

A randomized placebo-controlled trial of the efficacy of denosumab in Indian postmenopausal women with osteoporosis

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ABSTRACT

Introduction: Osteoporosis is a serious condition affecting up to 50% of Indian postmenopausal women. Denosumab reduces bone resorption by targeting the receptor activator of nuclear factor- κ B ligand. This study assessed the efficacy and safety of denosumab in Indian postmenopausal women with osteoporosis. **Materials and Methods:** In this double-blind, multicenter, phase 3 study, 250 Indian postmenopausal women aged 55 to 75 years (T-score <-2.5 and >-4.0 at the lumbar spine or total hip; serum 25(OH) D levels ≥ 20 ng/mL) were randomized to receive one subcutaneous dose of denosumab 60 mg or placebo. All subjects received oral calcium ≥ 1000 mg and vitamin D₃ ≥ 400 IU daily. The primary end point was mean percent change in bone mineral density (BMD) at the lumbar spine from baseline to Month 6. Secondary end points included mean percent change from baseline in BMD at total hip, femoral neck, and trochanter at Month 6 and median percent change from baseline in bone turnover markers at Months 1, 3, and 6. **Results:** Total 225 subjects (denosumab = 111, placebo = 114) completed the six-month study. Baseline demographics were similar between groups. A 3.1% (95% confidence interval, 1.9%, 4.2%) increase favoring denosumab versus placebo was seen for the primary end point ($P < 0.0001$). Denosumab demonstrated a significant treatment benefit over placebo for the secondary end points. There were no fractures or withdrawals due to adverse events. **Conclusions:** Consistent with results from studies conducted in other parts of the world, denosumab was well tolerated and effective in increasing BMD and decreasing bone turnover markers over a six-month period in Indian postmenopausal women.

Key words: Bone mineral density, bone turnover markers, denosumab, India, osteoporosis, postmenopausal

INTRODUCTION

Denosumab is a fully human monoclonal antibody that prevents receptor activator of nuclear factor- κ B

ligand (RANKL) from binding to its receptor.^[1] By this mechanism, denosumab reduces bone resorption and increases bone mineral density (BMD). Rates of decreased BMD in Indian women range from 20% to 50% depending on the geographic region within India.^[2-4] Because osteoporosis is a major health issue in India, this study (ClinicalTrials.gov identifier: NCT01495000; study number: DPH 114161) was designed to compare the efficacy and safety of a single dose of denosumab 60 mg versus placebo in Indian postmenopausal women with osteoporosis.

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MATERIALS AND METHODS

This was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, single-dose study conducted at 11 centers in India from January 2012 to February 2013.

Study population

Postmenopausal women aged 55 to 75 years of Indian origin with an absolute BMD value consistent with a T-score < -2.5 and > -4.0 at either the lumbar spine or total hip were eligible for the study. Exclusion criteria included bone metabolic diseases other than osteoporosis, current hyperparathyroidism or hypoparathyroidism, rheumatoid arthritis, malabsorption syndrome, or prior treatment with drugs that alter bone metabolism. Vitamin D deficiency also precluded entry into the study; subjects with vitamin D deficiency (defined as $25(\text{OH})\text{D} < 20$ ng/mL in this study) could be repleted and rescreened prior to study entry. Medications known or suspected to have activity on bone metabolism (other than calcium and vitamin D_3), such as bisphosphonates, parathyroid hormone, systemic hormone replacement therapy, calcitriol, or calcitonin were prohibited during the study. Other concomitant treatment could be prescribed if deemed necessary by the investigator to provide adequate supportive care. Subjects could withdraw from the study at any time, either by decision of the subject or at the discretion of the investigator, and withdrawn subjects were not replaced.

Study design

After a screening phase of up to 2.5 months, subjects were randomized to receive a single subcutaneous dose of either denosumab 60 mg (Amgen, Thousand Oaks, CA) or matching placebo and assessed for six months. Subjects received study treatment at baseline, and follow-up visits were scheduled at Months 1, 3, and 6 [Figure 1]. All subjects received daily oral calcium ≥ 1000 mg and vitamin $\text{D}_3 \geq 400$ international units (IU) supplementation throughout the study.

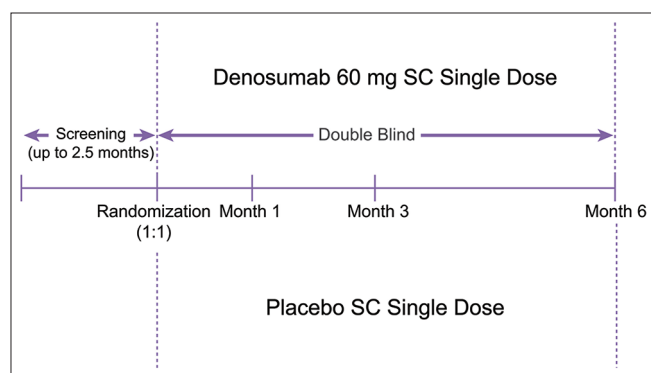


Figure 1: Study design. SC: subcutaneous

At screening, BMD and T-scores at the lumbar spine, hip, femoral neck, and trochanter and bone turnover marker levels were recorded. Fracture probabilities at baseline were computed using FRAX, a computer-based algorithm designed to estimate 10-year fracture probability (hip, clinical spine, humerus, or wrist fracture) based on clinical risk factors (body mass index [BMI], prior history of fracture, parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking, and alcohol intake [≥ 3 units]) alone or in combination with BMD.^[5] The FRAX model used in this study was calibrated for India (version 3.7) and included baseline BMD.

Changes in BMD and bone turnover markers over the course of six months were assessed. Dual energy X-ray absorptiometry (DXA) scans were performed using Hologic and GE Lunar DXA scanners to determine T-scores and BMD equivalents. Measurements for an individual subject were all performed using the same scanner. To maintain blinding, the DXA scan was recorded at investigational sites and analyzed at a central reading facility (Synarc Inc., Portland, OR), with the exception of the screening DXA scans, which were analyzed locally to determine subject eligibility. Levels of serum C-terminal telopeptide of type I collagen (s-CTX) and serum procollagen type I N propeptide (s-PINP) were measured from blood samples collected from fasted subjects. Subjects, investigators, and the sponsor were also blinded to the results of BMD, bone turnover markers, and other laboratory analyses throughout the duration of the study.

The study protocol, protocol amendments, and informed consent were approved by ethics committees and institutional review boards, in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and country-specific requirements. The study was conducted according to GCP guidelines from the Central Drugs Standard Control Organization, Ministry of Health, Government of India, and ICH GCP, as well as the Declaration of Helsinki 2008. Each subject provided written informed consent prior to participation in the study.

Study end points

The primary end point was the mean percent change in BMD at the lumbar spine from baseline to Month 6. Secondary end points included the mean percent change in BMD at total hip, femoral neck, and trochanter from baseline to Month 6 and median percent change in bone turnover markers from baseline to Months 1, 3, and 6.

Safety end points consisted of adverse events (AEs), including serious AEs (SAEs), AE withdrawals, AEs of special interest, vital signs, laboratory tests, and the incidence of anti-denosumab antibody formation. The serum of subjects was screened for anti-denosumab binding antibody using an electrochemiluminescent (ECL) bridging immunoassay. AEs of special interest included hypocalcemia, hypersensitivity, skin infection, new primary malignancy, delayed fracture healing, serious infection, osteonecrosis of the jaw (ONJ), and atypical femoral fracture (AFF). Potential events of ONJ and AFF were adjudicated by respective committees of experts who were blinded to treatment group assignment. Safety laboratory tests consisted of a complete blood count and chemistry panel including albumin-adjusted serum calcium and liver function tests.

Statistical analysis

The primary efficacy analysis for BMD used an analysis of covariance (ANCOVA) model adjusting for treatment and baseline BMD (as a continuous covariate), with the significance level set at 0.05. For subjects who withdrew after one month in the study, last observation carried forward was used for BMD analyses. Geographic region and region-by-treatment interaction were investigated but were not included in the final statistical model because of nonsignificance of region-by-treatment interaction ($P = 0.95$) at the 0.10 level. The analysis of the secondary efficacy end points of BMD used an ANCOVA model similar to the primary efficacy analysis. For the bone turnover markers at Months 1, 3, and 6, two-sided Wilcoxon rank sum tests with Hodges-Lehman estimates and 95%

confidence intervals (CIs) were used to compare percent changes between the two treatment groups.

For safety, continuous measures (laboratory evaluations, vital sign changes) were summarized by treatment group using descriptive statistics. Discrete measures (AEs and withdrawal rates) were summarized by the number and percentage of subjects by treatment group.

Exploratory analyses were performed for the primary efficacy end point (BMD at lumbar spine at Month 6) for subgroups based on baseline demographics. The study population was subsequently divided into subgroups by age (<65, ≥65 years), baseline BMI category (tertiles), baseline s-CTX (tertiles), machine type (Hologic, GE Lunar), 10-year probability of hip fracture (<3%, ≥3%), 10-year probability of major osteoporotic fracture (<20%, ≥20%), geographic region (North, West, Central, South), and previous use of osteoporotic medication (Yes, No). Least square estimates and 95% CIs for the treatment differences for each subgroup category were obtained via an ANCOVA model adjusting for baseline BMD, treatment, subgroup, and treatment by subgroup interaction.

RESULTS

Subject disposition and demographics

Total 551 subjects were screened, and 250 subjects were randomized and entered the study (denosumab = 124, placebo = 126) [Figure 2]. The intent-to-treat (ITT) population included the 250 subjects who received one dose of the study drug. Demography and safety were

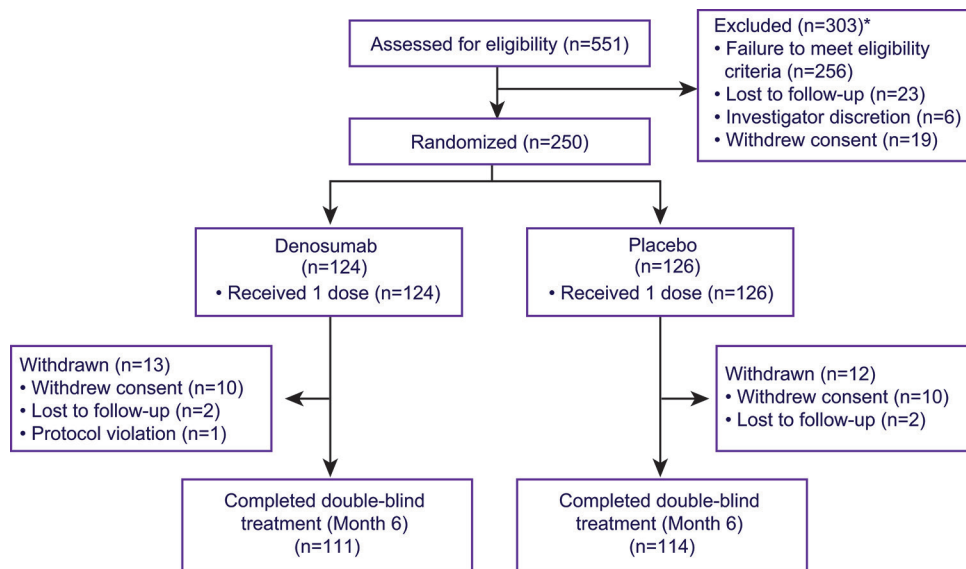


Figure 2: Subject disposition *Some subjects had more than one reason for failing screening. Two subjects were considered by the investigator to be screening failures (did not meet inclusion/exclusion criteria regarding BMD T-score). However, these subjects were randomized, received study medication, had efficacy measurements, and completed the study. BMD: bone mineral density

summarized based on the ITT population. Total 111 denosumab-treated and 114 placebo-treated subjects, respectively, completed the double-blind treatment, and 13 and 12 subjects, respectively, withdrew during the study [Figure 2]. The most common reason was withdrawal of consent to participate further in the study.

Baseline demographics were mostly similar between the treatment groups [Table 1]. Baseline T-scores and bone turnover marker levels were also comparable between treatment groups [Table 2]. The treatment groups were balanced with respect to the proportion of subjects with co-morbidities: 27% in denosumab group and 25% in placebo group with diabetes, 41% in denosumab group and 44% in placebo group with hypertension, and 2% with family history of cardiovascular disease in both groups. The 10-year fracture risk at baseline as determined by FRAX was also similar between groups [Table 2].

History of bone fracture was noted in 13 (10%) subjects in the denosumab group and six (5%) in the placebo group [Table 1]. Wrist fracture was the most common type (5 [4%] of denosumab-treated subjects and three [2%] of placebo-treated subjects). One subject from each group had a history of osteoporosis on the mother's side. Risk of fall was assessed at screening: 18 (15%) denosumab-treated and 21 (14%) placebo-treated subjects had poor vision, three (2%) denosumab-treated and six (5%) placebo-treated subjects had difficulty in walking, and zero (0%) denosumab-treated and one (<1%) placebo-treated subject had difficulty in balancing [Table 1].

Efficacy

The ITT efficacy (ITTE) population included those in the ITT population who had a baseline measure and at least one post-baseline efficacy measure during the double-blind treatment. For the primary end point, a 3.1% (95% CI, 1.9%, 4.2%) treatment difference in percent change in lumbar spine BMD from baseline at Month 6 was seen in the denosumab group compared with the placebo group ($P < 0.0001$) [Figure 3]. Denosumab demonstrated consistent treatment differences compared with placebo for the secondary end points. For total hip, femoral neck, and trochanter BMD, there was a 1.7% (95% CI, 0.9%, 2.5%; $P < 0.0001$), 2.3% (95% CI, 1.1%, 3.4%; $P = 0.0001$), and 1.8% (95% CI, 0.8%, 2.8%; $P = 0.0006$) mean difference from placebo, respectively [Figure 4]. Reductions in s-CTX and s-PINP (median treatment differences: -57.7% [95% CI, -65.2%, -50.4%, $P < 0.0001$] and -22.4% [95% CI, -28.1%, -17.1%, $P < 0.0001$], respectively) were seen within one month after denosumab administration [Figure 4]. At Month 6, median treatment differences for denosumab compared with placebo

Table 1: Baseline demographics (ITT population)

Characteristic	Denosumab (N=124)	Placebo (N=126)
Age, years, mean (SD)	62.6 (5.10)	62.6 (4.85)
Age range, n (%)		
<65 years	80 (65)	85 (67)
≥65 years	44 (35)	41 (33)
BMI, kg/m ² , mean (SD)	25.3 (4.36)	25.3 (4.46)
Years since menopause*, mean (SD)	14.8 (5.53)	14.9 (4.70)
History of fracture, n (%)		
Wrist fracture	5 (4)	3 (2)
Non-osteoporotic bone disease history, n (%)	0 (0)	0 (0)
Risk of fall, n (%)		
Poor vision	18 (15)	21 (17)
Walking difficulty	3 (2)	6 (5)
Balance difficulty	0 (0)	1 (<1)
Family history of osteoporosis, n (%)		
Mother's side	1 (<1)	1 (<1)
Father's side	0 (0)	0 (0)
Family history of hip fracture, n (%)		
Mother's side	0 (0)	0 (0)
Father's side	0 (0)	0 (0)

*Six subjects in each group aged <35 years at time of menopause were excluded. BMI: Body mass index, ITT: Intent-to-treat, SD: Standard deviation

Table 2: Summary of fracture risk (ITT population)

Characteristic	Denosumab (N=124)	Placebo (N=126)
Corrected T-score, mean (SD)		
Femoral neck	-2.5 (0.67)	-2.4 (0.76)
Total hip	-2.1 (0.78)	-2.0 (0.95)
Total spine	-3.2 (0.57)	-3.2 (0.62)
Trochanter	-2.2 (0.78)	-2.2 (0.88)
Bone turnover markers, mean (SD)		
s-CTX (pg/mL)	0.66 (0.426)	0.75 (0.472)
s-PINP (µg/L)	67.7 (33.02)	78.8 (64.31)
10-year probability (%) of hip fracture, mean (SD)*		
Measured by Hologic machine [†]	2.65 (2.354)	3.10 (3.094)
Measured by Lunar machine [‡]	3.22 (2.560)	2.82 (2.609)
10-year probability (%) of osteoporotic fracture, mean (SD)*		
Measured by Hologic machine [†]	7.11 (3.850)	7.84 (4.940)
Measured by Lunar machine [‡]	8.07 (4.348)	7.05 (4.006)

*Fracture probability was calculated using screening BMD measurements. [†]n=29 for the denosumab group, n=31 for the placebo group. [‡]n=83 for the denosumab group, n=84 for the placebo group. BMD: Bone mineral density, ITT: Intent-to-treat, s-CTX: Serum C-terminal telopeptide of type I collagen, SD: Standard deviation, s-PINP: Serum procollagen type I N propeptide

were -33.4% (95% CI, -40.8%, -26.0%; $P < 0.0001$) for s-CTX and -37.6% (95% CI, -44.2%, -31.2%; $P < 0.0001$) for s-PINP [Figure 4].

In the exploratory subgroup analyses of lumbar spine BMD, all point estimates indicated a benefit with denosumab with the entirety of the 95% CIs falling to the right of zero with the exceptions of the lowest baseline s-CTX tertile subgroup (0.084, 0.409) and the North and West regional subgroups [Figure 5].

Safety

Thirty-eight (31%) subjects in the denosumab group and 47 (37%) in the placebo group experienced AEs. No subject withdrew due to AEs, and there were no unanticipated AEs or AEs of special interest such as AFFs or ONJ events in the study. No unexpected laboratory or vital sign changes were observed, and no cases of binding anti-denosumab antibodies in any subjects were noted after six months.

The most common AE in the denosumab group was upper respiratory tract infection (eight subjects [6%]), and the most common AEs in the placebo group were asthenia, pyrexia, and hypertension (each in five subjects [4%]). In the denosumab group, two reports of arthralgia, and one report of back pain, mouth ulceration, and dizziness were

considered treatment-related by the investigator. In the placebo group, one report of arthralgia, gastroenteritis, liver abscess, skin candida, upper respiratory tract infection, eosinophilia, increased hepatic enzymes, asthma, dermatitis, and hypertension were deemed treatment-related. In both the groups, most AEs were mild or moderate. Six nonfatal SAEs were reported in four subjects. Cataract (nuclear; moderate in severity) occurred in one (<1%) denosumab-treated subject and was not deemed treatment-related. In the placebo group, SAEs occurred in three (2%) subjects. These SAEs included liver abscess and varicose vein rupture. One subject had three SAEs, including increased hepatic enzymes, asthenia, and hypotension. The only SAEs considered to be potentially related to the study medication were liver abscess and increased hepatic enzymes, which occurred in subjects receiving placebo. All SAEs resolved without complications.

DISCUSSION

This paper presents the first study on the effects of denosumab in Indian women with osteoporosis. Denosumab showed a benefit over placebo in increasing BMD at the lumbar spine, as well as at the total hip, femoral neck, and trochanter and decreasing bone turnover markers, s-CTX and s-PINP.

The high prevalence of osteoporosis or osteopenia in India, estimated at 50 million in 2013,^[6] may be the result of low dietary intake of calcium, calories, protein, lack of

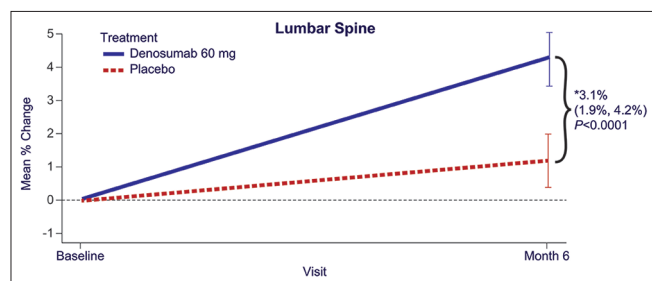


Figure 3: Primary end point: Mean percent change from baseline in BMD in lumbar spine (ITTE population) *Mean treatment difference (95% confidence interval [CI]) and P-value at six months based on ANCOVA. Error bars are 95% CIs from the model % change = treatment + baseline BMD. Denosumab group: n = 100; placebo group: n = 105. ANCOVA: Analysis of covariance; BMD: bone mineral density; ITTE: intent-to-treat efficacy

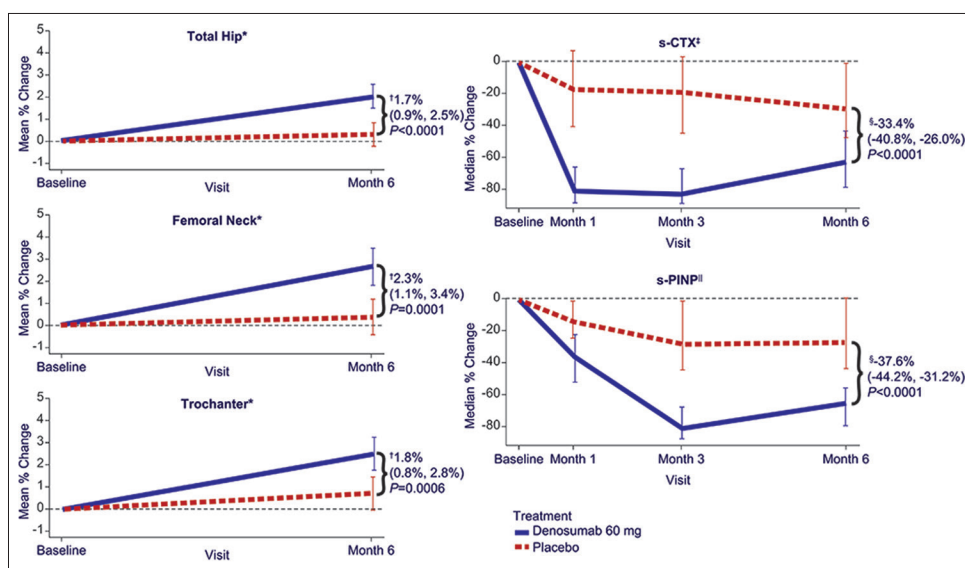


Figure 4: Secondary end points: Mean/median percent change from baseline in BMD in total hip, femoral neck, and trochanter and bone turnover markers (ITTE population) * Error bars are 95% confidence intervals (CIs) from the model % change = treatment + baseline BMD. Denosumab group: n = 87; placebo group: n = 86 † Mean treatment difference (95% CI) and P-value at six months based on ANCOVA. ‡ Error bars are (Q1, Q3). At Month 6, denosumab group: n = 105; placebo group: n = 113. § Median treatment difference (95% CI) and P-value at six months based on Hodges-Lehmann Estimate and Wilcoxon rank-sum test. ||Error bars are (Q1, Q3). At Month 6, denosumab group: n = 104; placebo group: n = 113. ANCOVA = Analysis of covariance; BMD: bone mineral density; ITTE: intent-to-treat efficacy; s-CTX: serum C-terminal telopeptide of type I collagen; s-PINP: serum procollagen type I N propeptide

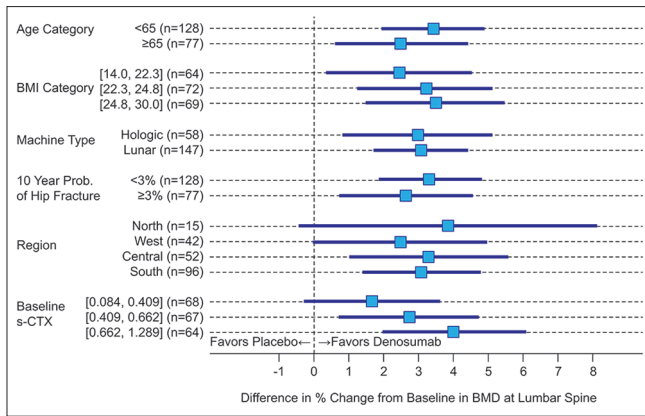


Figure 5: Percent change from baseline in lumbar spine BMD at Month 6 in exploratory subgroup analyses* (ITTE population) * Excludes biologically implausible data from one subject. BMD: bone mineral density; BMI: body mass index; ITTE: intent-to-treat efficacy; s-CTX: serum C-terminal telopeptide of type I collagen

exercise,^[2,7] and vitamin D insufficiency (defined in the study as serum 25-hydroxyvitamin D [25(OH)D] levels 10-20 ng/mL) and deficiency (levels <10 ng/mL).^[8] In Jammu (N = 158), 20% of women aged 25 to 65 years had osteoporosis (T-score <-2.5) and 37% had osteopenia (T-score ≤-1 and ≥-2.5), both of which were found to increase in incidence with age and menopause.^[4] Of 538 women of all ages attending medical camps in north Kerala, 44% had osteoporosis and 41% had osteopenia.^[3] In both Jammu and north Kerala, almost all women older than age 65 years had either osteoporosis or osteopenia.^[3,4] In a study of 200 peri- and postmenopausal women from Chandigarh, low BMD (osteopenia or osteoporosis) was found in 53% of the participants.^[2]

The severity of this condition is emphasized by the large number (440,000) of hip fractures experienced by the Indian population annually; 75% of these fractures occur in women.^[9] In the Rohtak district of northern India, the annual incidences of hip fractures in women and men aged 50 years or older were 159 and 105 per 100,000, respectively, in 2009.^[10]

Despite the study not being powered to conduct subgroup analyses, results of the exploratory analyses were consistent with the primary analysis. Denosumab demonstrated a positive treatment benefit over placebo on lumbar spine BMD at Month 6 in all subgroups. Although concerns may exist about decreased bone resorption resulting in AFF and ONJ, none of these events were reported during this short-term study. There were no fractures, fatalities, or occurrences of unanticipated AEs during this six-month period in either treatment arm. There were no AEs of hypocalcemia or shifts of clinical significance in laboratory values in serum

levels of calcium, phosphorous, or alkaline phosphatase reported in the study population; all subjects were instructed to take calcium and vitamin D throughout the study.

The present study was designed based on the pivotal multinational Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study (ClinicalTrials.gov identifier: NCT01457950; study number: 20030216),^[11] which first assessed the efficacy and safety of denosumab. In the FREEDOM study, subjects were enrolled from Europe, North America, and Australia and were predominantly of European ancestry. Subjects were randomized to receive subcutaneous denosumab 60 mg or placebo every six months for 36 months. A few differences in study methods between the FREEDOM and Indian study should be noted, including variations in the inclusion/exclusion criteria, vitamin D entry criteria (discussed below), and study end points. Although both study populations consisted of postmenopausal women with osteoporosis, there was a slight difference in the age range of the inclusion criteria: 55 to 75 years in the Indian study versus 60 to 90 years in the FREEDOM study. The multinational study evaluated the effect of denosumab on reducing fracture risk, with new vertebral fractures as the primary end point, whereas the current study in the Indian population was not designed to evaluate fractures and had a primary end point of mean percent change in lumbar spine BMD from baseline to Month 6. Both studies measured BMD by DXA and bone turnover markers, but in the FREEDOM study, measurements were taken at more long-term time points (up to 36 months). The safety and clinical data from the current study are limited to six months of treatment. A few differences in the study population and design were also seen, including sample size, mean BMI, and placebo response. As expected, the average BMI in the Indian population (25.3 kg/m²) was slightly lower than the BMI of the multinational population (26.0 kg/m²). A greater placebo response was observed in the Indian study, which could be attributed to the calcium and vitamin D supplementation in a population with diets normally absent of foods rich or fortified with calcium and vitamin D.^[12] Despite the aforementioned differences, denosumab demonstrated a similar effect on BMD overall in both the Indian and multinational populations.

Because of the differences in osteoporosis management guidelines at the time of study design,^[13] the minimum vitamin D entry criteria in the Indian study (20 ng/mL) was higher than in the FREEDOM study (12 ng/mL). A relatively high proportion of subjects in the Indian study underwent vitamin D repletion prior to study

entry, possibly because of the higher vitamin D threshold requirement, which may explain the small increase in lumbar spine BMD in the placebo group. Of the 250 randomized subjects in the current study, 35% had vitamin D deficiency at screening and required repletion (34% and 37% in the denosumab and placebo groups, respectively). Data on vitamin D repletion were not recorded in the FREEDOM study. The prevalence of low vitamin D levels in the Indian study corresponds with previous reports that have shown that vitamin D deficiency is a health issue in the Indian postmenopausal population.^[8,12]

Limitations of the study include the small sample size and short duration as mentioned previously. This study was conducted with a placebo control rather than an active comparator, therefore, data are limited on the use of denosumab compared with other available therapies for postmenopausal osteoporosis in this population.

Consistent with the results of the pivotal multinational study, denosumab compared with placebo was effective in increasing BMD at the lumbar spine, total hip, femoral neck, and trochanter and decreasing bone turnover markers in Indian postmenopausal women with osteoporosis. The observed safety profile was consistent with the known adverse-effect profile of denosumab. Denosumab can be an option for the treatment of postmenopausal osteoporosis in the Indian population.

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