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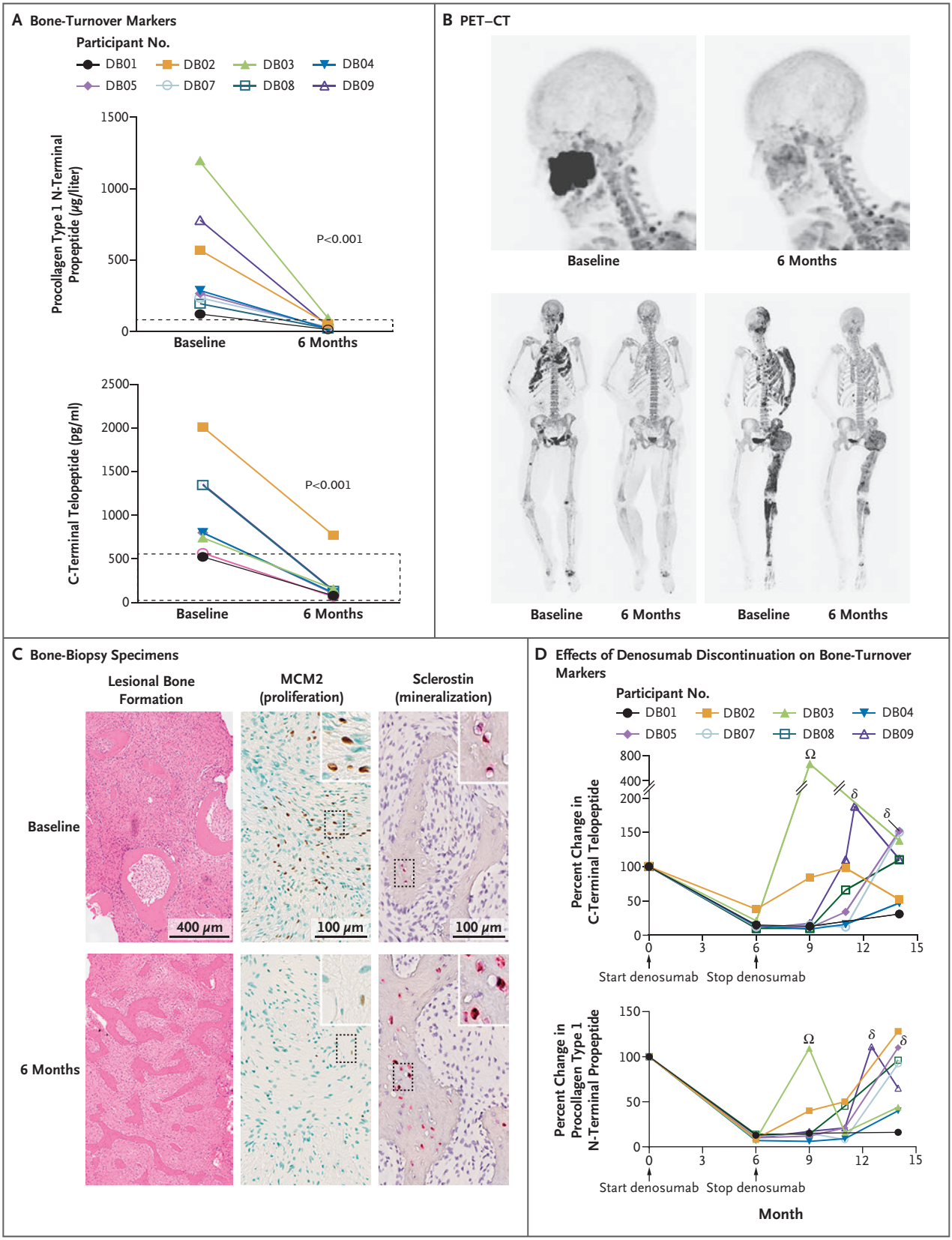
Safety and Efficacy of Denosumab for Fibrous Dysplasia of Bone

TO THE EDITOR: Fibrous dysplasia is a rare, mosaic disorder that leads to fractures, pain, and disability. Gain-of-function *GNAS* variants alter skeletal stem-cell differentiation, which results in the formation of expansile lesions that are composed of highly proliferative, partially mineralized fibro-osseous tissue.[1] Osteoclasts are prominent in fibrous dysplasia lesions; however, their pathogenic role is unknown.[2] Growing evidence suggests that targeting the receptor activator of nuclear factor κB ligand (RANKL), a pro-osteoclastic cytokine, is a potentially promising treatment strategy.[2-4] Denosumab is a RANKL inhibitor with potent but transient antiosteoclastic effects, and discontinuation of denosumab treatment is associated with a rebound in bone turnover.[3] Thus, there is a need to define the effects of denosumab treatment on lesions, as well as the duration of activity and the safety of denosumab in patients with fibrous dysplasia. We conducted a phase 2 study (ClinicalTrials.gov number, NCT03571191) with an emphasis on investigating lesion activity in fibrous dysplasia and rebound in bone turnover after discontinuation of denosumab treatment.

Eight women received high-dose denosumab for 6 months and were observed for 8 months after discontinuation of the therapy (Tables S1 and S2 and Figs. S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Participants received denosumab at a dose of 120 mg every 4 weeks, with loading doses on weeks 2 and 3 of treatment. Details of the study methods and results are included in the Supplementary Appendix, and additional details of the methods are provided in the protocol, available at NEJM.org. At 6 months, denosumab therapy was associated with marked reductions in the serum levels of the bone-formation marker procollagen type 1 N-terminal

Figure 1 (facing page). Effect of Denosumab Treatment on Bone-Turnover Markers and Lesion Activity as Assessed Radiologically.

Panel A shows the changes in the levels of the bone-formation marker procollagen type 1 N-terminal propeptide (P1NP) and the levels of the bone-resorption marker C-terminal telopeptide (CTX) in each participant. The dashed lines indicate the normal range for each assay. Panel B shows representative images from positron-emission tomography–computed tomography (PET–CT), which was performed after the administration of ^{18}F–sodium fluoride tracer. Qualitative changes in tracer uptake by the fibrous dysplasia lesions are shown in images from Participants DB01 (top), DB02 (bottom left), and DB09 (bottom right). Panel C shows representative stains of bone-biopsy specimens before (baseline) and 6 months after treatment with denosumab. Hematoxylin and eosin staining (images on left) shows increased lesional bone formation (Participant DB04). Immunohistochemical staining (images in middle) shows decreased expression of the cell-proliferation marker minichromosome maintenance 2 (MCM2) (Participant DB02). In situ hybridization staining (images on right) shows upregulation in mRNA expression of the bone-formation marker sclerostin (encoded by *SOST*) (Participant DB07). The dashed boxes refer to the insets. Panel D shows the effects of discontinuation of denosumab treatment on bone-turnover markers. The graphs show the percent changes from baseline in the resorption marker CTX (upper graph) and in the formation marker P1NP (lower graph) in each participant. The Greek letter Ω corresponds to the occurrence of severe hypercalcemia, and δ corresponds to the occurrence of mild asymptomatic hypercalcemia.



propeptide (median percent change, −92%; range, −93 to −87) and the bone-resorption marker C-terminal telopeptide (median percent change, −82%; range, −86 to −61) (Fig. 1A). Combined positron-emission tomography–computed tomography, in which uptake of ^{18}F–sodium fluoride tracer was used as a radiologic marker of lesion activity,[5] revealed a marked decrease in lesion activity (Fig. 1B and Fig. S3). Participants reported amelioration of complications associated with fibrous dysplasia, including an increase in pulmonary function in a participant with severe thoracic fibrous dysplasia and an improvement in vision in a participant with aggressive craniofacial fibrous dysplasia (Table S3). Examination of bone-biopsy specimens revealed reduced proliferation of cells associated with fibrous dysplasia, as well as osteogenic cell maturation and increased lesional bone formation (Fig. 1C and Figs. S4 and S5).

Participants received zoledronate 4 weeks after receiving the final dose of denosumab, with the administration of subsequent infusions of zoledronate as clinically indicated (Table S4). Laboratory test results were initially monitored at 4-week intervals; the frequency was subsequently increased to every 2 weeks after severe hypercalcemia developed in one participant. The affected participant began to have vomiting 12 weeks after she discontinued denosumab treatment; 3.5 weeks before vomiting began, her laboratory test results had been normal. At the time that vomiting began, the serum calcium level was markedly elevated (23 mg per deciliter; normal range, 8.6 to 10.2), and the C-terminal telopeptide level had increased to 670% of the baseline level (Fig. 1D). The participant received fluids, calcitonin, zoledronate, and additional doses of denosumab and recovered without evident sequelae. Of note, this participant had had extensive fibrous dysplasia, with the highest level of bone turnover in the cohort at baseline. After discontinuation of denosumab treatment, three additional participants had a rebound in bone turnover that was above the pretreatment level and was associated with mild-to-moderate asymptomatic hypercalcemia.

Treatment with denosumab may provide clinical benefit in patients with fibrous dysplasia by reducing lesion activity and enabling osteogenic cell maturation and bone formation. However, marked bone-turnover rebound with hypercalcemia occurs in some patients, particularly in those with a high disease burden. These findings provide further understanding of the pathogenesis of fibrous dysplasia and appear to support the use of denosumab as a mechanistically driven treatment strategy. Nevertheless, the potential occurrence of rebound hypercalcemia is an important consideration that necessitates caution.

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