Invasive Oral Procedures and Events in Postmenopausal Women With Osteoporosis Treated With Denosumab for Up to 10 Years

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Context: Antiresorptive therapy has been associated with osteonecrosis of the jaw (ONJ), an infrequent but potentially serious adverse event.

Objective: To assess information on invasive oral procedures and events (OPEs)—dental implants, tooth extraction, natural tooth loss, scaling/root planing, and jaw surgery—during the 7-year Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) Extension study and to present details of positively adjudicated ONJ cases.

Design: Randomized, double-blind, placebo-controlled, 3-year trial (FREEDOM) followed by 7 years of open-label denosumab (FREEDOM Extension). At Extension Year 3, women were asked to record their history of invasive OPEs since the start of the Extension to Year 2.5 and oral events in the prior 6 months. The questionnaire was then administered every 6 months until the end of the Extension.

Setting: Multicenter, multinational clinical trial.

Patients: Postmenopausal women with osteoporosis.

Interventions: Subcutaneous denosumab 60 mg or placebo every 6 months for 3 years, then 7 years of open-label denosumab.

Main Outcome Measures: Self-reports of OPEs and adjudicated cases of ONJ.

Results: Of respondents, 45.1% reported at least one invasive OPE. The exposure-adjusted ONJ rate in FREEDOM Extension was 5.2 per 10,000 person-years. ONJ incidence was higher in those reporting an OPE (0.68%) than not (0.05%).

Conclusions: Although invasive OPEs were common in these denosumab-treated women and were associated with an increased ONJ incidence, the overall rate of ONJ was low, and all cases with complete follow-up resolved with treatment. **(*J Clin Endocrinol Metab* 104: 2443–2452, 2019)**

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Abbreviations: AAOMS, American Association of Oral and Maxillofacial Surgeons; AE, adverse event; BMD, bone mineral density; FREEDOM, Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months; ONJ, osteonecrosis of the jaw; OPE, oral procedure and event.

Osteonecrosis of the jaw (ONJ) was first described in patients with cancer receiving high doses of zoledronic acid (4 mg IV monthly) (1) and subsequently observed with high-dose denosumab (120 mg subcutaneously once per month) in the same setting at rates of approximately 1% to 2% per year (2, 3). ONJ is a recognized adverse event associated with antiresorptive drug therapy and has been reported, but less frequently, in patients receiving lower doses of zoledronic acid (5 mg IV yearly) and denosumab (60 mg every 6 months), as well as oral bisphosphonates, in the setting of osteoporosis (~1/10,000 to 1/100,000 patient treatment-years) (4–6).

Guidelines for the management of patients being treated with antiresorptive agents for osteoporosis have been published and periodically updated to help providers minimize the risk for ONJ and diagnose, stage, and care for patients who develop ONJ (7, 8). Key recommendations include thorough dental screening and adequate treatment of existing dental issues before initiation of antiresorptive therapy, maintenance of good oral hygiene, and ongoing dental care with prompt attention to any dental issues arising during treatment. Recognized risk factors for ONJ are dentoalveolar surgery (especially tooth extraction), dentures, pre-existing inflammatory dental disease (*e.g.,* periodontal disease), increasing age, smoking, and corticosteroid use. Treatment recommendations for ONJ emphasize a conservative approach in mild cases, with escalating strategies based on increasing ONJ stage (including antibacterial mouth rinses, oral antibiotics, and surgical debridement) (8).

The Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) study was an international, randomized, placebo-controlled 3-year trial in which subcutaneous denosumab injection, 60 mg every 6 months, reduced the risk for new vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis compared with placebo (9). Upon completion of FREEDOM, patients were eligible to enroll in the FREEDOM Extension study to receive up to 7 additional years of denosumab therapy (5, 10–13). During FREEDOM, there were no adjudicated ONJ cases, whereas during FREEDOM Extension, the incidence was 5.2 per 10,000 patient-years (5). The present report assesses patient-reported invasive oral procedures and events (OPEs) in FREEDOM Extension in order to identify possible oral risk factors for the development of ONJ. These risk factors include dental implants, tooth extraction, natural tooth loss, scaling/root planing (extensive subgingival cleaning), and jaw surgery. Clinical details are presented for the 13 cases of adjudicated ONJ in FREEDOM Extension.

Materials and Methods

Details of FREEDOM and the Extension study have been previously described (5, 9). Briefly, patients eligible for FREEDOM were postmenopausal women age 60 to 90 years with a lumbar spine or total hip bone mineral density T-score <-2.5 at either site but ≥ -4.0 at both sites, with a history of no more than two moderate vertebral fractures and no severe vertebral fractures. Patients who missed no more than one dose of investigational product and completed the Year 3 FREEDOM study visit were eligible to participate in the 7-year open-label Extension study to continue receiving open-label subcutaneous denosumab, 60 mg every 6 months, regardless of original treatment assignment in FREEDOM (Fig. 1). Patients who received denosumab in both FREEDOM and the Extension study were classified as "long-term" denosumab patients, and those who received placebo in FREEDOM and denosumab in the Extension study were classified as "crossover" denosumab patients.

In accordance with the Declaration of Helsinki, the local or central ethics committee/institutional review board for each site approved the study protocol, and each participant provided written informed consent.

A questionnaire collected at Extension Year 3 (6 years after the start of FREEDOM) asked patients to recall their history of invasive OPEs during the first 2.5 years of the Extension. The investigator recorded whether the subject reported having a tooth extraction, natural tooth loss, dental implant placement, and/or scaling/root planing during this time period. At the same Extension Year 3 visit, patients who agreed to participate in the survey were also asked to complete an oral event questionnaire administered by the investigator that collected OPEs from the preceding 6 months; the questionnaire specifically asked (i) whether the patient had seen a dentist since the last visit and (ii) whether the patient had any tooth extractions, natural tooth loss, dental implants placed, scaling or root planing, or had undergone any jaw surgery since the last visit. This questionnaire was repeated at every 6-month study visit until the end of study. Information on jaw surgery was not collected in the initial questionnaire; therefore, any jaw surgery in the original FREEDOM Trial and in the first 2.5 years of the Extension study was not collected.

During the study, a predefined list of oral events was used to routinely search the clinical trial database to identify potential ONJ events. The methods for ONJ identification and adjudication were previously described for denosumab trials in the oncology setting (14, 15). Once a potential event was identified, a request for relevant medical data was sent to the reporting investigator. After the additional information was obtained, the case was sent for independent expert adjudication based on the American Association of Oral and Maxillofacial Surgeons (AAOMS) ONJ case definition (7, 8). Positively adjudicated ONJ was defined as exposed alveolar or palatal bone in the oral cavity where gingival or alveolar mucosa is normally found that did not heal after appropriate care by 8 weeks in a patient without a history of radiation to the head, face, or mouth (7). Cases sent for adjudication were classified as meeting or not meeting the predefined ONJ criteria.

Adverse event (AE) severity was graded by using the Amgen Standard AE Severity Scoring System; this generic grading scale is based on the Common Terminology Criteria for Adverse Events (CTCAE) guidelines. Grade 1/mild was assigned when a patient was aware of signs or symptoms but they were easily

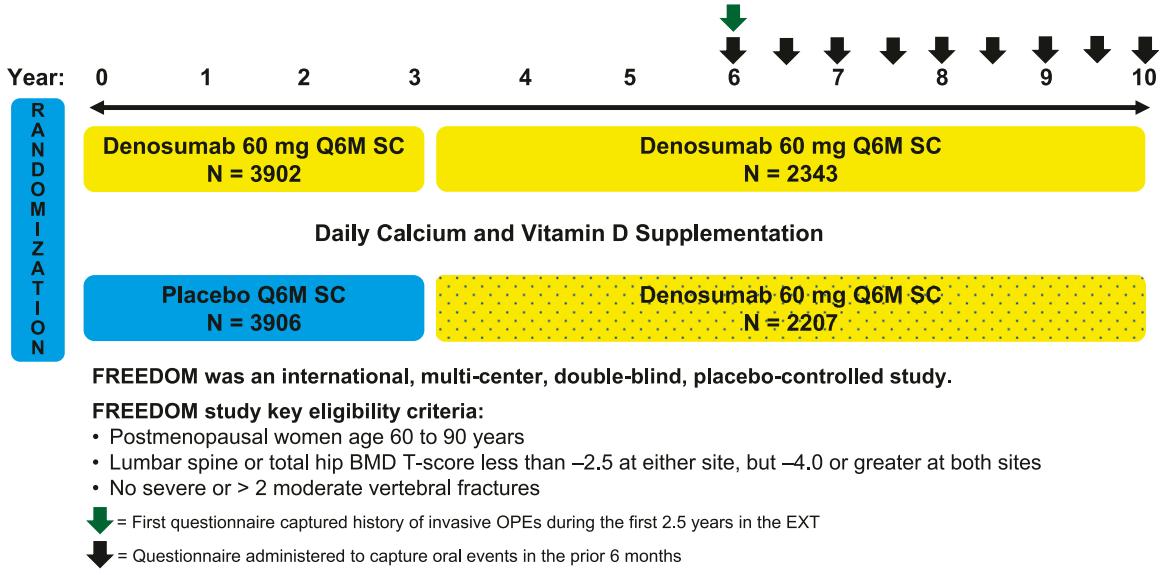

Figure 1. FREEDOM and FREEDOM Extension (EXT) study schema. Q6M, every 6 months; SC, subcutaneous.

tolerated. Grade 2/moderate was assigned when discomfort was great enough to cause interference with usual activity. Grade 3/severe AEs were incapacitating, causing an inability to work or do usual activity. The grade 4/life-threatening designation referred to an event in which the patient was, in the view of the investigator, at risk for death at the time of the event.

ONJ was also staged *post hoc* based on a review of initial safety reports using the AAOMS medication-related ONJ staging scale to provide a comparator to the AE Severity Scoring System used in this study (7, 8). Stage 0 was defined as no clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms. Stage 1 was exposed and necrotic bone or fistulae that probe to bone in patients who are asymptomatic and have no evidence of infection. Stage 2 was exposed and necrotic bone or fistulae that probe to bone, associated with infection, as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage. Stage 3 was exposed and necrotic bone or fistulae that probe to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (*i.e.*, inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla), resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor.

Possible inciting events that led to the development of ONJ were determined based on review of the safety reports by the sponsor as part of risk assessment and subsequently by the authors of this report. Time to ONJ healing was based on patient report to the investigator at any study visit following resolution of ONJ. If healing occurred after the patient completed or discontinued the study, time to healing was obtained from ongoing safety follow-up reports.

Results

Of the patients who enrolled in the Extension study, the demographic and disease characteristics at FREEDOM baseline were balanced between the long-term and crossover patients. At Extension baseline, lumbar spine and total hip BMD was higher in the active arm than in the placebo group; otherwise, baseline demographic characteristics were similar (Table 1).

Of the 4550 patients who enrolled in the Extension study, 78.9% (n = 3591) participated in the OPE survey. Of the 3591 patients completing at least one OPE survey, 1621 (45.1%) reported at least one invasive OPE. The reported incidence of specific invasive OPEs was similar between the long-term denosumab and crossover groups (Table 2): scaling/root planing (28.5% vs 29.1%, respectively), tooth extraction (24.6% vs 25.1%), dental implants (6.0% vs 5.8%), natural tooth loss (4.0% vs 4.2%), and jaw surgery (0.9% vs 0.9%).

There were 13 positively adjudicated cases of ONJ; 12 cases occurred among women who participated in the survey and 1 occurred in a woman who did not complete the survey. Overall ONJ incidence over 7 years was 0.68% (11/1621 patients) in women reporting invasive OPEs and 0.05% (1/1970 patients) in women reporting no invasive OPEs. The rates of invasive OPEs during the first 2.5 years (averaged to an every-6-months rate) and for each 6-month period during the Extension study were similar between patients receiving long-term denosumab and patients who crossed over from placebo in FREEDOM to denosumab in the Extension study (Fig. 2).

The 1 case without OPE survey results resolved with treatment. Of the 12 ONJ cases with survey results, 10 resolved with treatment, 1 was ongoing at the end of study but appeared to be healing, and 1 outcome was unknown because of withdrawal of consent.

ONJ case details

There were no positively adjudicated cases of ONJ in the 3-year placebo-controlled FREEDOM study. Details of the 13 ONJ cases that occurred during the FREEDOM

Table 1. Baseline Demographic and Disease Characteristics

	FREEDOM Baseline		Extension Baseline	
Characteristic	Long-Term (n = 2343)	Crossover (n = 2207)	Long-Term (n = 2343)	Crossover (n = 2207)
Age, y	71.9 (5.0)	71.8 (5.1)	74.9 (5.0)	74.8 (5.1)
Time since menopause, y	23.7 (7.3)	23.7 (7.4)	26.7 (7.3)	26.7 (7.4)
Prevalent vertebral fractures, n (%)	559 (24)	485 (22)	573 (24)	551 (25)
BMD T-score				
Lumbar spine	−2.8 (0.7)	−2.8 (0.7)	−2.1 (0.8)	−2.8 (0.8)
Total hip	−1.9 (0.8)	−1.9 (0.8)	−1.5 (0.8)	−1.9 (0.8)

Data are means with SDs unless otherwise noted.

Abbreviation: n, number of patients enrolled in the Extension.

Extension are summarized in Table 3. Six were in crossover patients (placebo in FREEDOM and denosumab in the Extension study) and seven were in long-term patients (denosumab in both FREEDOM and the Extension study). ONJ cases occurred after a period of up to 10 years of denosumab exposure, without clear relationship to duration of exposure (Fig. 3). Treatment of ONJ was successful in the 11 cases for which outcome was known. One case was recent and appeared to be healing at the last patient visit, and the status of the other case was unknown.

Inciting events

Of the 13 patients who developed ONJ, one or more tooth extractions were reported in 9 cases and were thought to be the inciting event in 4. Seven of the nine dental extractions involved two or three teeth, and the remaining two cases were single extractions. Dentures were involved in seven cases (cases 2, 4, 7, 8, 11, 12, and 13) and were considered to be the inciting event in two. Four patients did not have a clearly identifiable inciting event: case 5 was due to trauma related to an exostosis, case 9 presented with a "mouth sore," and cases 7 and 12 were associated with complex dental histories but were not attributable to a specific dental procedure or event. Natural tooth loss occurred in two patients and was not considered to be the inciting event in either case. Only one patient reported having scaling/root planing, and this procedure was not felt to be related to the development of ONJ (Table 3).

Of note, 212 patients (5.9%) underwent dental implants. One patient who had two implants developed ONJ related to delayed osseointegration (case 4). This patient continued to receive denosumab while being successfully treated for ONJ and retained the implants.

Denosumab continuation

Denosumab continuation after ONJ onset was defined as having received at least one dose of denosumab after the recorded ONJ onset date. Of the 13 patients with positively adjudicated ONJ, 8 (3 crossover and 5 long-term) received denosumab after ONJ onset, 2 did not receive denosumab after ONJ onset because they had reached the end of study participation, and 3 patients eligible to receive denosumab did not continue after ONJ onset.

Of the 8 patients who received denosumab after ONJ onset, 3 received one additional dose, 1 received two doses, 2 received three doses, 1 received six doses, and 1 received eight additional doses. The ONJ lesions in 7 of

Table 2. Invasive Oral Procedures and Events by Treatment Group

	7-Year FREEDOM Extension, n (%)		
Variable	Long-Term (n = 1860)	Crossover (n = 1731)	All (n = 3591)
Any invasive oral procedure or event	826 (44.4)	795 (45.9)	1,621 (45.1)
Scaling/root planing	531 (28.5)	503 (29.1)	1,034 (28.8)
Tooth extraction	458 (24.6)	434 (25.1)	892 (24.8)
Dental implant	112 (6.0)	100 (5.8)	212 (5.9)
Natural tooth loss	75 (4.0)	72 (4.2)	147 (4.1)
Jaw surgery[a]	17 (0.9)	16 (0.9)	33 (0.9)

Data are the number (percentage) of patients with observable data.

Abbreviation: n, number of patients who received at least one dose of investigational product in the Extension study and responded to at least one oral event questionnaire.

[a]Collected in the oral event questionnaire every 6 mo; therefore, information on jaw surgery in the first 2.5 y of the Extension study was not captured.

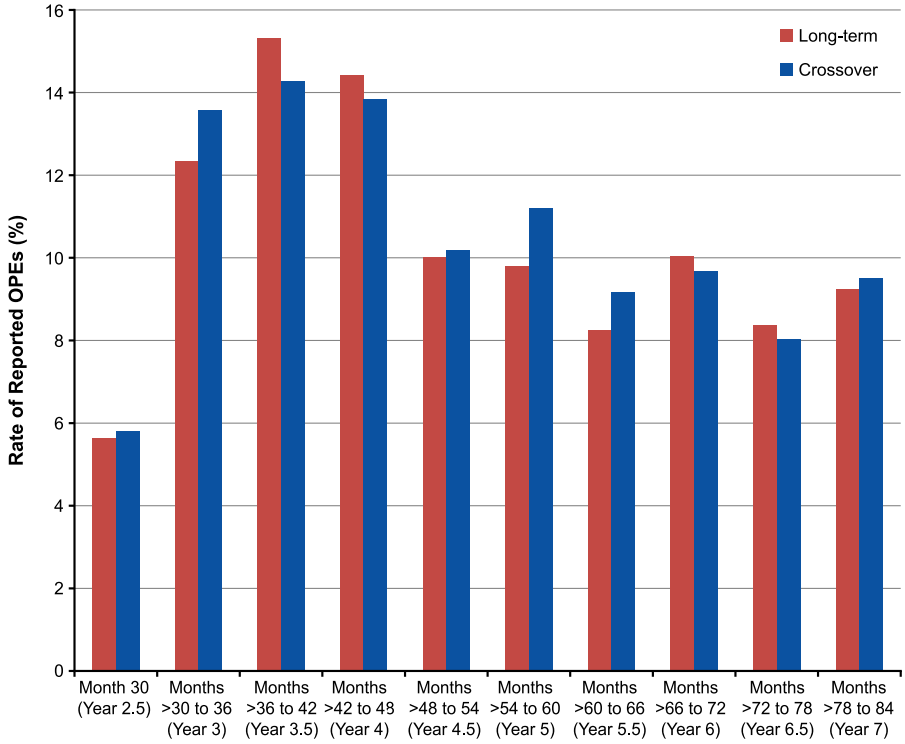

Figure 2. Rate of reported OPEs during the first 2.5 y (averaged to a 6-monthly rate) and for each 6-mo period during the FREEDOM Extension study in patients who received denosumab (long-term) or placebo (crossover) in FREEDOM.

the 8 patients who received denosumab after ONJ onset resolved, and the ONJ lesion in the other patient was ongoing at the end of study (Table 3).

ONJ clinical course

Clinical course details of the 13 ONJ cases are summarized in Fig. 4. Patient age ranged from 71 to 85 years and did not appear to be a risk factor for the development of ONJ. The time between the inciting event and confirmation of ONJ was not available for six patients and ranged from 3 months in cases 1 and 2 to 9 months in case 11 (a patient who had upper dentures).

Before ONJ onset, denosumab exposure ranged from 1.1 years in case 1 (a crossover patient who had two teeth extracted) to 9.6 years in case 10 (a long-term denosumab patient with a single tooth removed and pyogenic granuloma excised; Table 3). According to the Amgen Standard AE Severity Scoring System, two patients (cases 11 and 12) had AE grade 1 (mild); according to the AAOMS medication-related ONJ staging scale, three patients (cases 5, 8, and 9) had stage 1 ONJ. Nine patients had AE grade 2 (moderate) using the Amgen Standard AE Severity Scoring System, and nine patients had stage 2 ONJ using the AAOMS medication-related ONJ staging scale. Per the Amgen Standard AE Severity Scoring System, two patients (cases 8 and 9) had AE grade 3 (severe), and per the AAOMS medication-related ONJ staging scale, one patient (case 2) had stage 3 ONJ. Time to healing ranged from 3.1 months in case 2 to 20.0 months in case 4. The average time to healing was approximately 10 months (Table 4).

Discussion

Invasive OPEs were common in this group of postmenopausal women with osteoporosis who received denosumab for up to 10 years—approximately one third had a dental extraction, natural tooth loss, or a dental implant over the 7 years of data collection. ONJ was more frequently observed in women who reported an invasive OPE during the study: 0.68% (11/1621 patients) in women reporting invasive OPEs and 0.05% (1/1970 patients) in women reporting no invasive OPEs. Most cases of ONJ occurred after an invasive OPE, most commonly after tooth extraction(s). Despite the high frequency of OPEs, however, ONJ incidence was low. Most ONJ cases were mild to moderate in severity and resolved with appropriate dental therapy (one after as little as 3 months, but two required up to 20 months to heal). Ongoing denosumab pharmacovigilance activities continue to monitor ONJ as an AE of interest in patients receiving denosumab.

The pathophysiology of ONJ has not been fully explained but is most likely multifactorial (16). The initial step in the development of ONJ appears to be damage to the bone; exposure of this damaged bone

Table 3. ONJ Case Details

Case	Treatment Group	Age at ONJ Onset (y)	Denosumab After ONJ Onset (No. of Doses)	TEs	Case Details (Possible Inciting Event)	Treatment
Resolved cases						
1	Crossover	74	Yes (6)	2	Osseous surgery for crown lengthening; endodontic therapy following dental fracture,[a] bridge	Antibiotics
2	Crossover	85	Yes (3)	0	Improperly fitting partial upper and full lower dentures[a]	Antibiotics, surgery
3	Crossover	76	Yes (1)	1[a]	Periodontal disease	Antibiotics, surgery
4	Long-term	75	Yes (8)	2	Implants (#25 and #26) with a sinus lift[a] after TEs, upper dentures, gingival bleeding and calculus, draining fistula near affected area	Surgery
5	Long-term	77	Yes (1)	0	Trauma related to an exostosis	Oral rinse, antibiotics
6[b]	Long-term	76	Yes (2)	2[a]	Periodontal disease	Antibiotics, surgery
7[c]	Long-term	71	Yes (1)	2	Lower dentures, root canal, scalings/root planings, natural tooth loss, periodontal disease	Potassium chloride and analgesic gel, oral rinse, surgery
8[d]	Crossover	82	No (0)	2[a]	New dentures	Oral rinse, antibiotics, surgery
9	Crossover	81	No (0)	0	"Mouth sore"	Surgery
10	Long-term	82	No (0)	1	Pyogenic granuloma excised between tooth #26 and #27, xerostoma	Oral rinse
11	Long-term	78	No (0)	3[a]	Upper denture fitting	Oral rinse, antibiotics
Ongoing case						
12	Long-term	83	Yes (3)	2	Periodontal disease, upper and lower dentures	Oral rinse, antibiotics, surgery
Unknown status						
13[c]	Crossover	81	No (0)	0	Natural tooth loss; improperly fitting dentures[a]	No treatment

Abbreviation: TE, tooth extraction.

[a]Denotes possible inciting event.

[b]The patient in case 6 was receiving steroid therapy at the time of her OPE.

[c]The patients in cases 7 and 13 were current smokers.

[d]The patient in case 8 discontinued the study before OPE survey administration.

to the oral cavity leads to necrosis and subsequent infection (17). Inhibition of osteoclastic activity, caused by bisphosphonates and denosumab, prevents removal of necrotic and infected bone, delaying wound healing and leading to continued exposure of underlying bone to the oral environment and bacteria (8). It is therefore not unexpected that ONJ has been associated with invasive oral procedures in the setting of antiresorptive treatment. Tooth extraction, in keeping with our findings, has been previously reported as an oral event preceding the development of ONJ in patients with cancer receiving IV bisphosphonates. In a prospective study of 194 patients treated with oral bisphosphonates (97% for osteoporosis) who underwent at least one tooth extraction, the incidence of ONJ was 0.5% (18–20).

Age is also a well-known risk factor for periodontal disease, and by extension, age is also a risk factor for periodontal disease treatment, including scaling and root planing, and the extraction of unsalvageable teeth. This relationship is thought to be driven by the length of time the periodontal tissue has been exposed to bacterial plaque. An individual's cumulative oral history of periodontal disease with increasing age, with consequent increasing requirement for invasive OPEs, particularly on a background of osteoporosis, may help explain the reported increased ONJ risk with duration of bisphosphonate and denosumab treatment (21).

Strengths of this study include the large sample size contributing data to this analysis, providing high confidence in the low rate of confirmed ONJ events. A limitation of the study is that the actual number of invasive OPEs may be underestimated because of the limited capture of OPEs in medical charts and possible recall bias in patients with events that occurred in the first 2.5 years of the Extension study. Another limitation is that patient-reported "periodontal disease" may vary

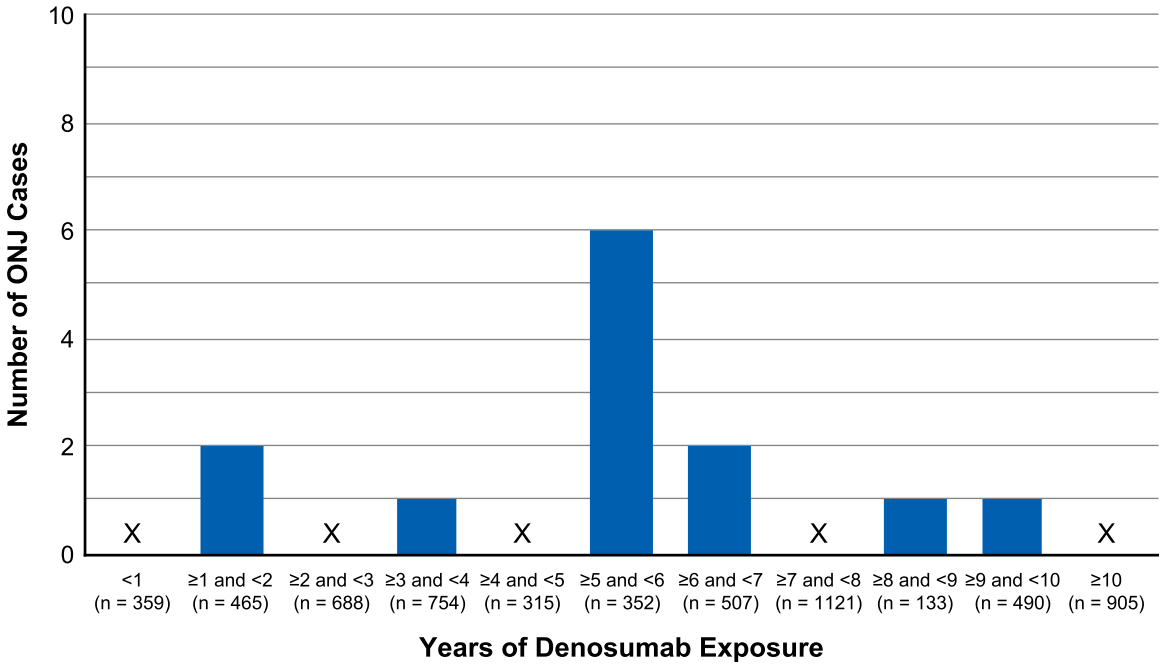

Figure 3. ONJ cases by years of denosumab exposure. n, number of patients at risk; X, no ONJ cases during this time period.

from dentist to dentist and may not represent the same disease state across patients. Understanding the contribution of denosumab therapy to overall ONJ risk is limited by the lack of a placebo control group during the FREEDOM Extension and lack of reliable data on the incidence of ONJ in a comparable untreated population. Finally, because time to healing of ONJ was recorded at the visit when healing was reported, the interval between assessments may have affected ability to accurately recall the exact date of resolution.

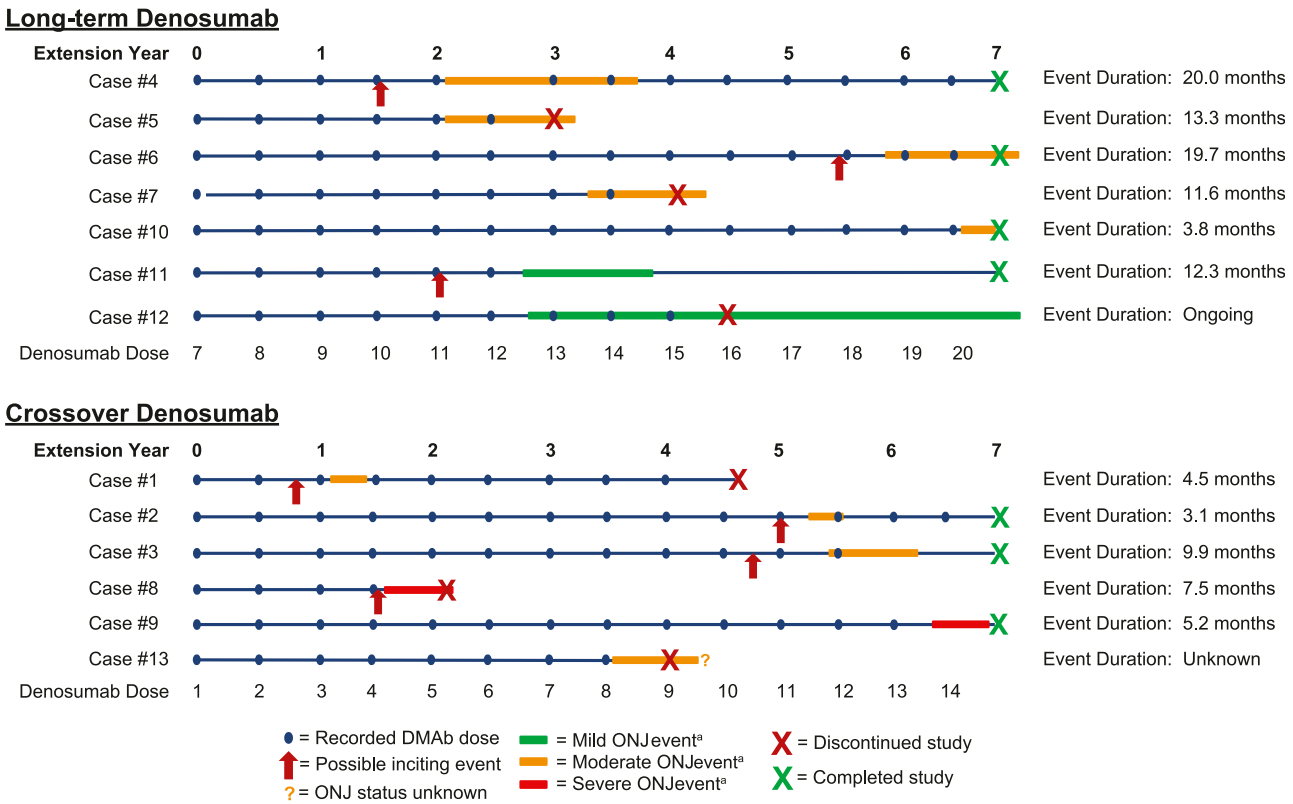

Figure 4. Clinical course timeline of ONJ cases. [a]ONJ severity graded by using the Amgen Standard AE Severity Scoring System. DMAb, denosumab.

Table 4. ONJ Clinical Course Details

Case	Treatment Group	Time Between Inciting Event Onset and ONJ Diagnosis (mo)	Denosumab Exposure at ONJ Onset (y)	ONJ AE Severity per Amgen AE Scale[a]	ONJ Stage per AAOMS[b]	Time to ONJ Healing (mo)
Resolved cases						
1[c]	Crossover	3	1.1	2	2	4.5
2[c]	Crossover	3	5.3	2	3	3.1
3[c]	Crossover	8	5.4	2	2	9.9
4[c]	Long-term	7	5.0	2	2	20.0
5[c]	Long-term	NA	5.1	2	1	13.3
6[c,d]	Long-term	5	8.9	2	2	19.7
7[c,e]	Long-term	NA	6.4	2	2	11.6
8[f]	Crossover	4	1.6	3	1	7.5
9	Crossover	NA	6.9	3	1	5.2
10	Long-term	NA	9.6	2	2	3.8
11	Long-term	9	5.7	1	2	12.3
Ongoing case						
12[c]	Long-term	NA	5.8	1	2	NA
Unknown status						
13[e]	Crossover	NA	3.5	2	2	Unknown

Abbreviation: NA, not applicable.

[a]AE severity determined by using the Amgen Standard AE Severity Scoring System (1, mild: aware of signs or symptoms, but symptoms easily tolerated; 2, moderate: discomfort enough to cause interference with usual activity; 3, severe: incapacitating with inability to work or do usual activity; 4, life-threatening: an event in which the patient was, in the view of the investigator, at risk for death at the time of the event; 5, fatal).

[b]Staged per the AAOMS medication-related ONJ 2014 update (stage 1: exposed and necrotic bone, or fistulae that probe to bone, in patients who are asymptomatic and have no evidence of infection; stage 2: exposed and necrotic bone, or fistulae that probe to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage; stage 3: exposed and necrotic bone, or fistulae that probe to bone, in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (*i.e.*, inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor (7, 8).

[c]patients who received at least one dose of denosumab after ONJ onset.

[d]The Patient in case 6 was receiving steroid therapy at the time of her OPE.

[e]The patients in cases 7 and 13 were current smokers.

[f]The patient in case 8 discontinued study before OPE survey administration.

Management of patients with osteoporosis receiving denosumab should include routine dental care and treatment, such as scaling/root planing when indicated, because nearly 30% of patients reported receiving this procedure and none developed ONJ as a result. Although 212 patients reported dental implants during the study, the procedure was associated with only one case of ONJ, in the context of a complicated dental history. In general, little evidence supports that changes in normal dental procedures are necessary, and no data suggest that a "drug holiday" or attempts to time certain OPEs with denosumab would be beneficial in these patients. Indeed, a program of active dental surveillance and intervention significantly reduced the incidence of ONJ in patients with multiple myeloma receiving antiresorptive drug therapy (22). The effects of denosumab are rapidly reversible when the drug is discontinued without follow-on therapy, which has implications for osteoporosis management. Denosumab discontinuation leads to a transient increase in bone resorption markers to above baseline levels, peaking approximately 12 months after the last dose, with associated decline of BMD and return of fracture risk to that of untreated patients (23). Multiple vertebral fractures have been observed in patients who have stopped denosumab, including a patient whose denosumab dose was delayed in anticipation of a dental procedure (24). Guidelines reflect that a drug holiday should not be implemented with denosumab and suggest that risk-benefit should be carefully considered before discontinuation of antiresorptive therapy based on concerns around ONJ (8, 25). In patients with multiple risk factors for ONJ, dental appliances should be confirmed to fit well and not create "sores." On the basis of the data presented here, it seems prudent that, if more than one extraction is required, the extractions should be staged, and primary closure of extraction sockets should be used, as deemed appropriate, by the treating dental surgeon. Similarly, individual patient presentation may dictate that a chlorhexidine mouth rinse is appropriate until the area is healed and that antibiotic administration be prophylactically prescribed if the patient has poor wound-healing potential (*e.g.*, high-dose corticosteroid use, smoker, and/or patient with uncontrolled diabetes).

In summary, denosumab reduces vertebral, nonvertebral, and hip fracture risk, with previously published 10-year data showing ongoing increases in BMD, low fracture rates, and a favorable safety profile (5). In this analysis of postmenopausal women with osteoporosis treated with up to 10 years of denosumab, invasive OPEs were common, overall ONJ incidence was low. Most cases of ONJ observed in this study occurred after a reported invasive OPE and healed with appropriate dental treatment, despite ongoing denosumab therapy in most cases. Results from this analysis suggest that denosumab therapy may be continued during routine oral procedures and dental care and that the low risk for ONJ should be weighed against the previously demonstrated fracture prevention benefits of denosumab therapy in postmenopausal women with osteoporosis.

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References

1. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003;**61**(9):1115–1117.
2. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;**377**(9768):813–822.
3. Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, Scagliotti GV, Sleeboom H, Spencer A, Vadhan-Raj S, von Moos R, Willenbacher W, Woll PJ, Wang J, Jiang Q, Jun S, Dansey R, Yeh H. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol*. 2011;**29**(9):1125–1132.
4. Grbic JT, Black DM, Lyles KW, Reid DM, Orwoll E, McClung M, Bucci-Rechtweg C, Su G. The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid: data from the health outcomes and reduced incidence with zoledronic acid once yearly clinical trials program. *J Am Dent Assoc*. 2010;**141**(11):1365–1370.
5. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, Czerwiński E, Fahrleitner-Pammer A, Kendler DL, Lippuner K, Reginster JY, Roux C, Malouf J, Bradley MN, Daizadeh NS, Wang A, Dakin P, Pannacciulli N, Dempster DW, Papapoulos S. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017;**5**(7):513–523.
6. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E; American Society for Bone and Mineral Research. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2007;**22**(10):1479–1491.
7. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B; American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws--2009 update. *J Oral Maxillofac Surg*. 2009;**67**(5 Suppl):2–12.
8. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F; American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. *J Oral Maxillofac Surg*. 2014;**72**(10):1938–1956.
9. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;**361**(8):756–765.
10. Papapoulos S, Chapurlat R, Libanati C, Brandi ML, Brown JP, Czerwiński E, Krieg MA, Man Z, Mellström D, Radominski SC, Reginster JY, Resch H, Román Ivorra JA, Roux C, Vittinghoff E, Austin M, Daizadeh N, Bradley MN, Grauer A, Cummings SR, Bone HG. Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. *J Bone Miner Res*. 2012;**27**(3):694–701.
11. Bone HG, Chapurlat R, Brandi ML, Brown JP, Czerwinski E, Krieg MA, Mellström D, Radominski SC, Reginster JY, Resch H, Ivorra JA, Roux C, Vittinghoff E, Daizadeh NS, Wang A, Bradley MN, Franchimont N, Geller ML, Wagman RB, Cummings SR, Papapoulos S. The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. *J Clin Endocrinol Metab*. 2013;**98**(11):4483–4492.
12. Ferrari S, Adachi JD, Lippuner K, Zapalowski C, Miller PD, Reginster JY, Törring O, Kendler DL, Daizadeh NS, Wang A, O'Malley CD, Wagman RB, Libanati C, Lewiecki EM. Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years. *Osteoporos Int*. 2015;**26**(12):2763–2771.

13. Papapoulos S, Lippuner K, Roux C, Lin CJ, Kendler DL, Lewiecki EM, Brandi ML, Czerwiński E, Franek E, Lakatos P, Mautalen C, Minisola S, Reginster JY, Jensen S, Daizadeh NS, Wang A, Gavin M, Libanati C, Wagman RB, Bone HG. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study. *Osteoporos Int*. 2015;**26**(12):2773–2783.
14. Thomas D, Carriere P, Jacobs I. Safety of denosumab in giant-cell tumour of bone. *Lancet Oncol*. 2010;**11**(9):815.
15. Stopeck AT, Lipton A, Body J-J, Steger GG, Tonkin K, Boer RH, Lichinitser M, Fujiwara Y, Yardley DA, Viniegra M, Fan M, Jiang Q, Dansey R, Jun S, Braun A. Reply to V. Fusco et al. *J Clin Oncol*. 2011;**29**(17):e523–e524.
16. Reid IR, Cundy T. Osteonecrosis of the jaw. *Skeletal Radiol*. 2009; **38**(1):5–9.
17. Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS. Factors associated with osteonecrosis of the jaw among bisphosphonate users. *Am J Med*. 2008;**121**(6):475–483 e3.
18. Kyrgidis A, Vahtsevanos K, Koloutsos G, Andreadis C, Boukovinas I, Teleioudis Z, Patrikidou A, Triaridis S. Bisphosphonate-related osteonecrosis of the jaws: a case-control study of risk factors in breast cancer patients. *J Clin Oncol*. 2008;**26**(28):4634–4638.
19. Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis CG, Boukovinas I, Koloutsos GE, Teleioudis Z, Kitikidou K, Paraskevopoulos P, Zervas K, Antoniades K. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. *J Clin Oncol*. 2009;**27**(32):5356–5362.
20. Kunchur R, Need A, Hughes T, Goss A. Clinical investigation of C-terminal cross-linking telopeptide test in prevention and management of bisphosphonate-associated osteonecrosis of the jaws. *J Oral Maxillofac Surg*. 2009;**67**(6):1167–1173.
21. AlJehani YA. Risk factors of periodontal disease: review of the literature. *Int J Dent*. 2014;**2014**:182513.
22. Sim IeW, Sanders KM, Borromeo GL, Seymour JF, Ebeling PR. Declining Incidence of Medication-Related Osteonecrosis of the Jaw in Patients With Cancer. *J Clin Endocrinol Metab*. 2015; **100**(10):3887–3893.
23. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, Roux C, Törring O, Valter I, Wang AT, Brown JP. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. *J Bone Miner Res*. 2018;**33**(2):190–198.
24. Leaney A, Sztal-Mazer S. Rebound vertebral fracture in the dental chair during a tooth extraction whilst on a treatment holiday from denosumab to avoid ONJ! *Bone*. 2018;**108**:43.
25. Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, Kleerekoper M, Lewiecki EM, Miller PD, Narula HS, Pessah-Pollack R, Tangpricha V, Wimalawansa SJ, Watts NB. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis - 2016–executive summary. *Endocr Pract*. 2016;**22**(9):1111–1118.