference) ± SE (p-value)*
LSM percent change in lumbar spine BMD from baseline at month 6 ± SE (*p*-value)	5.69 ± 0.88 (<0.0001)	5.08 ± 1.19 (<0.0001)	0.61 ± 1.46 (0.68)	5.20 ± 0.68 (<0.0001)	4.35 ± 0.92 (<0.0001)	0.84 ± 1.11 (0.44)
LSM percent change in lumbar spine BMD from baseline at month 12 ± SE (*p*-value)	7.26 ± 1.05 (<0.0001)	7.31 ± 1.40 (<0.0001)	–0.05 ± 1.72 (0.97)	6.80 ± 0.96 (<0.0001)	6.70 ± 1.30 (<0.0001)	0.10 ± 1.57 (0.94)

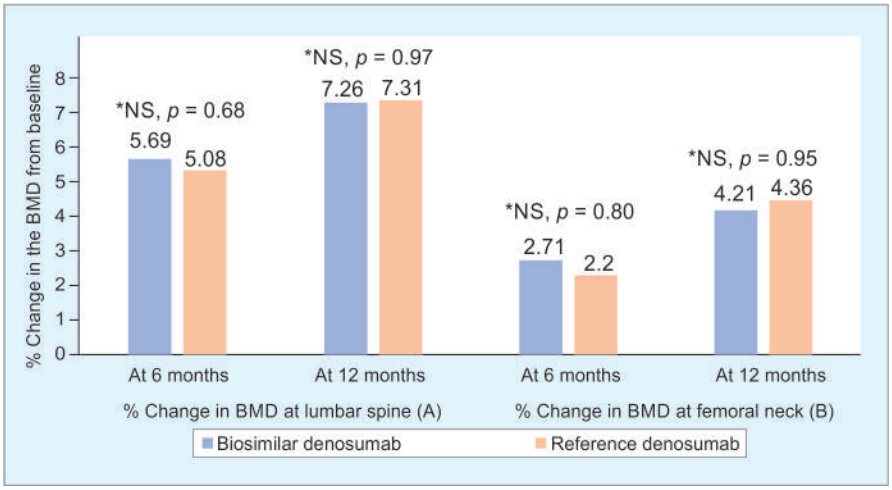

Fig. 2: Percentage change in BMD at lumbar spine and femoral neck at months 6 and 12 (mITT population); *NS, non significant

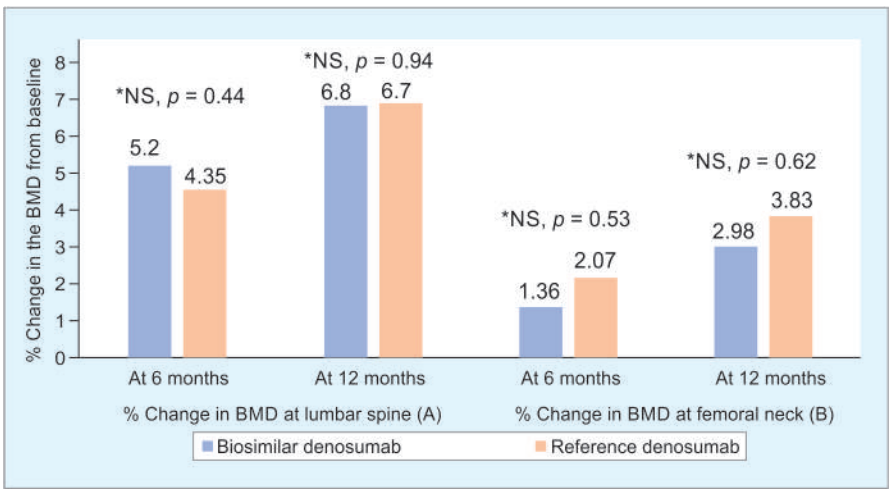

Fig. 3: Percentage change in BMD at lumbar spine and femoral neck at months 6 and 12 (PP population); *NS, non significant

Safety

A total of 86 treatment-emergent adverse events were reported in 55 (31.1%) patients. Among these reported adverse events, four events were serious adverse events (SAEs). Treatment-emergent antidenosumab antibodies were detected in two patients (1.85%) in the Treatment A group at month 6, while at the end of the study, none of the patients tested positive for the antidenosumab antibody. A summary of treatment-emergent adverse events is provided in Table 6.

Four SAEs—compression fracture, vocal cord paralysis, pulmonary tuberculosis, and Parkinson's disease—were experienced during the study period. Two participants experienced SAEs following the administration of biosimilar denosumab. One participant (0.9%) experienced compression fracture, and one participant (0.9%) experienced vocal cord paralysis and pulmonary tuberculosis. Compression fracture and pulmonary tuberculosis were mild, and vocal cord paralysis was severe; however, all three were unlikely related to the study drug. Following the administration of reference denosumab, one participant (1.6%) experienced Parkinson's disease, which was mild and unlikely related to the study drug.

Discussion

As a fully human monoclonal antibody, denosumab acts on RANK-L and is key in regulating bone resorption in osteoporotic postmenopausal women. Research studies have demonstrated that denosumab effectively reduces vertebral, nonvertebral, and hip fractures compared to placebo. It also

Table 3: Percentage change in femoral neck BMD from baseline to months 6 and 12 (mITT and PP population)

	mITT population			*PP population*		
	Treatment A (biosimilar denosumab)	*Treatment B (reference denosumab)*	*LSM percent change difference (test–reference) ± SE (p-value)*	*Treatment A (biosimilar denosumab)*	*Treatment B (reference denosumab)*	*LSM percent change difference (test–reference) ± SE (p-value)*
LSM percent change in femoral neck BMD from baseline at month 6 ± SE (*p*-value)	2.71 ± 1.24 (0.003)	2.20 ± 1.67 (0.19)	0.51 ± 2.05 (0.80)	1.36 ± 0.68 (0.04)	2.07 ± 0.94 (0.03)	–0.70 ± 1.13 (0.53)
LSM percent change in femoral neck BMD from baseline at month 12 ± SE (*p*-value)	4.21 ± 1.42 (0.003)	4.36 ± 1.910 (0.024)	–0.14 ± 2.34 (0.95)	2.98 ± 1.03 (0.004)	3.83 ± 1.43 (0.008)	–0.84 ± 1.72 (0.62)

Table 4: Changes in CTX from baseline at months 6 and 12

Parameter	*Biosimilar denosumab (T) (n = 116)*	*Reference denosumab (R) (n = 61)*	*p-value*
Change from baseline to month 6*	–0.06	–0.1124	0.52
Change from baseline to month 12*	–0.20 (0.06)	–0.16 (0.05)	0.53

*$p < 0.001$ for change from baseline; values presented as LSM (SE)

Table 5: The geometric LSM of biosimilar denosumab (T) and reference denosumab (R) and its ratio (T/R) % obtained from the analysis of ln-transformed parameters

	Biosimilar denosumab (T) (n = 15)	*Reference denosumab (R) (n = 16)*	*T/R (%)*
Cmax (ng/mL)	5350.610	5642.280	94.83
$^{\&\$}$AUC0–120d (hr × ng/mL)	5356755.800	5316247.082	100.76
$^{@\$}$AUC0-∞ (hr × ng/mL)	7428544.114	6864530.624	108.22

$^{\$}N = 14$ for reference product (R), $^{\&}N = 10$ for test product (T), $^{@}N = 8$ for test product (T)

Table 6: Summary of treatment emergent adverse events by system organ class

System organ class preferred term	*Treatment A (n = 116)*	*Treatment B (n = 61)*	*Overall (n = 177)*
Gastrointestinal disorders			
Abdominal pain lower *n* (%) E	0 (0.0) 0	1 (1.6) 1	1 (0.6) 1
Diarrhea *n* (%) E	1 (0.9) 1	1 (1.6) 1	2 (1.1) 2
Gastritis *n* (%) E	3 (2.6) 4	1 (1.6) 2	4 (2.3) 6
Nausea *n* (%) E	2 (1.7) 2	0 (0.0) 0	2 (1.1) 2
Toothache *n* (%) E	0 (0.0) 0	1 (1.6) 1	1 (0.6) 1
General disorders and administration site conditions			
Pyrexia *n* (%) E	4 (3.4) 4	1 (1.6) 1	5 (2.8) 5
Infections and infestations			
Nasopharyngitis *n* (%) E	2 (1.7) 2	0 (0.0) 0	2 (1.1) 2
Upper respiratory tract infection *n* (%) E	6 (5.2) 8	1 (1.6) 2	7 (4.0) 10
Investigations			
Aspartate aminotransferase increased *n* (%) E	2 (1.7) 2	0 (0.0) 0	2 (1.1) 2
Blood creatinine increased *n* (%) E	3 (2.6) 3	0 (0.0) 0	3 (1.7) 3
Metabolism and nutrition disorders			
Dehydration *n* (%) E	0 (0.0) 0	2 (3.3) 2	2 (1.1) 2
Iron deficiency anemia *n* (%) E	3 (2.6) 3	1 (1.6) 1	4 (2.3) 4
Musculoskeletal and connective tissue disorders			
Arthralgia *n* (%) E	1 (0.9) 2	1 (1.6) 1	2 (1.1) 3
Back pain *n* (%) E	5 (4.3) 5	1 (1.6) 1	6 (3.4) 6
Compression fracture *n* (%) E	2 (1.7) 2	0 (0.0) 0	2 (1.1) 2
Myalgia *n* (%) E	3 (2.6) 3	0 (0.0) 0	3 (1.7) 3
Pain in extremity *n* (%) E	3 (2.6) 3	0 (0.0) 0	3 (1.7) 3
Trigger finger *n* (%) E	0 (0.0) 0	1 (1.6) 1	1 (0.6) 1
Nervous system disorders			
Headache *n* (%) E	1 (0.9) 1	2 (3.3) 2	3 (1.7) 3
Parkinson's disease *n* (%) E	0 (0.0) 0	1 (1.6) 1	1 (0.6) 1

improves bone mineral composition, bone mass, and structural integrity while decreasing bone resorption. Denosumab shows greater efficacy in enhancing BMD compared to alendronate, ibandronate, or risedronate. It is usually well tolerated, with most of the adverse effects being mild to moderate in nature. Subcutaneous denosumab [Prolia® (USA, Europe)] is approved in multiple countries for biannual use in managing postmenopausal women with a high likelihood of fractures and is also authorized for those who have not responded to or cannot tolerate other osteoporosis treatments.[7]

Placebo was initially demonstrated in a dose-ranging phase II trial of 4 years, including postmenopausal women with reduced BMD or osteoporosis. Administration of subcutaneous denosumab every 6 months led to significant improvements in BMD after both 12 months[8] and 48 months.[9,10] Among the dosages tested, 30 mg administered every 3 months and 60 mg given every 6 months showed the most pronounced biological effects with minimal exposure.[8]

The phase III FREEDOM trial was a significant international study involving 7,868

postmenopausal women with osteoporosis. It investigated the impact of denosumab on reducing fracture risk over a period of >36 months. Participants were randomly assigned to administer either inj. denosumab 60 mg subcutaneously or a placebo every 6 months for a duration of 36 months. Denosumab was found to significantly reduce the occurrence of new vertebral fractures, showing a decline of 68% ($p < 0.001$) compared to placebo. Furthermore, participants treated with denosumab showed a relative gain in BMD of 3.9 and 5.5% at the lumbar spine compared to baseline after 6 and 12 months, respectively, compared to those on placebo.[6] This study demonstrated a comparable or greater gain in BMD at the lumbar spine (7.25%) at 6 and 12 months with biosimilar denosumab, relative to the results observed in the FREEDOM study.

In this phase III, prospective, randomized, double-blind, active-controlled, multicentric study, we evaluated the efficacy and safety of biosimilar denosumab (Enzene Biosciences LTD) compared to reference denosumab (Prolia®; Amgen Inc.) in osteoporotic postmenopausal women. Consistent with the FREEDOM trial findings, our study demonstrated a statistically significant enhancement in the percentage change from baseline to months 6 and 12 in BMD at both the lumbar spine and femoral neck for each treatment group. A statistically insignificant difference was found in the LSM percentage change in BMD at these sites across the two treatment groups. The BMD results demonstrated noninferiority of biosimilar denosumab compared to reference denosumab for both the femoral neck and lumbar spine, as the lower limit of the confidence interval was above –15%.

The SAEs experienced following the administration of biosimilar denosumab were unlikely related to the study drug. In hematological and biochemical parameter changes, no statistical difference was noted from baseline to 12 months. Based on the safety analysis, it was demonstrated that adverse events observed with biosimilar denosumab were similar to those observed with reference denosumab as well as those reported in the Prolia® Summary of Product Characteristics (SMPC).[11]

There was no statistically significant difference noted in ln-transformed primary pharmacokinetic parameters Cmax, AUC0-120d, and AUC0-∞. Hence, it can be concluded that biosimilar denosumab does not have a significant pharmacokinetic difference when compared with reference denosumab. By the end of the study, no patients tested positive for treatment-emergent antidenosumab antibodies.

A biosimilar is a biologic medication that is similar to an FDA-approved biologic medication, known as the reference product. It is clinically equivalent to the reference product in terms of safety and efficacy. Biosimilars lower drug prices, thus improving patient adherence. Experts and doctors believe that the usage of biosimilar drugs can reduce the cost of biologics, thereby enhancing patient access to these life-saving medications.

Conclusion

The authors report similar results on BMD at 6 months and 1 year in this first comparative study between a biosimilar and denosumab. Therefore, biosimilar denosumab is expected to improve the quality of life for patients with osteoporosis while being cost effective.

The clinical trial was conducted in strict compliance with ethical standards.

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