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Pharmacodynamic and efficacy of the denosumab patient compared to the reference product Prolia in postmenopausal osteoporosis women.

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Abstract : A substantial proportion of the population of females in India falls in the perimenopausal and postmenopausal age groups. One of the complications associated with older age in women is the weakening of bones and the fall in bone mineral density (BMD). This has a severe debilitating consequence in a woman's life and leads to reduced quality of life along with a greater incidence of fractures. If the fracture involves the hip or the vertebrae, it can cause immobility and be devastating. Postmenopausal osteoporosis is linked with the deficiency of estrogen that occurs with the cessation of the function of the ovaries as age progresses. The function of estrogen in the bone remodeling process is very well understood after years of research; estrogen plays a part in both the formation of bone as well as the prevention of the resorption of bone. A diagnosis can be made by dual-energy X-ray absorptiometry (DEXA). It is the gold standard and can spot low bone density at particular sites. The treatment options are selected according to the severity and rate of progression and factors pertaining to each patient. All postmenopausal women should be made aware of this disorder, and they should be encouraged to cultivate a healthy lifestyle through the implementation of a proper diet and inculcation of a regular exercise routine. Smoking and drinking alcohol should be limited, and calcium and vitamin D supplementation should be started in all women of the postmenopausal age group with or without osteoporosis. In patients who have been diagnosed with the disorder, pharmacological intervention is done. Drugs should be selected based on their side effects and contradictions. Follow-up is essential, and patient compliance should be carefully monitored. This article attempts to review the existing literature on this very prevalent disorder to spread awareness about it so that all postmenopausal women can take the necessary steps to prevent the weakening of their bones, and deal with its progression.

Keywords: fractures, estrogen, bone remodeling process, dual-energy x-ray absorptiometry, bone formation, postmenopausal osteoporosis, bone mineral density.

Results: Total 25 subjects (denosumab = 14, prolia = 11) completed the six-month study. Baseline demographics were similar between groups. A 3.1% (95% confidence interval, 1.8%, 4.4%) increase favoring denosumab versus prolia was seen for the primary end point ($P < 0.0001$). Denosumab demonstrated a significant treatment benefit over prolia 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.

I. INTRODUCTION

INTRODUCTION

The World Health Organisation (WHO) defines menopause as the complete cessation of menstruation in a woman for one year or more [1]. Perimenopause is irregular menstruation before menopause. Its duration is variable. The average age of Indian women is 46.2 years at menopause [2]. According to the sample registration system statistical report of 2018, 27.7% of the total female population of India falls in the age group of 40 years and above [3]. Given the large population size of older women and the fact that the risk of bone loss and weakening is substantially associated with age as well as menopausal age and its duration, there is a need to understand this disorder and learn about its diagnosis and management. This study aims to review the current literature on this widespread disorder that plagues up to 62% of postmenopausal women [4]. To understand this disorder, we have first attempted

to comprehend the components of the human bone. The human skeleton provides a framework for the body. It is composed of a collection of bones secured together by tendons, ligaments, muscles, and cartilage. The bones, which house and protect tissues and organs of the body, are embedded with calcium phosphate crystals and collagen fibers [5]. Bones are composed of a compact component called the cortical bone and a spongy or cancellous compartment, which is known as the trabecular bone and which holds the red marrow. An estimated 80% of the mass of the bone consists of compact bone, and the spongy bone comprises the remaining 20% [6]. The overall strength of a bone is contributed by both the compact and spongy bone [5]. The cortical bone is a network of osteons: dense lamellar units arranged in parallel, concentric circles. A system of Volkmann's canals and Haversian canals connect these osteons and are responsible for nurturing them. The boundary between the osteon and the surrounding extraosteonal bony matrix is marked by a microscopic structure known as the "cement line" [6-9]. It imparts mechanical strength to the bone [10]. The cortical bone is sandwiched between an outer connective tissue envelope known as the "periosteum" and an inner membrane known as the "endosteum" [6]. The cortical bone is protective and performs mechanical functions [11]. The trabecular bone is a porous, spongy structure that is highly heterogeneous and has varying degrees of anisotropy. It has a higher content of water compared to the cortical bone and a lower percentage of calcium. It contains no blood vessels and is supplied by the surrounding bone marrow. The trabeculated bone tissue stores calcium phosphate crystals, and its primary functions include the transfer of mechanical load from the surface of articulation to the cortex and shock absorption on account of its hydraulic properties [5,6,8,12]. The trabecular bone provides strength and is associated with most metabolic functions [11].
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NEED OF THE STUDY.

Our study, called Fracture Reduction Evaluation of Denosumab in Osteoporosis 6 Months (FREEDOM), was an international, randomized, placebo-controlled trial. Subjects were randomly assigned to receive subcutaneous injections of either 60 mg of denosumab or placebo at study sites 6 months. Randomization was stratified according to 5-year age groups.
Women between the ages of 60 and 90 years with a bone mineral density T score of less than −2.5 at the lumbar spine or total hip were eligible for inclusion. Women were excluded if they had conditions that influence bone metabolism or had taken oral bisphosphonates for more than 3 years. If they had taken bisphosphonates for less than 3 years, they were eligible after 12 months without treatment. Women were also excluded if they had used intravenous bisphosphonates, fluoride, or strontium for osteoporosis within the past 5 years; or parathyroid hormone or its derivatives, corticosteroids, systemic hormone-replacement therapy, selective estrogen-receptor modulators, or tibolone, calcitonin, or calcitriol within 6 weeks before study enrollment.

RESEARCH METHODOLOGY

- Must be signed before first study-related activity.
- Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Appendix Error! Reference source not found., Regulatory, Ethical, and Study Oversight Considerations.
- Recheck eligibility criteria as applicable at baseline.
- Medical history includes substance usage, smoking status, alcohol consumption, past history of fracture, history of hip fracture in parents.
- Data for patients must be frozen before initiating the transition-extension period randomization so to ensure blinding for initial 6-month study is not affected. Considering that all data entry needs to be completed before randomization for transition-extension period, patient can be randomized in the transition-extension period for up to 21 days after completion of EOS visit of period of the initial 6 months study.
- Periodontal examination to rule out risk factors for ONJ at screening and as clinically required during
- study including switching period as applicable.
- Pre-dose vitals: Within 1 hour prior to each dosing in clinical facility
- Chest X-ray (PA view), if not done in last 3 months.
- DXA scan performed in the past will not be considered during screening for eligibility assessment. Bone mineral density will be measured using DXA scan will be performed exclusively for screening and eligibility criteria assessment at the lumbar spine, total hip during screening period. Screening DXA will be used as baseline DXA.
- Additional lateral spine X-rays may be taken in cases of a suspected clinical vertebral fracture.

Study Design- Randomized, Active-Controlled Study Comparing ,Pharmacodynamics, efficacy of Denosuma

Figure 1 - Study design. SC: subcutaneous

Study Subject

The study was conducted at bedded tertiary care hospital equipped with modern diagnostic and treatment facilities. Patients visiting this hospital come from different geographical regions.

Study Duration.

Total 180 days (approximately 6 Months) (for patients who have been part of Pd assessment and have been randomized in Reference group and identified for single transition treatment).

Sampling

Study was carried out on approximately 14 denosumab patients with osteoarthritis and 11 prolia patient in each treatment group. Total patient will be 25.

Sample Size Calculation When comparing two means in a study the formula is as follows:

Calculate the sample size for infinite population

$S = (z)^2 p (1 – p) / m^2$

$S= (1.44)^2 0.5(1-0.5) / (0.15)^2$

S= 1.44*1.44*0.5*0.5/0.0225

S= 0.5184/0.0225

S= 25

S= sample size for infinite population

Z= z score is determined based on confidence level

P= population proportion (assumed to be 50% = 0.5)

M= marginal of error

3.4 Statistical tools and econometric models

The primary efficacy analysis for BMD used an analysis of covariance (ANOVA) 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 ANOVA model similar to the primary efficacy analysis. For the bone turnover markers at Months 1, 3, and 6, two-sided 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 ANOVA model adjusting for baseline BMD, treatment, subgroup, and treatment by subgroup interaction.

IV. RESULTS AND DISCUSSION

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Subject disposition and demographics

Total 51 subjects were screened, and 25 subjects were randomized and entered the study (denosumab = 14, prolia = 11) [Figure 2]. The intent-to-treat population included the 25 subjects who received one dose of the study drug. Demography and safety were summarized based on the population. Total 14 denosumab-treated and 11 prolia-treated subjects, respectively, completed, and 13 and 12 subjects, respectively, withdrew during the study .The most common reason was withdrawal of consent to participate further in the study.

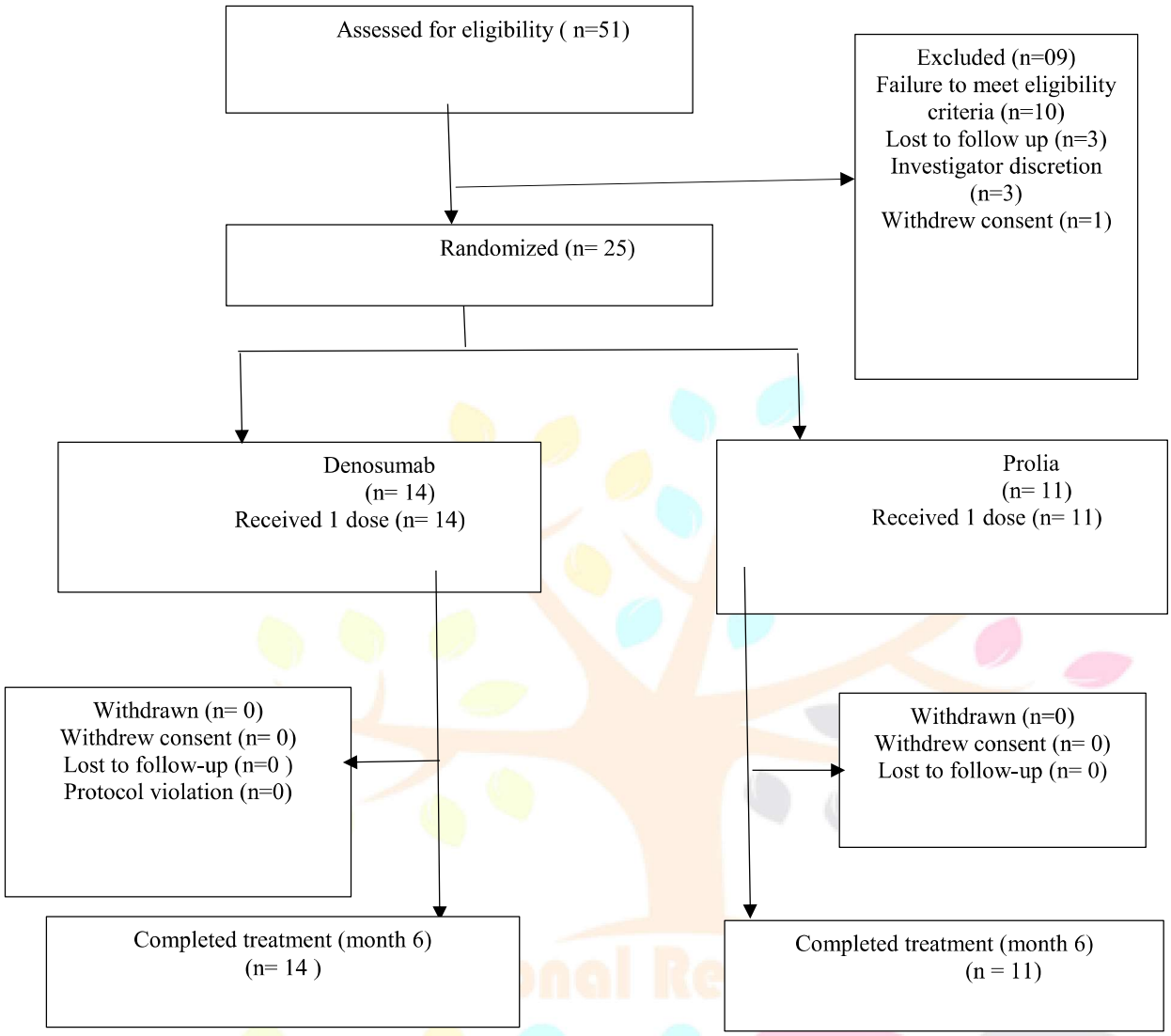

Figure 2- Subject disposition Some subjects had more than one reason for failing screening. Two subjects were considered by the investigator to be screening failures (did not meet inclusion/exclusion criteria regarding BMD T-score). However, these subjects were randomized, received study medication,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

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.

Baseline demographics were mostly similar between the treatment groups . Baseline T-scores and bone turnover marker levels were also comparable between treatment groups . The treatment groups were balanced with respect to the proportion of subjects with co-morbidities: 27% in denosumab group and 25% in prolia group with diabetes, 41% in denosumab group and 44% in prolia 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-1 Baseline demographics

Characteristic	Denosumab (N= 14)	Prolia (N= 11)
Age, years, mean	62.6	62.6
Age range,n (%)		
<65 years	8	5
>65 years	6	5
BMI, Kg/m^2 ,mean	25.3	25.3
Years since menopause*	14.8	14.9
History of fracture, n (%)	7	6
Wrist fracture	5	3
Non- osteoporotic bone disease	0	0
History, n (%)		
Risk of fall, n (%)		
Poor vision	8	5
Walking difficulty	3	6
Balance difficulty	0	1
Family history of osteoporosis, n (%)		
Mothers side	1	1
Fathers side	0	0
Family history of hip fracture, n (%)		
Mothers side	0	0
Fathers side	0	0

TABLE-2 Summary of fracture risk

Characteristic	Denosumab (N= 14)	Prolia (N= 11)
Corrected T-score, mean		
Femoral neck	-2.5	-2.4
Total hip	- 2.1	- 2.4
Total spine	- 3.2	- 3.2
Trochanter	- 2.2	- 2.2
Bone turnover markers,		
s- CTX (pg/mL)	0.66	0.75
s- PINP (µg/L)	67.7	78.8
10-year probability (%) of hip fracture		
Measured by Hologic machine	2.65	3.10
Measured by Lunar machine	3.22	2.82
10-year probability (%) of osteoporotic fracture		
Measured by Hologic machine	7.11	7.84
Measured by Lunar machine	8.07	7.05

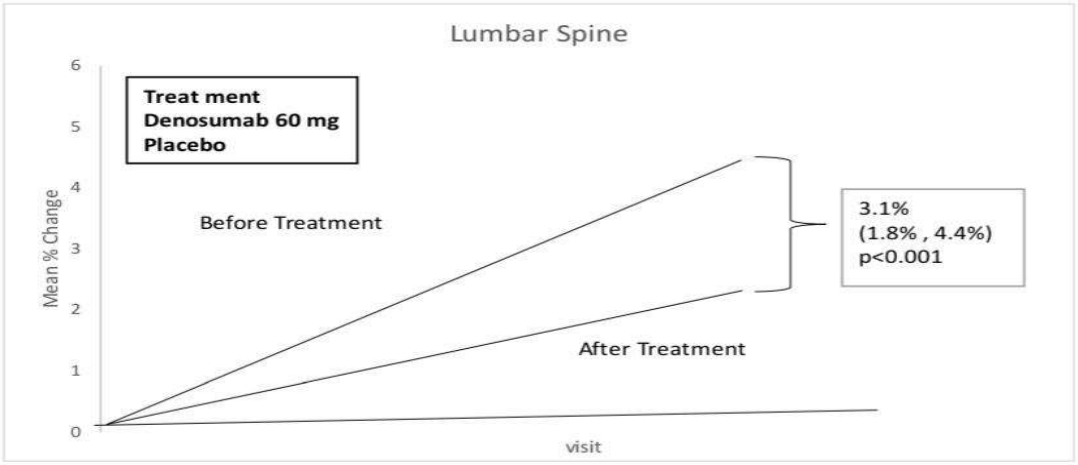

Figure 3- Primary end point: Mean percent change from baseline in BMD in lumbar spine (ITTE population) *Mean treatment difference (95% confidence interval [CI]) and *P*-value at six months based on ANOVA. Error bars are 95% CIs from the model % change = treatment + baseline BMD. Denosumab group: *n* = 14; prolia group: *n* = 11. ANOVA: Analysis of covariance; BMD: bone mineral density; intent-to-treat efficacy.

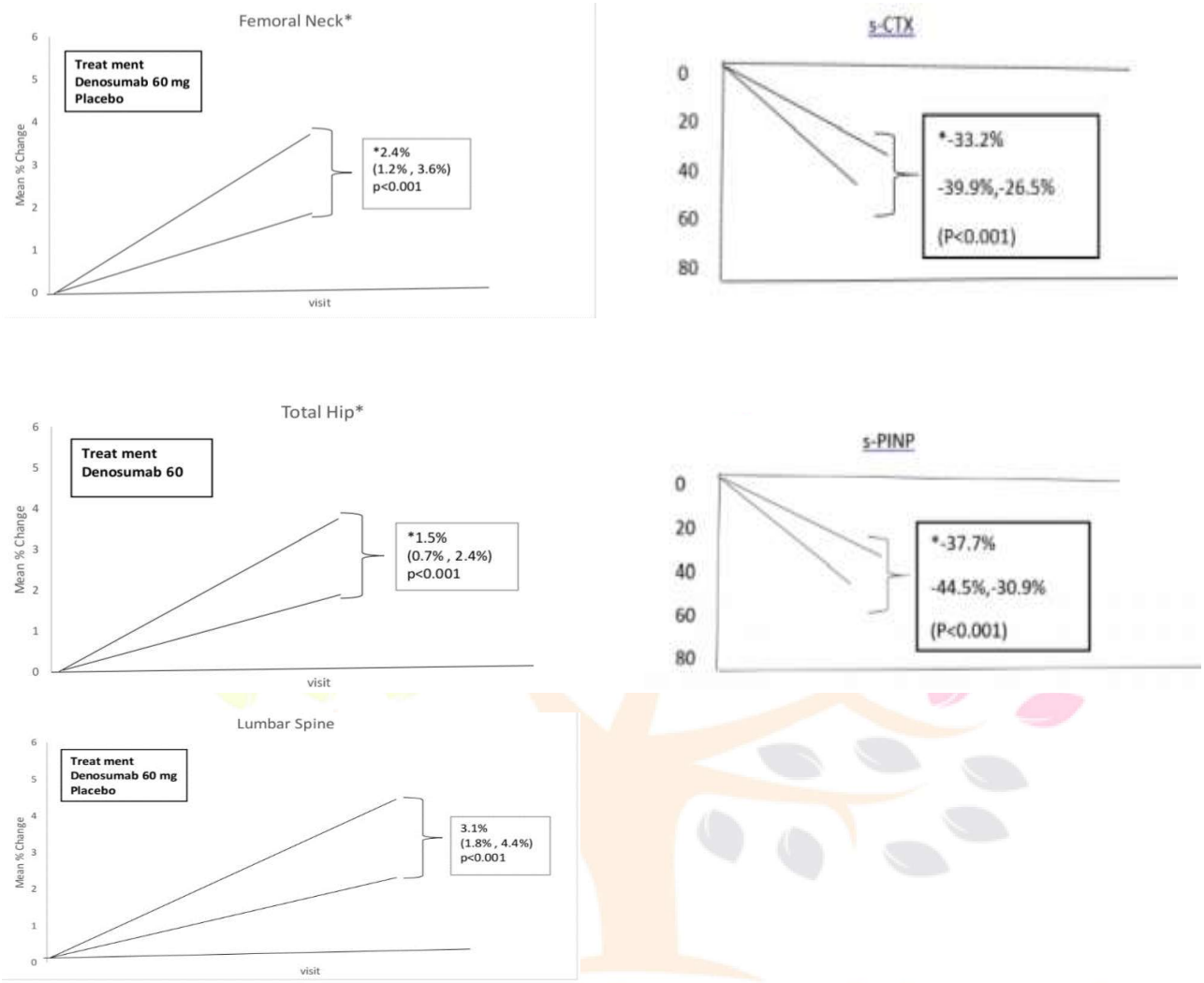

Figure 4- Secondary end points: Mean/median percent change from baseline in BMD in total hip, femoral neck, and trochanter and bone turnover markers Error bars are 95% confidence intervals (CIs) from the model % change = treatment + baseline BMD. Denosumab group: *n* = 14; prolia group: *n* = 11 † Mean treatment difference (95% CI) and *P*-value at six months based on ANOVA. Error bars are. At Month 6, denosumab group: *n* = 14; prolia group: *n* = 14. Median treatment difference (95% CI) and *P*-value at six months based on. ||Error bars are (Q1, Q3). At Month 6, denosumab group: *n* = 14; prolia group: *n* = 11. ANOVA = Analysis of covariance; BMD: bone mineral density; intent-to-treat efficacy; s-CTX: serum C-terminal telopeptide of type I collagen; s-PINP: serum procollagen type I N propeptide.

Safety

fourteen (35%) subjects in the denosumab group and 11 (27%) in the prolia 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.

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.

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