22 June 2017
EMA/493205/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prolia

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/001120/II/0062

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Declarations

X The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

Assessment Timetable / Steps taken for the assessment

Timetable	Planned dates	Actual dates
Start of procedure:	17 October 2016	17 October 2016
CHMP Rapporteur Assessment Report	18 November 2016	21 November 2016
PRAC Rapporteur Assessment Report	18 November 2016	21 November 2016
PRAC members comments	23 November 2016	n/a
Updated PRAC Rapporteur Assessment Report	24 November 2016	n/a
PRAC Outcome	1 December 2016	1 December 2016
CHMP members comments	5 December 2016	
Updated CHMP Rapporteur Assessment Report	8 December 2016	8 December 2016
Request for Supplementary Information	15 December 2016	15 December 2016
Submission	16 February 2017	16 December 2016
Re-start of procedure	21 February 2017	
CHMP Rapporteur Assessment Report	22 March 2017	27 March 2017
PRAC Rapporteur Assessment Report	24 march 2017	27 March 2017
PRAC members comments	29 March 2017	n/a
Updated PRAC Rapporteur Assessment Report	30 March 2017	n/a
PRAC Outcome	06 April 2017	06 April 2017
CHMP members comments	10 April 2017	n/a
Updated CHMP Rapporteur Assessment Report	12 April 2017	n/a
2nd Request for supplementary information:	21 April 2017	21 April 2017
Submission	23 May 2017	23 May 2017
Re-start of procedure	24 May 2017	
PRAC Rapporteur Assessment Report	29 May 2017	30 May 2017
PRAC members comments	31 May 2017	n/a
Updated PRAC Rapporteur Assessment Report	01 June 2017	n/a
CHMP Rapporteur Assessment Report	07 June 2017	30 May 2017
PRAC Outcome	09 June 2017	09 June 2017
CHMP members comments	12 June 2017	n/a
Updated CHMP Rapporteur Assessment Report	15 June 2017	n/a
Opinion	22 June 2017	22 June 2017

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
AGSD	Amgen Global Safety Database
CDS	Core Data Sheet
MedDRA	Medical Dictionary for Regulatory Activities
MVF	multiple vertebral fractures
Q6M	every 6 months

1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 3 October 2016 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.4 and 4.8 of the SmPC in relation to multiple vertebral fractures (MVF) following discontinuation of Prolia treatment based on an analysis of osteoporosis-related fracture data in subjects who discontinued investigational product and remained on study in either the Prolia phase 3 pivotal fracture study (Study 20030216) or its study extension (Study 20060289). The Package Leaflet is updated accordingly. An updated Risk Management Plan (RMP) is submitted to include multiple vertebral fractures (MVF) following discontinuation of Prolia treatment as a new important risk. In addition, the applicant took the opportunity to make minor editorial changes throughout the Product Information and update the information on local representatives in the Package leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

1.2. Rationale for the proposed change

This variation follows a post-hoc analysis of osteoporosis-related fracture data in subjects who discontinued investigational product and remained on study in either the Prolia phase 3 pivotal fracture study (Study 20030216) or its study extension (Study 20060289) to better understand the incidence of fracture following treatment discontinuation.

The MAH interpretation of the data is that multiple vertebral fractures may occur following discontinuation of Prolia treatment, particularly in patients with a history of vertebral fracture.

2. Overall conclusion and impact on the benefit/risk balance

A pivotal 3-year, placebo-controlled, phase 3 Study 20030216 compared Prolia treatment with placebo in patients with osteoporosis. Women who completed Study 20030216 (the parent study) and had completed the 36-month visit could enrol in the extension Study 20060289, in which all subjects were to receive open-label Prolia treatment for another 7 years to provide additional safety and efficacy data.

The MAH expresses a concern regarding multiple new vertebral fractures (MVF) following treatment discontinuation with Prolia based on a post-hoc analysis of osteoporosis-related fracture data in subjects who discontinued investigational product and remained on study in either the Prolia phase 3 pivotal fracture study (Study 20030216) or its study extension (Study 20060289). A total of 1471 patients in these clinical studies have available follow-up data after treatment discontinuation and

114 of these patients fractured during this off-treatment follow-up period of approximately 10 months. The MAH proposes new warnings in the SmPC and PL in relation to *potential occurrence of multiple vertebral fractures (MVF) following discontinuation of Prolia treatment, particularly in patients with history of vertebral fractures.* . The MAH also proposes to add "Multiple vertebral fractures following discontinuation of Prolia treatment" as an important identified risk in the RMP. A Dear Investigator Letter (DIL), relating to multiple vertebral fractures following discontinuation of Prolia treatment, has been circulated by the MAH earlier.

In the view of the CHMP, the current data does not support a warning for increased MVF incidence following treatment discontinuation:

- The MAH´s current interpretation of the data from studies 20030216 and 20060289 is that, in subjects who sustained a new vertebral fracture after Prolia cessation, there was a greater incidence of multiple vertebral fractures than in subjects discontinuing placebo. However, the total number of subjects with new vertebral fractures was lower in the Prolia discontinuation group. Further, there is no biologically plausible mechanism or a clear rationale of why treatment cessation would not increase single vertebral fractures but only ≥2 vertebral fractures.

- In study 20030216, the rate of off-treatment new vertebral fractures was identical in the subjects who discontinued placebo and in the subjects that discontinued denosumab: 12.7 and 12.4 per 100 subject-years. There were no imbalances in patients who had two, three or four vertebral off-treatment fractures. These groups had comparable baseline risk with regard to age and baseline risk.

- The rate of on-treatment vertebral fractures seems similar in long-term and cross-over groups in study 20060289. Off-treatment new vertebral fractures rate was slightly higher in the subjects who discontinued long-term denosumab (21.9 per 100 subject-years) compared to the subjects that discontinued cross-over denosumab (17.1 per 100 subject-years). The number of patients who had two, three or four vertebral off-treatment fractures was low and there was no pattern that this would be more common in any group.

- Compared to study 20030216, the off-treatment new vertebral fractures rates as well as >2 vertebral fractures in study 20060289 were higher. The patients who discontinued study 20060289 were older and had slightly more vertebral fractures already while on treatment. It is clear that any direct comparison that mixes off-treatment vertebral fracture data from these two studies is not valid.

- Subjects who discontinued were older and had more baseline vertebral fractures and prior non-vertebral fractures than the subjects who completed. They had also considerably more on-treatment vertebral fractures than those who completed. Discontinuations due to requirement for alternative therapy were not balanced, either. Besides the underlying reasons for discontinuation such as concomitant other serious diseases, different therapeutic strategies after discontinuation may affect the fracture outcomes after discontinuation.

- Both single and multiple vertebral fractures occur in this high risk population without treatment and during treatment. The scientific value of stimulated non-study reports of fractures occurring after treatment is therefore low, increasing the uncertainty of the data being the basis for the MAH's recommendations.

- There is no evidence to suggest that withdrawal of Prolia accelerates the appearance of fractures, which continue to follow the natural progression of osteoporosis, and the Product Information is not intended to describe such natural disease progression.

- There are known long-term risks with Prolia due to increased suppression of bone remodelling such as osteonecrosis of the jaw and atypical femur fractures. Indirectly, the proposed warning would promote lifelong Prolia treatment. However, the optimal duration of Prolia treatment for osteoporosis has not been established. Therefore, the need for continued treatment should be re-evaluated periodically on an individual patient basis, particularly after 5 or more years of use. To support further direct claims in relation to continued long-term treatment, or recommendations against treatment discontinuation, and to evaluate the benefits vs risks of planned cessation (treatment holiday) would need to be substantiated by robust clinical trial data such as a randomized withdrawal trial after 3-5 year of treatment. Of note, the MAH has recently proposed also *hypercalcemia following treatment discontinuation* as a potential risk for Prolia. A randomized withdrawal trial could also address this issue. The MAH clarified that they do not have any plans to conduct a randomized withdrawal study.

Overall, the data does not support a conclusion that justifies a warning for increased MVF incidence following treatment discontinuation. The argument from the MAH that these ad hoc analyses with serious methodological concerns have been published (please refer to section 4.5 of this report) does not change the fact that the data presented in this variation application does not indicate an increased risk of multiple vertebral fractures after treatment discontinuation when assessed objectively.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.4 and 4.8 of the SmPC in relation to multiple vertebral fractures (MVF) following discontinuation of Prolia treatment based on an analysis of osteoporosis-related fracture data in subjects who discontinued investigational product and remained on study in either the Prolia phase 3 pivotal fracture study (Study 20030216) or its study extension (Study 20060289). The Package Leaflet is updated accordingly. An updated Risk Management Plan (RMP) is submitted to include multiple vertebral fractures (MVF) following discontinuation of Prolia treatment as a new important risk. In addition, the applicant took the opportunity to make minor editorial changes throughout the Product Information and update the information on local representatives in the Package leaflet.

☒ is not recommended for approval.

Grounds for refusal:

Whereas

- Current data does not support a warning for increased multiple new vertebral fractures (MVF) incidence in subjects after Prolia cessation, based on data from studies 20030216 and 20060289, in particular as: the total number of subjects with new vertebral fractures was

lower in the Prolia discontinuation group; there is no biologically plausible mechanism why treatment cessation would not increase single vertebral fractures but only ≥2 vertebral fractures; there were numerous imbalances of parameters for subjects who discontinued compared to subjects who completed, such as more on-treatment vertebral fractures or underlying reasons for discontinuation; the scientific value of stimulated non-study reports of fractures occurring after treatment is questioned as it increases the uncertainty of the data; as well as other uncertainties of the data from the two studies

the CHMP has recommended the refusal of the variation to the terms of the marketing authorisation.

4. Scientific discussion

4.1. Introduction

Prolia (denosumab 60 mg every 6 months [Q6M]) is a fully human monoclonal antibody with high affinity and specificity for RANK ligand that binds to and neutralizes the activity of human RANK ligand. Prolia was approved in the European Union (EU) via the Centralised Procedure in May 2010 and is indicated for:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.

Some reports in the literature have described patients sustaining multiple vertebral fractures (MVF) following Prolia discontinuation (Popp et al, 2016; Rodriquez et al, 2016; Anastasilakis and Makras, 2016). To better understand the incidence of fracture following treatment discontinuation, an analysis was performed of osteoporosis-related fracture data in subjects who discontinued investigational product and remained on study in either the Prolia phase 3 pivotal fracture study (Study 20030216) or its extension study (Study 20060289).

The purpose of this clinical overview addendum is to provide support for an update to the Core Data Sheet (CDS) for Prolia (Prolia CDS version 18) and corresponding changes to EU product information that incorporates information on a new identified risk, MVF following discontinuation of Prolia treatment.

4.2. Methods

Clinical Study Data Evaluation

The 3-year, placebo-controlled, phase 3 Study 20030216 demonstrated that Prolia treatment, compared with placebo, reduces the incidence of new vertebral fractures, nonvertebral fractures, and hip fractures in postmenopausal women with osteoporosis. Women who completed Study 20030216 (the parent study), completed the 36-month visit, and did not miss more than 1 dose of investigational product could enrol in the extension Study 20060289, in which all subjects were to receive open-label Prolia treatment for another 7 years to provide additional safety and efficacy data.

Subjects were included in the current analyses if they discontinued treatment after receiving at least 2 doses of investigational product (either placebo or denosumab in Study 20030216, or denosumab in Study 20060289) but remained in the study for ≥ 7 months after the last dose of investigational product (i.e., the 6-month dosing interval plus a 1-month study visit window). The incidence of fracture was assessed after denosumab discontinuation in Studies 20030216 and 20060289, as well as after placebo discontinuation in Study 20030216 as a surrogate for the off-treatment background rate of fracture.

Aggregate Review of the MAH's Global Safety Database

Signal evaluation using the Amgen Global Safety Database (AGSD) was conducted on Prolia post marketing cases cumulatively through 01 October 2015 to identify off-treatment fractures. The fractures identified from this assessment were reviewed for evidence of MVF and an updated search of Prolia post marketing cases from the AGSD for MVF following Prolia treatment discontinuation was conducted for the period of 02 October 2015 through 09 February 2016. In addition, a cumulative search through 09 February 2016 was conducted of Prolia clinical study cases.

To capture all cases potentially relevant to MVF, a search of the AGSD was performed with Medical Dictionary for Regulatory Activities (MedDRA; version 18.1) using a narrow search of the term *Fractures.* A medical review of all fracture cases, independent of reporter's relationship attribution, was then conducted to identify MVF following treatment discontinuation with Prolia, defined by a last dose latency of > 6 months.

Literature Review

A literature search of both PubMed and Google Scholar was performed for articles published between 2000 and 2016 reporting rates of MVF following discontinuation of anti-osteoporosis therapies and rates of MVF in populations potentially eligible for treatment with Prolia (ie, women with postmenopausal osteoporosis, men with osteoporosis, men with prostate cancer using hormone ablation therapy, women receiving adjuvant aromatase inhibitor therapy for breast cancer).

4.3. Results

Clinical Study Data

Four hundred seventy subjects in the placebo group of Study 20030216 and 1001 subjects in the combined denosumab groups of Studies 20030216 and 20060289 had available follow-up data after treatment discontinuation. The mean follow-up time per subject during the post-treatment period (from last dose of investigational product plus 7 months to end-of-study) was 0.8 years in the placebo group and 0.84 years in the combined denosumab group.

Fractures were reported during the period following investigational product discontinuation in 9.1% of subjects who discontinued placebo and 7.1% of subjects who discontinued denosumab. Most of these fractures were new vertebral fractures, which were reported for 6.2% of subjects who discontinued placebo and 5.6% of subjects who discontinued denosumab (Table 3-1). The proportion of subjects with MVF (≥ 2 new vertebral fractures) was numerically higher in subjects who discontinued denosumab (3.4%) compared with subjects who discontinued placebo (2.1%). Consistently among subjects with new vertebral fracture after treatment discontinuation, a greater percentage of those who discontinued denosumab (34/56 [60.7%]) than placebo (10/29 [34.5%])

sustained MVF. Logistic regression models found that the presence of prior vertebral fractures, either before or during treatment, was the strongest predictor of MVF following treatment discontinuation (odds ratio 2.1 to 3.4). Femoral neck bone mineral density loss after treatment cessation was a weak covariate.

Table 3-1. Off-treatment Summary (Studies 20030216 and 20060289 Off-treatment Subjects)

	FREEDOM Placebo (N = 470)	Combined DMAb (N = 1001)
Subjects who fractured during off-treatment - n (%)	43 (9.1%)	71 (7.1%)
New vertebral fracture	29 (6.2%)	56 (5.6%)
Multiple new vertebral fractures	10 (2.1%)	34 (3.4%)
Subjects with prevalent vertebral fracture before treatment	122	255
New vertebral fracture	12 (9.8%)	19 (7.5%)
Multiple new vertebral fractures	5 (4.1%)	15 (5.9%)
Exposure-adjusted subject incidence during off-treatment - n / exp (r)		
Osteoporotic fracture	43 / 355.12 (12.1)	71 / 773.32 (9.2)
New and worsening vertebral fracture	31 / 363.82 (8.5)	56 / 786.66 (7.1)
New vertebral fracture	29 / 363.82 (8.0)	56 / 786.66 (7.1)
Single new vertebral fractures	19 / 371.35 (5.1)	22 / 822.60 (2.7)
Multiple new vertebral fractures	10 / 370.59 (2.7)	34 / 800.34 (4.2)
Exposure-adjusted subject incidence of new vertebral fracture during off-treatment - (n / N1) exp (r)		
Prevalent vertebral fracture before treatment	(12 / 122) 83.20 (14.4)	(19 / 255) 157.31 (12.1)
No prevalent vertebral fracture before treatment	(17 / 348) 280.62 (6.1)	(37 / 746) 629.35 (5.9)

N = Number of subjects included in the off-treatment analysis
n = Number of subjects
e = Number of fractures; r = fracture rate per 100 subject-years ([e / Subj-yr] * 100)
IP = Investigational product
Percentages based on the number of subjects in the off-treatment follow-up
Off-treatment follow-up is the period between (last dose + 7 months) and end of study.
Subjects who received 2 to 5 doses of investigational product and were followed for ≥ 7 months after the last dose were included in the off-treatment analysis.

Source: t14-12-005-501-offtx-sum-comb-dmab-216pbo.rtf (Date Generated: 20MAY2016:11:06:57)

Comment: A total of 1471 patients in the clinical study have available follow-up data after treatment discontinuation and 114 of these patients fractured during this off-treatment follow-up period of approximately 10 months.

Based on the table above, the MAH expresses a concern regarding multiple new vertebral fractures following treatment discontinuation with Prolia. However, a more comprehensive analysis of the

fractures during the treatment and following discontinuation in different treatment groups is needed before any conclusions can be made.

Firstly, the MAH is asked to present a flow chart of patients in studies 20030216 and 20060289. The flow chart should include the number of patients in different treatment arms who

a. discontinued without any follow-up,

b. discontinued and had off-treatment follow-up as defined by the MAH

c. completed the studies

Secondly, the main baseline characteristics of patients who discontinued (with and without follow-up) during study 20030216 should be compared with patients who completed this placebo-controlled study. The Applicant is asked to comment any differences in reasons for discontinuation in the placebo and denosumab groups, respectively.

The main study 20060289 baseline characteristics of patients who discontinued (with and without follow-up) during study 20060289 should be compared with patients who completed this extension study. The Applicant is asked to comment any differences in reasons for discontinuation between denosumab arms with different treatment durations.

Thirdly, the MAH is requested to calculate the fracture rates as well as exposure adjusted subject incidences during the placebo-controlled study 20030216 for patients in the placebo and denosumab arms: 1. for patients who completed study 20030216 2. for patients who discontinued - while they still were on treatment 3. for patients who discontinued - when they were off-treatment.

Same calculations of the fracture rates as well as exposure adjusted subject incidences are requested for the extension study 20060289: 1. for patients who completed study 20060289 2. for patients who discontinued - while they still were on treatment 3. for patients who discontinued - when they were off-treatment.

Finally, the MAH is requested to present available data on fracture rates as well as exposure adjusted subject incidences for patients who completed study 20060289 and had follow up thereafter, with or without treatment.

Aggregate Review of the MAH's Global Safety Database

Clinical Study Cases

A cumulative total of 449 Prolia clinical study case reports of fractures (523 events) were retrieved from AGSD. Medical review identified 78 case reports with evidence suggesting discontinuation or interruption of Prolia with the last dose administered ≥ 6 months prior to the fracture. Of the 78 cases, 27 were vertebral fractures (single or multiple; 24 of the 78 cases involved 2 or more fractures and 11 of these were cases of MVF (8 occurred following end of study in either Study 20060289 [6 cases] or Study 20050233 [2 cases]). There was no apparent pattern between treatment duration and number of fractures. Treatment duration was reported for 8 of the 11 cases and ranged from 6 to 8 doses prior to the first vertebral fracture for 3 cases and 13 to 19 doses for the remaining 5 cases. The last dose latency ranged from 189 days to 529 days. Nine cases had a prior history of fracture and concomitant steroid use was reported for 6 cases.

Post-marketing Cases

Cumulatively through 09 February 2016, 2587 post marketing case reports of fractures associated with the use of Prolia were retrieved from AGSD. Medical review identified 22 cases of MVF with evidence suggesting discontinuation or interruption of Prolia therapy with the last dose > 6 months prior to the fracture. There was no apparent association between treatment duration and the number of fractures. Treatment duration information was provided for 10 of the 22 cases and ranged from 1 to 2 doses prior to the first vertebral fracture for 4 cases, 3 to 4 doses for 3 cases, and 5 to 6 doses for the remaining 3 cases. The last dose latency ranged from 181 days to 704 days. Two cases with last dose latency > 180 days were due to a missed or delayed dose, but Prolia treatment was continued. Four of the 22 cases reported a history of prior fracture and no information was provided for the remaining 18 cases.

The estimated cumulative number of patient-years of exposure to Prolia through commercial distribution was approximately 5 294 962 as of 09 February 2016 and the cumulative reporting rate through 09 February 2016 for MVF occurring > 6 months after Prolia cessation was 0.42 per 100 000 patient-years.

Literature Review

A search of the PubMed and Google Scholar databases revealed no relevant information with respect to rates of MVF following antiresorptive treatment discontinuation.

4.4. Discussion

MAH conclusions on Benefits and Risks

Overall, the fracture rate among subjects who discontinued Prolia treatment was low and comparable to that in subjects who discontinued placebo. Among subjects who sustained a new vertebral fracture after Prolia cessation, however, there was a greater incidence of MVF than in subjects discontinuing placebo. Prior vertebral fracture, either before or during study treatment, was the strongest predictor of MVF after treatment cessation.

Multiple vertebral fractures may occur following discontinuation of Prolia treatment, particularly in patients with a history of vertebral fracture.

The overall benefit-risk profile for Prolia remains favourable in the approved indications.

Comment:

MAH interpretation of the data is that in subjects who sustained a new vertebral fracture after Prolia cessation, there is a greater incidence of multiple vertebral fractures than in subjects discontinuing placebo. However, the total number of vertebral fractures is lower.

The MAH is requested to present a rationale or a biologically plausible mechanism of why treatment cessation would **not** increase single vertebral fractures but only ≥2 vertebral fractures.

4.5. Literature References

Anastasilakis AD, Makras P. Multiple clinical vertebral fractures following denosumab discontinuation. *Osteoporosis Int*. 2016;27:1929-1930.

Popp AW, Zysset PK, Lippuner K. Rebound-associated vertebral fractures after discontinuation of denosumab – from clinic and biomechanics. *Osteoporos Int*. 2016; 27:1917-1921.

Gonzalez-Rodriguez E, Stoll D, Aubry-Rozier B, Hans D, Lamy O. Is denosumab discontinuation associated with a severe increased fracture risk? about 7 women with 28 spontaneous vertebral fractures 9 to 16 months after the last dose of denosumab. Presented at *Endocrine Society's 98th Annual Meeting*, 02 April 2016, abstract SAT-377.

4.6. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:
Multiple vertebral fractures following discontinuation of Prolia treatment is considered as an important identified risk.

Overall conclusion on the RMP

The proposed changes to the RMP are not acceptable at this time point. RMP version remains as the latest approved.

4.7. Changes to the Product Information

(The MAH changes proposed to the SmPC are indicated by ***bold italics*** for additions and by ~~strikethrough~~ for text that has been deleted.)

MAH proposes to add the following language in Section 4.4 of the SmPC, Special Warnings and Precautions for Use:

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment

Multiple vertebral fractures may occur following discontinuation of treatment with Prolia, particularly in patients with a history of vertebral fracture.

Advise patients not to interrupt Prolia therapy without their physician's advice. Evaluate the individual benefit/risk before discontinuing treatment with Prolia. If Prolia treatment is discontinued, consider transitioning to an alternative antiresorptive therapy.

MAH has added the Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment to adverse drug reactions (ADR) table as an uncommon ADR and added following text in Section 4.8 Undesirable effects:

Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment

In the osteoporosis clinical trial program, multiple vertebral fractures were reported uncommonly in patients following discontinuation of treatment with Prolia, particularly in those with a history of vertebral fractures.

Based on the clinical trial case reports from the Amgen Global Safety Database (8 cases) and the 34 subjects with MVF from the 20030216 and 20060289 combined analysis, the frequency is ~0.18% (42/32,148 clinical trial subjects as of PBRER9 data cut-off). Therefore, MVF following discontinuation of Prolia treatment is considered Uncommon.

The Package Leaflet (PL) is proposed to be updated accordingly, as follows:

If you stop using Prolia

To get the most benefit from your treatment, it is important to use Prolia for as long as your doctor prescribes it for you. Please talk to your doctor before you consider stopping the treatment.

After your treatment with Prolia is stopped, it is possible that broken bones in your spine may occur especially if you have a history of broken bones in the spine. Do not stop taking Prolia without first talking with your doctor. If your Prolia treatment is stopped, discuss other available treatment options with your doctor.

Uncommon side effects (may affect up to 1 in 100 people):

- fever, vomiting and abdominal pain or discomfort (diverticulitis),
- ear infection,
- ***broken bones in the spine after stopping Prolia (multiple vertebral fractures).***

Comment:

The proposed changes are not accepted.

5. Assessment of the responses to the 1st request for supplementary information

Clinical aspects

Question 1

The main study 20060289 baseline characteristics of patients who discontinued (with and without follow-up) during study 20060289 should be compared with patients who completed this extension study. The Applicant is asked to comment any differences in reasons for discontinuation between denosumab arms with different treatment durations.

Response:

Table 1. Study 20060289 Baseline Characteristics

	Cross-over Denosumab (N = 2206)			Long-term Denosumab (N = 2343)		
	Subjects who Discontinued IP With Follow-up[a] (N = 318)	Subjects who Discontinued IP Without Follow-up[b] (N = 708)	Subjects who Completed IP[c] (N = 1180)	Subjects who Discontinued IP With Follow-up[a] (N = 360)	Subjects who Discontinued IP Without Follow-up[b] (N = 743)	Subjects who Completed IP[c] (N = 1240)
At Study 20060289 Baseline						
Age (years)						
n	318	708	1180	360	743	1240
Mean	75.9	76.0	73.7	75.7	76.1	73.9
SD	5.1	5.4	4.7	5.0	5.2	4.6
At Study 20060289 Baseline						
Prevalent vertebral FX - n (%)	82 (25.8)	203 (28.7)	266 (22.5)	85 (23.6)	191 (25.7)	297 (24.0)
Prior nonvertebral FX - n (%)	126 (39.6)	247 (34.9)	381 (32.3)	143 (39.7)	241 (32.4)	396 (31.9)
At Study 20060289 Baseline						
Lumbar spine BMD T-score						
n	315	697	1173	355	736	1234
Mean	-2.80	-2.79	-2.83	-2.17	-2.08	-2.17
SD	0.73	0.83	0.73	0.77	0.88	0.75
At Study 20060289 Baseline						
Total hip BMD T-score						
n	314	694	1171	357	734	1232
Mean	-2.02	-2.01	-1.88	-1.54	-1.59	-1.44
SD	0.84	0.83	0.79	0.84	0.82	0.78
At Study 20030216 Baseline						
10-year probability of a major osteoporotic fracture						
n	318	708	1180	360	743	1240
Mean	18.07	17.64	15.96	17.45	17.50	16.61
SD	9.76	10.48	9.03	9.85	9.89	9.27
At Study 20030216 Baseline						
10-year probability of a hip fracture						
n	318	708	1180	360	743	1240
Mean	7.54	7.45	5.92	7.14	7.34	6.31
SD	7.43	8.40	6.37	7.35	7.86	6.78
Median	4.87	5.00	4.09	4.98	5.03	4.36
Q1, Q3	2.84, 10.18	2.64, 8.85	2.14, 7.35	2.35, 9.73	2.58, 8.79	2.39, 7.68
Min, Max	0.40, 59.60	0.08, 88.89	0.11, 57.87	0.09, 56.09	0.11, 66.55	0.18, 65.69

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N = Number of subjects who received ≥ 1 dose of investigational product

[a] Subjects who discontinued treatment after receiving ≥ 2 doses of investigational product and were followed for ≥ 7 months after the last dose

[b] Subjects who discontinued treatment after receiving 1 dose of investigational product, or receiving ≥ 2 doses of investigational product and were followed for < 7 months after the last dose

[c] Subjects who completed 14 doses of investigational product

Table 2. Study 20060289 Reasons for Investigational Product Discontinuation

	Cross-over Denosumab (N = 2206)			Long-term Denosumab (N = 2343)		
	Subjects who Discontinued IP With Follow-up[a] (N = 318)	Subjects who Discontinued IP Without Follow-up[b] (N = 708)	Subjects who Completed IP[c] (N = 1180)	Subjects who Discontinued IP With Follow-up[a] (N = 360)	Subjects who Discontinued IP Without Follow-up[b] (N = 743)	Subjects who Completed IP[c] (N = 1240)
Reasons for IP discontinuation – n (%)						
Consent withdrawn	127 (39.9)	282 (39.8)	0 (0.0)	130 (36.1)	283 (38.1)	0 (0.0)
Adverse event	65 (20.4)	91 (12.9)	0 (0.0)	91 (25.3)	104 (14.0)	0 (0.0)
Other	35 (11.0)	136 (19.2)	0 (0.0)	43 (11.9)	158 (21.3)	0 (0.0)
Lost to follow-up	45 (14.2)	22 (3.1)	0 (0.0)	42 (11.7)	14 (1.9)	0 (0.0)
Completed[d]	14 (4.4)	66 (9.3)	1180 (100.0)	18 (5.0)	68 (9.2)	1240 (100.0)
Requirement for alternative therapy	6 (1.9)	7 (1.0)	0 (0.0)	10 (2.8)	5 (0.7)	0 (0.0)
Death	3 (0.9)	83 (11.7)	0 (0.0)	9 (2.5)	90 (12.1)	0 (0.0)
Noncompliance	10 (3.1)	9 (1.3)	0 (0.0)	8 (2.2)	5 (0.7)	0 (0.0)
Protocol deviation	5 (1.6)	4 (0.6)	0 (0.0)	4 (1.1)	4 (0.5)	0 (0.0)
Administrative decision	8 (2.5)	6 (0.8)	0 (0.0)	3 (0.8)	9 (1.2)	0 (0.0)
Ineligibility determined	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.6)	3 (0.4)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
[a] Subjects who discontinued treatment after receiving ≥ 2 doses of investigational product and were followed for ≥ 7 months after the last dose
[b] Subjects who discontinued treatment after receiving 1 dose of investigational product, or receiving ≥ 2 doses of investigational product and were followed for < 7 months after the last dose
[c] Subjects who completed 14 doses of investigational product
[d] Subjects who reported 'COMPLETED' investigational product on the CRF

Assessment of the MAH's response

Subjects who discontinued follow-up study 20060289 were approximately two years older (76 years) than subjects who completed the study (74 years). Subjects who discontinued had also more baseline vertebral fractures and prior non-vertebral fractures as well as lower baseline total hip BMD score. Consequently, calculated 10-year probabilities of a major osteoporotic fracture/ hip fracture were lower in the subjects who completed the study compared to patients who discontinued.

There were no differences in baseline lumbar spine BMD, sCTX or vitamin D.

Adverse events were the most common reason for discontinuation in patients with follow up after discontinuation (20-25%) whereas "unspecified other reasons" was most common in patients without follow-up. Approximately 2% discontinued due to requirement for alternative therapy.

Conclusion:

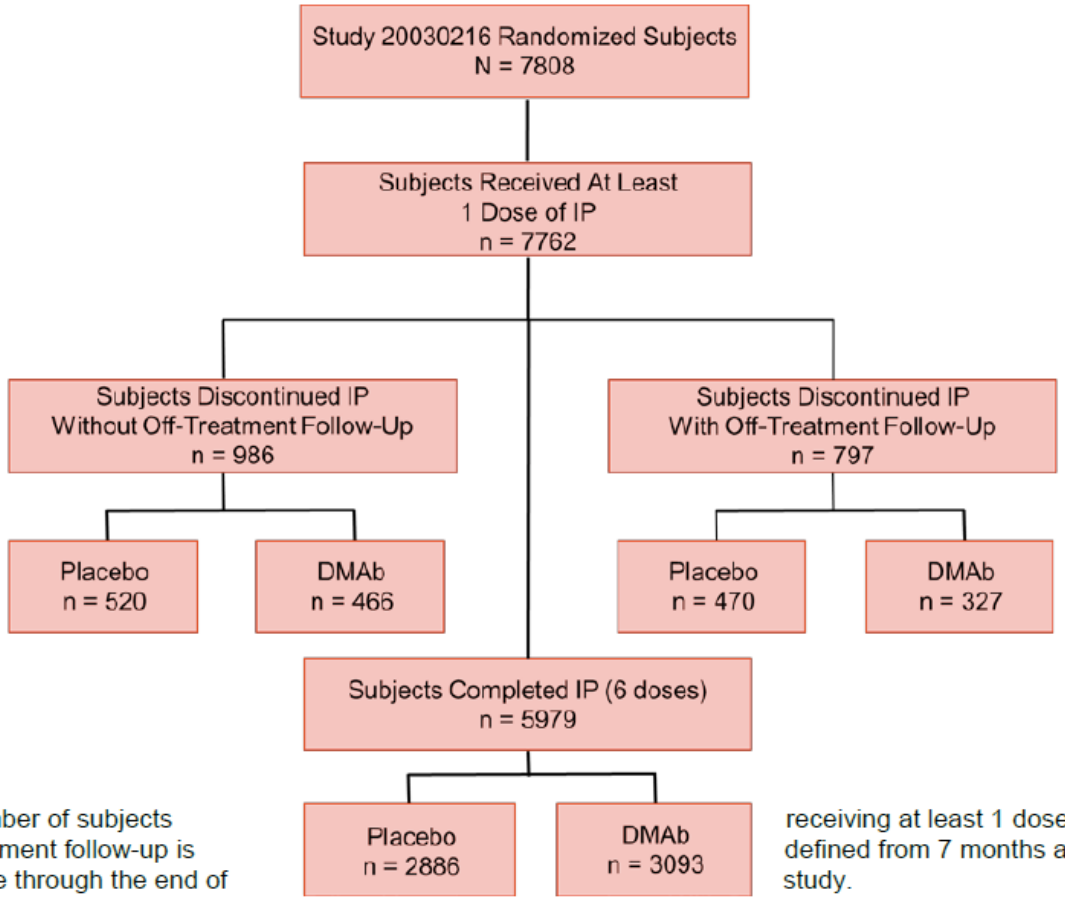
Requested information provided. Issue resolved.

Question 2

The MAH is asked to present a complete flow chart of patients in studies 20030216 and 20060289. The flow chart should include the number of patients in different treatment arms who:
a. discontinued without any follow-up,
b. discontinued and had off-treatment follow-up as defined by the MAH
c. completed the studies

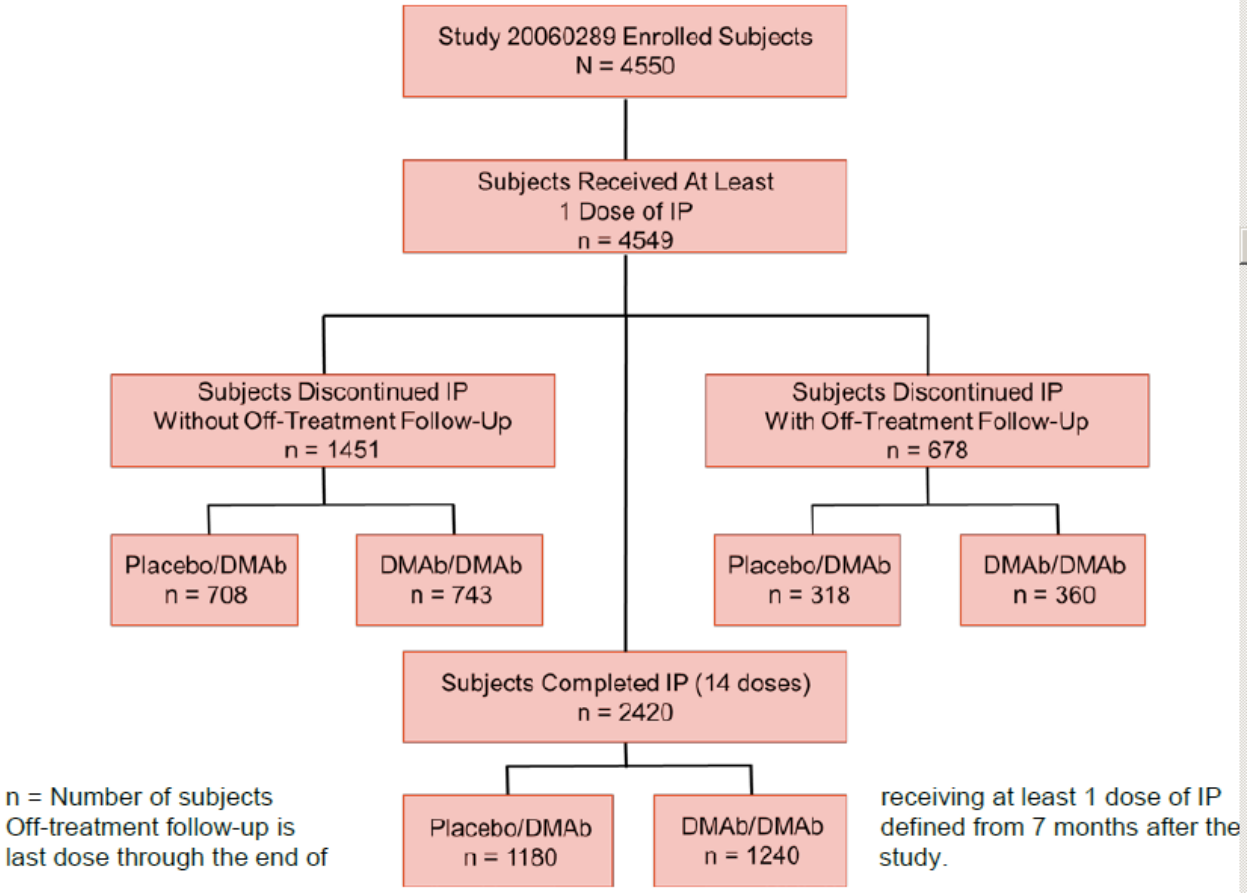
Response:

Figure 1. Study 20030216 Study Subject Disposition



n = Number of subjects receiving at least 1 dose of IP
Off-treatment follow-up is defined from 7 months after the last dose through the end of study.

Figure 2. Study 20060289 Study Subject Disposition



Conclusion
Issue resolved. No need to update overall conclusion.

Question 3

The main baseline characteristics of patients who discontinued (with and without follow-up) during study 20030216 should be compared with patients who completed this placebo-controlled study. The Applicant is asked to comment any differences in reasons for discontinuation in the placebo and denosumab groups, respectively.

Response:

Table 3. Study 20030216 Baseline Characteristics

	Placebo (N = 3876)			Denosumab 60 mg Q6M (N = 3886)		
	Subjects who Discontinued IP With Follow-up[a] (N = 470)	Subjects who Discontinued IP Without Follow-up[b] (N = 520)	Subjects who Completed IP[c] (N = 2886)	Subjects who Discontinued IP With Follow-up[a] (N = 327)	Subjects who Discontinued IP Without Follow-up[b] (N = 466)	Subjects who Completed IP[c] (N = 3093)
Age (years)						
n	470	520	2886	327	466	3093
Mean	73.0	74.0	71.9	73.3	73.4	72.0
SD	5.2	5.4	5.1	5.2	5.5	5.1
Prevalent vertebral FX - n (%)	122 (26.0)	155 (29.8)	633 (21.9)	89 (27.2)	107 (23.0)	731 (23.6)
Prior nonvertebral FX - n (%)	149 (31.7)	168 (32.3)	855 (29.6)	107 (32.7)	149 (32.0)	902 (29.2)
Lumbar spine BMD T-score						
n	470	520	2882	327	466	3089
Mean	-2.84	-2.79	-2.84	-2.76	-2.82	-2.83
SD	0.74	0.74	0.68	0.79	0.74	0.68
Total hip BMD T-score						
n	465	517	2878	326	463	3076
Mean	-2.05	-2.06	-1.86	-1.96	-2.02	-1.86
SD	0.86	0.81	0.79	0.86	0.84	0.80
10-year probability of a major osteoporotic fracture						
n	470	520	2886	327	466	3093
Mean	18.38	19.36	16.71	18.85	17.92	16.98
SD	10.38	9.92	9.54	10.81	9.76	9.55
10-year probability of a hip fracture						
n	470	520	2886	327	466	3093
Mean	7.72	8.45	6.64	8.42	7.50	6.81
SD	8.27	7.94	7.22	9.25	7.52	7.34
Median	5.49	6.07	4.44	5.57	5.56	4.65
Q1, Q3	2.97, 9.78	3.43, 10.54	2.34, 8.26	2.99, 10.94	2.91, 9.70	2.41, 8.37
Min, Max	0.36, 82.01	0.41, 58.05	0.08, 88.89	0.22, 78.09	0.22, 77.30	0.09, 66.55

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N = Number of subjects who received ≥ 1 dose of investigational product

[a] Subjects who discontinued treatment after receiving ≥ 2 doses of investigational product and were followed for ≥ 7 months after the last dose

[b] Subjects who discontinued treatment after receiving 1 dose of investigational product, or receiving ≥ 2 doses of investigational product and were followed for < 7 months after the last dose

[c] Subjects who completed 6 doses of investigational product

Table 4. Study 20030216 Reasons for Investigational Product Discontinuation

	Placebo (N = 3876)			Denosumab 60 mg Q6M (N = 3886)		
	Subjects who Discontinued IP With Follow-up[a] (N = 470)	Subjects who Discontinued IP Without Follow-up[b] (N = 520)	Subjects who Completed IP[c] (N = 2886)	Subjects who Discontinued IP With Follow-up[a] (N = 327)	Subjects who Discontinued IP Without Follow-up[b] (N = 466)	Subjects who Completed IP[c] (N = 3093)
Reasons for IP discontinuation - n (%)						
Adverse event	124 (26.4)	79 (15.2)	0 (0.0)	104 (31.8)	88 (18.9)	0 (0.0)
Consent withdrawn	92 (19.6)	230 (44.2)	0 (0.0)	64 (19.6)	211 (45.3)	0 (0.0)
Subject request	54 (11.5)	32 (6.2)	0 (0.0)	54 (16.5)	30 (6.4)	0 (0.0)
Requirement for alternative therapy	60 (12.8)	9 (1.7)	0 (0.0)	24 (7.3)	6 (1.3)	0 (0.0)
Other	17 (3.6)	19 (3.7)	0 (0.0)	22 (6.7)	11 (2.4)	0 (0.0)
Completed[d]	19 (4.0)	38 (7.3)	2886 (100.0)	16 (4.9)	28 (6.0)	3093 (100.0)
Lost to follow-up	16 (3.4)	22 (4.2)	0 (0.0)	12 (3.7)	22 (4.7)	0 (0.0)
Protocol deviation	16 (3.4)	11 (2.1)	0 (0.0)	11 (3.4)	11 (2.4)	0 (0.0)
Administrative decision	3 (0.6)	2 (0.4)	0 (0.0)	7 (2.1)	2 (0.4)	0 (0.0)
Noncompliance	4 (0.9)	13 (2.5)	0 (0.0)	6 (1.8)	8 (1.7)	0 (0.0)
Disease progression	56 (11.9)	7 (1.3)	0 (0.0)	5 (1.5)	5 (1.1)	0 (0.0)
Death	8 (1.7)	50 (9.6)	0 (0.0)	2 (0.6)	36 (7.7)	0 (0.0)
Ineligibility determined	1 (0.2)	8 (1.5)	0 (0.0)	0 (0.0)	8 (1.7)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
[a] Subjects who discontinued treatment after receiving ≥ 2 doses of investigational product and were followed for ≥ 7 months after the last dose
[b] Subjects who discontinued treatment after receiving 1 dose of investigational product, or receiving ≥ 2 doses of investigational product and were followed for < 7 months after the last dose
[c] Subjects who completed 6 doses of investigational product
[d] Subjects who reported 'COMPLETED' investigational product on the CRF

Study 20030216 baseline characteristics and reasons for investigational product (IP) discontinuation in subjects who received at least 1 dose of IP and discontinued IP with and without follow-up are presented in Table 3 and Table 4, respectively.

No meaningful differences in age, prior vertebral fracture status, lumbar spine and total hip bone mineral density (BMD) T-scores, body mass index (BMI), serum C-telopeptide of type I collagen (CTX) and 25-hydroxy vitamin D concentrations, or 10-year probability of a hip fracture or a major osteoporotic fracture were observed between subjects who discontinued IP (with or without post-IP discontinuation follow-up) and subjects who completed the IP.

The same pattern of reasons for IP discontinuation was observed between subjects who discontinued IP with follow-up and those who discontinued IP without follow-up in both treatment groups (ie, placebo and denosumab). Within each treatment group, the percentage of subjects who discontinued IP due to an adverse event, subject request, requirement for an alternative therapy, and disease progression was numerically higher among those subjects who discontinued IP and remained on-study compared with those who discontinued IP and study participation. The percentage of subjects who discontinued IP due to withdrawal of consent, death, or ineligibility determined was numerically higher among those subjects who discontinued IP and remained on-study compared with those who discontinued IP and study participation. Furthermore, as expected, requirement for alternative therapy and disease progression as reasons for discontinuation were numerically higher among subjects who discontinued placebo (with post-IP discontinuation follow-up) compared with subjects who discontinued denosumab (with post-IP discontinuation follow-up). None of these small differences, however, are likely to affect the outcomes of the analyses.

Assessment of the MAH's response

Subjects who discontinued placebo-controlled study 20030216 were 1-2 years older (73-74 years) than subjects who completed the study (72 years).

Subjects who discontinued had also more baseline vertebral fractures and prior non-vertebral fractures as well as lower baseline total hip BMD score. Consequently, calculated 10-year probabilities of a major osteoporotic fracture/ hip fracture were lower in the subjects who completed the study compared to patients who discontinued.

There were no major differences in baseline lumbar spine BMD, BMI, sCTX or vitamin D.

The baseline characteristics of patients who discontinued vs those who continued in study 20030216 was very similar to the study 20060289.

Adverse events were the most common reason for discontinuation in patients with follow up after discontinuation (26-32%) whereas "consent withdrawn" was most common in patients without follow-up.

Of note, 12.8% in the placebo group discontinued due to requirement of alternative therapy vs. 7.3% in the denosumab group. Besides the underlying reasons for discontinuation such as concomitant other serious diseases, different therapeutic strategies after discontinuation may affect the fracture outcomes after discontinuation.

Conclusion:

Requested information provided. Issue resolved.

Question 4

The MAH is requested to calculate the fracture rates as well as exposure adjusted subject incidences during the placebo-controlled study 20030216 for patients in the placebo and denosumab arms: 1. for patients who completed study 20030216; 2. for patients who discontinued - while they still were on treatment; 3. for patients who discontinued - when they were off-treatment.

Response:

As most vertebral fractures are morphometric vertebral fractures, and their identification depends on scheduled spine x-rays without exact fracture date, vertebral fractures have always been analyzed as a subject incidence endpoint in pivotal fracture trials of osteoporosis medications, including Study 20030216. In order to enable comparisons between on- and off-treatment fracture incidences in subjects with varying follow-up time, both crude rate and exposure-adjusted subject incidences are reported.

Crude and exposure-adjusted vertebral fracture incidence rates for subjects who (1) completed the investigational product (IP), (2) discontinued IP with follow-up, or (3) discontinued IP without follow-up in the placebo and denosumab arms of Study 20030216 are presented in Table 5. These data show the following:

1. As expected, both crude and exposure-adjusted on-treatment subject incidence rates were higher in the placebo, as compared to the denosumab group, in subjects who completed the IP, those who discontinued IP with follow-up, and those who discontinued IP without follow-up.

2. Within each treatment group (ie, placebo or denosumab), both crude and exposure-adjusted subject incidence rates were higher among subjects who discontinued IP with follow-up compared to those who discontinued IP without follow-up.

3. As expected, exposure-adjusted off-treatment subject incidence rate of new vertebral fracture was higher compared to the on-treatment rate in the denosumab, but not the placebo treatment group.

4. The exposure-adjusted subject incidence rate of new vertebral fracture following placebo discontinuation was higher compared to the incidence rate following denosumab discontinuation.

Table 5. Study 20030216 Vertebral Fracture Summary by Treatment Completion Status

	Placebo (N = 3876)			Denosumab 60 mg Q6M (N = 3886)		
	Subjects who Discontinued IP With Follow-up[a] (N = 470)	Subjects who Discontinued IP Without Follow-up[b] (N = 520)	Subjects who Completed IP[c] (N = 2886)	Subjects who Discontinued IP With Follow-up[a] (N = 327)	Subjects who Discontinued IP Without Follow-up[b] (N = 466)	Subjects who Completed IP[c] (N = 3093)
On-treatment new vertebral fracture						
n (%)	58 (12.3)	27 (5.2)	158 (5.5)	18 (5.5)	9 (1.9)	45 (1.5)
Follow-up (subject-years)	832.46	715.68	8902.33	577.49	606.74	9537.51
Rate per 100 subject-years	7.0	3.8	1.8	3.1	1.5	0.5
(95% CI)	(5.2, 8.7)	(2.4, 5.1)	(1.5, 2.0)	(1.7, 4.6)	(0.5, 2.5)	(0.3, 0.6)
Off-treatment new vertebral fracture						
n (%)	29 (6.2)			15 (4.6)		
Follow-up (subject-years)	363.82			262.99		
Rate per 100 subject-years	8.0			5.7		
(95% CI)	(5.1, 10.9)			(2.8, 8.6)		

N = Number of subjects who received ≥ 1 dose of investigational product in Study 20030216
[a] Subjects who discontinued treatment after receiving ≥ 2 doses of investigational product and were followed for ≥ 7 months after the last dose
[b] Subjects who discontinued treatment after receiving 1 dose of investigational product, or receiving ≥ 2 doses of investigational product and were followed for < 7 months after the last dose
[c] Subjects who completed 6 doses of investigational product

Assessment of the MAH's response

Subjects who completed denosumab treatment had the lowest vertebral fracture incidences. Subjects who completed placebo treatment had significantly lower fracture incidences compared to subjects who discontinued placebo. The proportion discontinuing treatment was not proportional between placebo and denosumab groups among those with follow-up. The incidence rates above are therefore not directly comparable. In addition, the off-treatment new vertebral fracture subject incidences are not sufficiently precise to allow a conclusion that it is different in placebo or denosumab treated subjects after discontinuation.

The Applicant has not presented data on all vertebral fractures (fracture rates) in the study but only subject incidences. The scope of the variation was specifically multiple vertebral fractures, and the rate of all fractures after discontinuation (independently if they occurred in the same or different patients) should be presented. The data currently available does not justify a warning for increased MVF incidence after treatment discontinuation.

Conclusion

Issue not resolved.

Question 5

Similar calculations as in question 4 (fracture rates as well as exposure adjusted subject incidences) are requested for the extension study 20060289:

1. For patients who completed study 20060289; 2. for patients who discontinued – while they still were on treatment; 3. for patients who discontinued - when they were off treatment.

Response:

As most vertebral fractures are morphometric vertebral fractures, and their identification depends on scheduled spine x-rays without exact fracture date, vertebral fractures have always been analyzed as a subject incidence endpoint in pivotal fracture trials of osteoporosis medications, including Study 20060289.

Crude and exposure-adjusted vertebral fracture incidence rates for subjects who (1) completed the investigational product (IP), (2) discontinued IP with follow-up, or(3) discontinued IP without follow-up in the long-term and cross-over groups of Study 20060289 are presented in Table 6.

These data show the following:

1. As expected, the on-treatment crude vertebral fracture subject incidence rates were slightly higher among subjects who completed the study compared to those who discontinued IP (with or without follow-up) in both the long-term and cross-over groups, because the former subjects (who completed all 14 injections) were in the study longer than the latter.

2. Exposure-adjusted vertebral fracture subject incidence rates were similar across subjects who completed the IP, discontinued IP with follow-up, and discontinued IP without follow-up, in both the long-term and cross-over groups.

3. Finally, both crude and exposure-adjusted off-treatment vertebral fracture subject incidence rates were higher compared to the on-treatment incidence rates within each group, but similar between the long-term and cross-over groups.

Table 6. Study 20060289 Vertebral Fracture Summary by Treatment Completion Status

	Cross-over Denosumab (N = 2206)			Long-term Denosumab (N = 2343)		
	Subjects who Discontinued IP With Follow-up[a] (N = 318)	Subjects who Discontinued IP Without Follow-up[b] (N = 708)	Subjects who Completed IP[c] (N = 1180)	Subjects who Discontinued IP With Follow-up[a] (N = 360)	Subjects who Discontinued IP Without Follow-up[b] (N = 743)	Subjects who Completed IP[c] (N = 1240)
On-treatment new vertebral fracture						
n (%)	12 (3.8)	38 (5.4)	75 (6.4)	19 (5.3)	49 (6.6)	89 (7.2)
Follow-up (subject-years)	1182.39	2400.68	8364.61	2284.39	4862.76	12524.22
Rate per 100 subject-years	1.0	1.6	0.9	0.8	1.0	0.7
(95% CI)	(0.4, 1.6)	(1.1, 2.1)	(0.7, 1.1)	(0.5, 1.2)	(0.7, 1.3)	(0.6, 0.9)
Off-treatment new vertebral fracture						
n (%)	20 (6.3)			21 (5.8)		
Follow-up (subject-years)	227.01			297.77		
Rate per 100 subject-years	8.8			7.1		
(95% CI)	(4.8, 12.8)			(3.9, 10.2)		

N = Number of subjects who received ≥ 1 dose of denosumab in Study 20060289

On-treatment starts from the first dose of denosumab: at Study 20030289 baseline for cross-over denosumab subjects and at Study 20030216 baseline for long-term denosumab subjects.

[a] Subjects who discontinued treatment after receiving ≥ 2 doses of denosumab and were followed for ≥ 7 months after the last dose

[b] Subjects who discontinued treatment after receiving 1 dose of denosumab, or receiving ≥ 2 doses of denosumab and were followed for < 7 months after the last dose

[c] Subjects who completed 14 doses of denosumab

Assessment of the MAH's response

The Applicant has not presented data on all vertebral fractures (fracture rates) in the study as requested but only subject incidences. The scope of the variation was specifically multiple vertebral fractures, and the rate of all fractures after discontinuation (independently if they occurred in the same or different patients) should be presented before final conclusions.

In Table 6, the MAH has presented baseline data for the cross over group at time for cross over, but for the long-term denosumab group at start of the initial study; i.e. 3 years earlier. This was not the data presentation asked for, and these data are not readily comparable. This table should be updated and show the numbers of new vertebral fractures (on and off treatment) at baseline of study 20060289, as requested and indicated in the heading of the table (RSI).

Conclusion

Issue not resolved.

Question 6

The MAH is requested to present available data on fracture rates as well as exposure adjusted subject incidences for patients who completed study 20060289 and had follow-up thereafter, with or without treatment.

Response:

Study 20060289 completed in 2015 after up to 10 years of treatment with denosumab did not include further study subject follow-up after the trial ended. However, fracture data are available for a number of subjects who completed the study as a result of post-marketing safety reports and scientific publications, as follows:

• Post-marketing safety reports indicated that 11 women who completed Study 20060289 at 2 sites (#761 in Estonia and #791 in Latvia) sustained vertebral fracture following denosumab discontinuation. On 01 December 2016, the United States Food and Drug Administration (US FDA) requested additional information on the number of subjects who may have been at risk for vertebral fracture following denosumab discontinuation who were enrolled at the above 2 sites. There were 146 subjects at the 2 study sites (Site 761, Estonia, N = 125; Site 791, Latvia, N = 21) who completed the Month 84 visit of Study 20060289, 11 of whom experienced vertebral fracture after study completion. Amgen also provided additional information to further characterize this cohort of 146 subjects to describe their degree of skeletal fragility. The results of these analyses are included in the response to question (RTQ) submitted to the US FDA on 13 December 2016, which is attached.

• Two abstracts presented at the 2016 American Society for Bone and Mineral Research (ASBMR) Annual Meeting reported the results of a follow-up study conducted by 2 different Study 20060289 Investigators - 1 in Argentina and 1 in Switzerland:

o The Argentina Investigator aimed at describing the changes in bone mineral density and occurrence of fragility fractures in a group of 38 postmenopausal women with osteoporosis who had been enrolled in and completed Study 20060289 at that site. Among the 38 study participants, 17 women had received denosumab for 7 years, and 21 women for 10 years; none of the women had received bisphosphonate after denosumab discontinuation. Mean gap time between last denosumab dose in Study 20060289 and post-denosumab discontinuation follow-up was 17 ± 1 months (range: 16-20 months). The study showed that 4 subjects sustained a new vertebral fracture and 1 subject sustained a wrist fracture upon stopping treatment (Zanchetta et al, 2016;).

o In Switzerland, 9 study participants who had received 10 years of denosumab therapy were evaluated 1 year after trial completion. All women were reported to have experienced bone loss by dual-energy x-ray absorptiometry (DXA). No clinical fractures were reported, though 1 former study participant was noted to have a morphometric vertebral fracture by DXA (Popp et al, 2016;).

Assessment of the MAH's response

Study 20060289 was completed in 2015 and did not include further formal study subject follow-up after the trial ended. Results from a randomized withdrawal could have been informative. The scientific value of stimulated reports of fractures occurring after treatment is low as multiple fractures occur in this high risk population also without treatment and during treatment.

Issue not further pursued.

Question 7

The MAH claims that Prolia treatment cessation does increase risk of single vertebral fractures but only ≥ 2 vertebral fractures. The MAH should discuss any biologically plausible mechanism/rationale of this.

Response:

Amgen has performed multiple ad-hoc analyses from Studies 20030216 and 20060289 to investigate possible risk factors for the higher incidence of multiple, but not single, vertebral fracture following denosumab discontinuation.

Of note, the duration of follow-up was shorter for those subjects who sustained single vertebral fracture (median 0.65 years) compared with those who sustained multiple vertebral fracture (MVF) (median 1.67 years) in the extension Study 20060289, and it is possible that additional vertebral fracture events might have been observed in subjects with off-treatment single new vertebral fracture, had the follow-up period been longer.

No meaningful differences were detected between subjects who sustained only single off-treatment new vertebral fracture and those who sustained multiple off-treatment new vertebral fracture with respect to a number of potential risk factors, including number of denosumab doses received, age and bone mineral density (BMD) T-score at the beginning of the off-treatment period, serum C-telopeptide of type I collagen (CTX) at Study 20030216 baseline, or distribution or severity of off-treatment vertebral fracture.

Notably, among subjects with available total hip BMD data during the off-treatment period in Studies 20030216 and 20060289, mean annualized off-treatment BMD loss was greatest among subjects who sustained multiple off-treatment vertebral fracture and greater among those who sustained single off-treatment vertebral fracture compared with those with no off-treatment vertebral fracture (+0.6% and –1.9% after stopping placebo and denosumab, respectively, for those with no off-treatment vertebral fracture; -1.3% and -2.2% for those with single off-treatment vertebral fracture; and -1.2% and -3.5% for those with multiple off-treatment vertebral fracture).

Therefore, a larger and/or more rapid BMD loss after denosumab discontinuation may contribute to explain the higher risk of multiple, but not single, vertebral fracture following denosumab discontinuation, as compared to placebo discontinuation.

The mechanism for an increased risk of MVF following cessation of Prolia therapy is currently unknown.

In the osteoprotegerin (OPG) knockout mouse, where RANK/RANKL interaction permits osteoclast, formation, and survival, osteoporosis develops due to increased osteoclast activity in the absence of OPG. These mice develop spontaneous fractures early in life. The severity of osteoporosis in OPG knockout mice demonstrates that the skeleton is unable to compensate for the lack of endogenous OPG. This finding highlights the essential role for OPG in protecting bone (Bucay et al, 1998; Min et al, 2000).

This preclinical model may provide a surrogate for biological plausibility where cessation of denosumab permits RANK/RANKL activity for a transient period of time until the bone mechanostat resets activity to baseline level. The bone mechanostat concept suggests that skeletons, even those with low bone mass, appear to possess a bone mineral density “set point” that might be genetically determined (Frost, 1987). The bone mechanosensory concept hypothesizes that each individual has

a pre-set level of bone density and remodeling that is influenced by a variety of genetic and biomechanical stressors on the skeleton. Bone mass could not return to this set point from a higher level of bone mass without an increase in bone resorption above baseline. Consistent with this concept, discontinuation of denosumab treatment would be associated with increases in RANK/RANKL - and subsequent bone remodeling as measured by biochemical markers of bone turnover - to values above baseline that subsequently return to the skeleton's individual setpoint. With this transient increase in remodelling, bone loss would be expected to be more marked in cancellous than cortical bone, because the former has greater surface area over which bone resorption can take place. This is the reason why trabecular-rich regions, such as the spine, have higher incidence of fracture at times of rapid bone turnover. Therefore, the rapid BMD loss that occurs after denosumab discontinuation may contribute to a higher risk of vertebral compression fractures in susceptible subjects, such as those who have a history of fragility fracture.

Assessment of the MAH's response

There is no known mechanism for an increased risk of multiple but not single vertebral fractures following cessation of Prolia therapy.

Conclusion

Issue not further pursued. Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

Question 8

The MAH is asked to comment if any possible increased risk of vertebral fractures after Prolia discontinuation would depend on preceding treatment duration.

Response:

Amgen has performed multiple ad-hoc analyses from Studies 20030216 and 20060289 to investigate possible risk factors for off-treatment vertebral fracture. Multiple logistic regression models with stepwise selection procedure were used to identify possible determinants of off-treatment vertebral fracture risk, which also included Prolia treatment duration. Duration of Prolia treatment was not a significant determinant of either any (ie, single or multiple) or multiple off-treatment vertebral fracture.

Assessment of the MAH's response

According to Applicant, duration of Prolia treatment was not a significant determinant of either any (ie, single or multiple) or multiple off-treatment vertebral fracture. These analyses were not submitted by the MAH for assessment.

Conclusion

Issue not further pursued here. The table 2 in the RSI will inform about the off-treatment fractures in the cross-over and long-term denosumab groups.

6. Assessment of the responses to the 2nd request for supplementary information

Question 1

The MAH's claim for a label update concerns multiple vertebral fractures. The incidence of all fractures after discontinuation (independently if they occurred in the same or different patients) should be presented in the study 20030216 and 20060289, not only subject incidences, before final conclusions. This was not presented in the previous round as requested. In addition, in the previous round, a table that mixed data from study 20030216 was provided for the long-term denosumab group. The MAH should pay attention to what is asked for and present numbers for vertebral fractures for the long-term denosumab group in study 20060289 this time in the table 2 below, as indicated in the table heading.

The MAH is asked to fill in numbers to the three tables below, in order to clarify the available study data after discontinuations in the four different study population arms. 95% confidence intervals should be provided for the fracture incidence and subject incidence rates.

1. Table 1. Off-treatment Summary (Study 20030216 Off-treatment Subjects)

	Placebo (N = 470)	DMAb (N = 327)
Total number off-treatment new vertebral fractures - n		
Exposure adjusted fracture incidence during off-treatment – n /exp (r; 95% C)		
Subjects who fractured during off-treatment - n (%)		
New vertebral fracture		
Single new vertebral fracture		
Two new vertebral fractures		
Three new vertebral fractures		
Four or more new vertebral fractures		
Exposure-adjusted subject incidence during off-treatment - n / exp (r; 95% C)		
Osteoporotic fracture (clinical)		
New vertebral fracture		
Single new vertebral fracture		
Two new vertebral fractures		

	Placebo (N = 470)	DMAb (N = 327)
Three new vertebral fractures		
Four or more new vertebral fractures		
Age at discontinuation n (%)		
-60		
61-70		
71-80		
81-90		
91-		
Subjects with prevalent vertebral fracture before discontinuation n (%)		
Subjects with prevalent vertebral fracture before study start n (%)		

2. Table 2. Off-treatment Summary (20060289 Off-treatment Subjects)

	Cross over DMAb (N = 318)	Long-term DMAb (N = 360)
Total number off-treatment new vertebral fractures - n		
Exposure adjusted fracture incidence during off-treatment – n /exp (r; 95% CI)		
Subjects who fractured during off-treatment - n (%)		
New vertebral fracture		
Single new vertebral fracture		
Two new vertebral fractures		
Three new vertebral fractures		
Four or more new vertebral fractures		
Exposure-adjusted subject incidence during off-treatment - n / exp (r; 95% CI)		
Osteoporotic fracture		
New vertebral fracture		
Single new vertebral fracture		
Two new vertebral fractures		

	Cross over DMAb (N = 318)	Long-term DMAb (N = 360)
Three new vertebral fractures		
Four or more new vertebral fractures		
Age at discontinuation n (%)		
-60		
61-70		
71-80		
81-90		
91-		
Subjects with prevalent vertebral fracture before discontinuation n (%)		
Subjects with prevalent vertebral fracture before study start n (%)		

3. Table 3. Off-treatment Summary (Studies 20030216 and 20060289 Off-treatment Subjects)

	FREEDOM Placebo (N = 470)	Combined DMAb (N = 1001)
Total number off-treatment new vertebral fractures - n		
Exposure adjusted fracture incidence during off-treatment – n /exp (r; 95% CI)		
Subjects who fractured during off-treatment - n (%)		
New vertebral fracture		
Single new vertebral fracture		
Two new vertebral fractures		
Three new vertebral fractures		
Four or more new vertebral fractures		
Exposure-adjusted subject incidence during off-treatment - n / exp (r; 95% CI)		
Osteoporotic fracture		
New vertebral fracture		
Single new vertebral fracture		
Two new vertebral fractures		

	FREEDOM Placebo (N = 470)	Combined DMAb (N = 1001)
Three new vertebral fractures		
Four or more new vertebral fractures		
Age at discontinuation n (%)		
-60		
61-70		
71-80		
81-90		
91-		
Subjects with prevalent vertebral fracture before discontinuation n (%)		
Subjects with prevalent vertebral fracture before study start n (%)		

Response:

Table 1 provides an off-treatment summary of subjects included in Study 20030216 taking placebo or denosumab. Table 2 provides an off-treatment summary of subjects included in Study 20060289 in both the cross-over denosumab, and long-term denosumab treatment groups. Table 3 provides an off-treatment summary of subjects included in both Studies 20030216 and 20060289.

The analysis including subjects from both Study 20030216 and Study 20060289 (Table 3), combined to increase the sample size, shows that exposure-adjusted new vertebral fracture incidence during the off-treatment period is numerically higher among subjects who discontinued denosumab in Study 20030216 or Study 20060289 compared with those who discontinued placebo in Study 20030216 (17.5 versus 12.7 per 100 subject-years). Consistent with the analyses previously submitted, while the incidence of single off-treatment new vertebral fracture is numerically lower among subjects who discontinued denosumab compared with those who discontinued placebo (2.2% versus 4.0%), more subjects who discontinued denosumab sustained > 1 off-treatment new vertebral fracture, especially 4 or more new vertebral fractures, compared with those who discontinued placebo (Table 3). While there is no apparent imbalance in off-treatment new vertebral fracture incidence between subjects who discontinued denosumab and those who discontinued placebo in Study 20030216 (Table 1), it has to be taken into account that subjects in Study 20030216 were younger than in Study 20060289 and, as a result, their overall fracture risk was lower than in the extension study. In fact, the number of subjects sustaining > 1 new vertebral fracture after denosumab discontinuation increases from Study 20030216 (Table 1) to Study 20060289 (Table 2), thus supporting the results of the combined analysis (Table 3).

Assessment of the MAH's responses:

The MAH has provided tables as requested.

In study 20030216, rate of off-treatment new vertebral fractures was identical in the subjects who discontinued placebo and in the subjects that discontinued denosumab: 12.7 and 12.4 per 100 subject-years. There were no imbalances in patients who had two, three or four vertebral off-treatment fractures.

These groups had comparable baseline risk with regard to age and baseline risk.

In study 20060289, off-treatment new vertebral fractures rate was slightly higher in the subjects who discontinued long-term denosumab (21.9 per 100 subject-years) compared to the subjects that discontinued cross-over denosumab (17.1 per 100 subject-years). There number of patients who had two, three or four vertebral off-treatment fractures was low and there was no pattern that this would be more common in any group.

The rate of on-treatment vertebral fractures seems similar in long-term and cross-over groups.

Compared to study 20030216, the off-treatment new vertebral fractures rates as well as >2 vertebral fractures in study 20060289 were higher. This could at least partly be explained that the patients who discontinued study 20060289 were older. It is clear that any direct comparison that mixes off-treatment vertebral fracture data from these two studies is not valid.

Conclusion:

The Assessment report and conclusions have been updated accordingly.

Table 2. Off-treatment Summary
(Study 20030216 Off-treatment Subjects)

	Placebo (N = 470)	Denosumab 60 mg Q6M (N = 327)
Total number off-treatment new vertebral fractures - n	48	33
Exposure adjusted fracture incidence during off-treatment - n / exp (r) (95% CI)	48 / 378.12 (12.7) (9.6, 16.8)	33 / 266.67 (12.4) (8.8, 17.4)
Subjects who fractured during off-treatment - n (%)		
New vertebral fracture	29 (6.2%)	15 (4.6%)
Single new vertebral fracture	19 (4.0%)	7 (2.1%)
Two new vertebral fractures	6 (1.3%)	5 (1.5%)
Three new vertebral fractures	2 (0.4%)	1 (0.3%)
Four or more new vertebral fractures	2 (0.4%)	2 (0.6%)
Exposure-adjusted subject incidence during off treatment - n / exp (r) (95% CI)		
Osteoporotic fracture (clinical)	41 / 355.12 (11.5) (8.0, 15.1)	23 / 257.37 (8.9) (5.3, 12.6)
New vertebral fracture	29 / 363.82 (8.0) (5.1, 10.9)	15 / 262.99 (5.7) (2.8, 8.6)
Single new vertebral fracture	19 / 371.35 (5.1) (2.8, 7.4)	7 / 265.26 (2.6) (0.7, 4.6)
Two new vertebral fractures	6 / 373.73 (1.6) (0.3, 2.9)	5 / 264.45 (1.9) (0.2, 3.6)
Three new vertebral fractures	2 / 376.29 (0.5) (-0.2, 1.3)	1 / 266.67 (0.4) (-0.4, 1.1)
Four or more new vertebral fractures	2 / 376.82 (0.5) (-0.2, 1.3)	2 / 266.63 (0.8) (-0.3, 1.8)

N = Number of subjects who discontinued treatment after receiving 2 to 5 doses of investigational product and were followed for ≥ 7 months after the last dose in Study 20030216

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Table 1. Off-treatment Summary
(Study 20030216 Off-treatment Subjects)

	Placebo (N = 470)	Denosumab 60 mg Q6M (N = 327)
Age at discontinuation - n (%)		
61 - 70	82 (17.4%)	57 (17.4%)
71 - 80	318 (67.7%)	224 (68.5%)
81 - 90	70 (14.9%)	45 (13.8%)
≥ 91	0	1 (0.3%)
Subjects with prevalent vertebral fracture before discontinuation - n (%)	155 (33.0%)	98 (30.0%)
Subjects with prevalent vertebral fracture before study start - n (%)	122 (26.0%)	89 (27.2%)

N = Number of subjects who discontinued treatment after receiving 2 to 5 doses of investigational product and were followed for ≥ 7 months after the last dose in Study 20030216

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Table 3. Off-treatment Summary
(Study 20060289 Off-treatment Subjects)

	Placebo / Denosumab 60 mg Q6M (N = 318)	Denosumab / Denosumab 60 mg Q6M (N = 360)
Total number off-treatment new vertebral fractures - n	42	71
Exposure adjusted fracture incidence during off-treatment - n / exp (r) (95% CI)	42 / 246.09 (17.1) (12.6, 23.1)	71 / 324.63 (21.9) (17.3, 27.6)
Subjects who fractured during off-treatment - n (%)		
New vertebral fracture	20 (6.3%)	21 (5.8%)
Single new vertebral fracture	8 (2.5%)	7 (1.9%)
Two new vertebral fractures	8 (2.5%)	4 (1.1%)
Three new vertebral fractures	1 (0.3%)	2 (0.6%)
Four or more new vertebral fractures	3 (0.9%)	8 (2.2%)
Exposure-adjusted subject incidence during off treatment - n / exp (r) (95% CI)		
Osteoporotic fracture (clinical)	23 / 222.56 (10.3) (6.0, 14.7)	25 / 294.50 (8.5) (5.0, 12.0)
New vertebral fracture	20 / 227.01 (8.8) (4.8, 12.8)	21 / 297.77 (7.1) (3.9, 10.2)
Single new vertebral fracture	8 / 238.27 (3.4) (1.0, 5.7)	7 / 320.18 (2.2) (0.5, 3.8)
Two new vertebral fractures	8 / 235.00 (3.4) (1.0, 5.8)	4 / 324.58 (1.2) (0.0, 2.4)
Three new vertebral fractures	1 / 246.09 (0.4) (-0.4, 1.2)	2 / 320.49 (0.6) (-0.2, 1.5)
Four or more new vertebral fractures	3 / 245.93 (1.2) (-0.2, 2.6)	8 / 306.40 (2.6) (0.8, 4.5)

N = Number of subjects who discontinued treatment after receiving ≥ 2 doses of denosumab and were followed for ≥ 7 months after the last dose in Study 20060289

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Table 2. Off-treatment Summary
(Study 20060289 Off-treatment Subjects)

	Placebo / Denosumab 60 mg Q6M (N = 318)	Denosumab / Denosumab 60 mg Q6M (N = 360)
Age at discontinuation - n (%)		
61 - 70	15 (4.7%)	20 (5.6%)
71 - 80	166 (52.2%)	203 (56.4%)
81 - 90	129 (40.6%)	130 (36.1%)
≥ 91	8 (2.5%)	7 (1.9%)
Subjects with prevalent vertebral fracture before discontinuation - n (%)	92 (28.9%)	95 (26.4%)
Subjects with prevalent vertebral fracture before study start - n (%)	82 (25.8%)	84 (23.3%)

N = Number of subjects who discontinued treatment after receiving ≥ 2 doses of denosumab and were followed for ≥ 7 months after the last dose in Study 20060289

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Table 4. Off-treatment Summary
(Studies 20030216 and 20060289 Off-treatment Subjects)

	FREEDOM Placebo (N = 470)	Combined DMAb (N = 1001)
Total number off-treatment new vertebral fractures - n	48	146
Exposure adjusted fracture incidence during off-treatment - n / exp (r) (95% CI)	48 / 378.12 (12.7) (9.6, 16.8)	146 / 836.28 (17.5) (14.8, 20.5)
Subjects who fractured during off-treatment - n (%)		
New vertebral fracture	29 (6.2%)	56 (5.6%)
Single new vertebral fracture	19 (4.0%)	22 (2.2%)
Two new vertebral fractures	6 (1.3%)	17 (1.7%)
Three new vertebral fractures	2 (0.4%)	4 (0.4%)
Four or more new vertebral fractures	2 (0.4%)	13 (1.3%)
Exposure-adjusted subject incidence during off treatment - n / exp (r) (95% CI)		
Osteoporotic fracture (clinical)	41 / 355.12 (11.5) (8.0, 15.1)	71 / 773.32 (9.2) (7.0, 11.4)
New vertebral fracture	29 / 363.82 (8.0) (5.1, 10.9)	56 / 786.66 (7.1) (5.2, 9.0)
Single new vertebral fracture	19 / 371.35 (5.1) (2.8, 7.4)	22 / 822.60 (2.7) (1.6, 3.8)
Two new vertebral fractures	6 / 373.73 (1.6) (0.3, 2.9)	17 / 822.92 (2.1) (1.1, 3.1)
Three new vertebral fractures	2 / 376.29 (0.5) (-0.2, 1.3)	4 / 832.15 (0.5) (0.0, 1.0)
Four or more new vertebral fractures	2 / 376.82 (0.5) (-0.2, 1.3)	13 / 817.85 (1.6) (0.7, 2.5)

N = Number of subjects included in the Study 20030216 and Study 20060289 off-treatment analyses

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Table 3. Off-treatment Summary
(Studies 20030216 and 20060289 Off-treatment Subjects)

	FREEDOM Placebo (N = 470)	Combined DMAb (N = 1001)
Age at discontinuation - n (%)		
61 - 70	82 (17.4%)	90 (9.0%)
71 - 80	318 (67.7%)	591 (59.0%)
81 - 90	70 (14.9%)	304 (30.4%)
≥ 91	0	16 (1.6%)
Subjects with prevalent vertebral fracture before discontinuation - n (%)	155 (33.0%)	285 (28.5%)
Subjects with prevalent vertebral fracture before study start - n (%)	122 (26.0%)	255 (25.5%)

N = Number of subjects included in the Study 20030216 and Study 20060289 off-treatment analyses

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Question 2

Table 6 from the response should be updated and show the numbers of new vertebral fractures (on and off treatment) at baseline of study 20060289, as requested and indicated in the heading of the table.

Table 6. Study 20060289 Vertebral Fracture Summary by Treatment Completion Status

	Cross-over Denosumab (N = 2206)			Long-term Denosumab (N = 2343)		
	Subjects who Discontinued IP With Follow-up[a] (N = 318)	Subjects who Discontinued IP Without Follow-up[b] (N = 708)	Subjects who Completed IP[c] (N = 1180)	Subjects who Discontinued IP With Follow-up[a] (N = 360)	Subjects who Discontinued IP Without Follow-up[b] (N = 743)	Subjects who Completed IP[c] (N = 1240)
On-treatment new vertebral fracture						
Number of fractures	Xx	Xx	Xx	Xx	Xx	Xx
Follow-up (subject-years)	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx	xxx.xx
Rate per 100 subject-years	x.x	x.x	x.x	x.x	x.x	x.x
(95% CI)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)	(x.x, x.x)
Off-treatment new vertebral fracture						
Number of fractures	Xx			Xx		
Follow-up (subject-years)	xxx.xx			xxx.xx		
Rate per 100 subject-years	x.x			x.x		
(95% CI)	(x.x, x.x)			(x.x, x.x)		

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N = Number of subjects who received ≥ 1 dose of denosumab in Study 20060289
On-treatment starts from the first dose of denosumab at Study 20030289 baseline for cross-over and long-term denosumab subjects.-
[a] Subjects who discontinued treatment after receiving ≥ 2 doses of denosumab and were followed for ≥ 7 months after the last dose
[b] Subjects who discontinued treatment after receiving 1 dose of denosumab, or receiving ≥ 2 doses of denosumab and were followed for < 7 months after the last dose
[c] Subjects who completed 14 doses of denosumab

Response:

The table has been updated, consistent with the Agency's request (see Table 4).

Assessment of the MAH's responses:

The table has been updated as requested.

In study 20060289, off-treatment new vertebral fractures rate was slightly higher in the subjects who discontinued long-term denosumab (21.9 per 100 subject-years) compared to the subjects that discontinued cross-over denosumab (17.1 per 100 subject-years).

The rate of on-treatment vertebral fractures seems similar in long-term and cross-over groups.

Compared to study 20030216, the off-treatment new vertebral fractures rates in study 20060289 were higher. This could at least partly be explained that the patients who discontinued study 20060289 were older. It is clear that a comparison that mixes off-treatment vertebral fracture data from these two studies is not valid.

Conclusion:

The Assessment report and conclusions have been updated accordingly.

Table 5. Study 20060289 Number of Vertebral Fractures Summary by Treatment Completion Status

	Cross-over Denosumab (N = 2206)			Long-term Denosumab (N = 2343)		
	Subjects who Discontinued IP With Follow-up[a] (N = 318)	Subjects who Discontinued IP Without Follow-up[b] (N = 708)	Subjects who Completed IP[c] (N = 1180)	Subjects who Discontinued IP With Follow-up[a] (N = 360)	Subjects who Discontinued IP Without Follow-up[b] (N = 743)	Subjects who Completed IP[c] (N = 1240)
On-treatment new vertebral fractures						
Number of fractures	24	73	107	28	95	89
Follow-up (subject-years)	1196.28	2400.68	8364.61	1248.75	2623.36	8789.97
Rate per 100 subject-years	2.0	3.0	1.3	2.2	3.6	1.0
(95% CI)	(1.3, 3.0)	(2.4, 3.8)	(1.1, 1.5)	(1.5, 3.2)	(3.0, 4.4)	(0.8, 1.2)
Off-treatment new vertebral fractures						
Number of fractures	42			71		
Follow-up (subject-years)	246.09			324.63		
Rate per 100 subject-years	17.1			21.9		
(95% CI)	(12.6, 23.1)			(17.3, 27.6)		

N = Number of subjects who received ≥ 1 dose of denosumab in Study 20060289
On-treatment follow-up starts from the first dose of denosumab at Study 20060289 baseline for cross-over and long-term denosumab subjects.
Off-treatment follow-up starts from 7 months after the last dose in Study 20060289 through the end of the study.
[a] Subjects who discontinued treatment after receiving ≥ 2 doses of denosumab and were followed for ≥ 7 months after the last dose
[b] Subjects who discontinued treatment after receiving 1 dose of denosumab, or receiving ≥ 2 doses of denosumab and were followed for < 7 months after the last dose
[c] Subjects who completed 14 doses of denosumab

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Question 3

Table 5. "Study 20030216: Vertebral Fracture Summary by Treatment Completion Status" should be updated with number of fractures [instead of subjects with fractures n (%)] in line with updated table 6 above.

Response:

The table has been updated, consistent with the Agency's request (see Table 5).

Assessment of the MAH's responses:

The table has been updated as requested.

In study 20030216, rate of off-treatment new vertebral fractures was identical in the subjects who discontinued placebo and in the subjects that discontinued denosumab: 12.7 and 12.4 per 100 subject-years.

Conclusion:

The Assessment report and conclusions have been updated accordingly.

Table 6. Study 20030216 Number of Vertebral Fractures Summary by Treatment Completion Status

	Placebo (N = 3876)			Denosumab 60 mg Q6M (N = 3886)		
	Subjects who Discontinued IP With Follow-up[a] (N = 470)	Subjects who Discontinued IP Without Follow-up[b] (N = 520)	Subjects who Completed IP[c] (N = 2886)	Subjects who Discontinued IP With Follow-up[a] (N = 327)	Subjects who Discontinued IP Without Follow-up[b] (N = 466)	Subjects who Completed IP[c] (N = 3093)
On-treatment new vertebral fractures						
Number of fractures	81	30	203	19	14	64
Follow-up (subject-years)	867.86	715.68	8902.33	591.07	606.74	9537.51
Rate per 100 subject-years	9.3	4.2	2.3	3.2	2.3	0.7
(95% CI)	(7.5, 11.6)	(2.9, 6.0)	(2.0, 2.6)	(2.1, 5.0)	(1.4, 3.9)	(0.5, 0.9)
Off-treatment new vertebral fractures						
Number of fractures	48			33		
Follow-up (subject-years)	378.12			266.67		
Rate per 100 subject-years	12.7			12.4		
(95% CI)	(9.6, 16.8)			(8.8, 17.4)		

N = Number of subjects who received ≥ 1 dose of investigational product in Study 20030216
On-treatment follow-up starts from the first dose of investigational product at Study 20030216 baseline.
Off-treatment follow-up starts from 7 months after the last dose of investigational product in Study 20030216 through the end of the study.
[a] Subjects who discontinued treatment after receiving ≥ 2 doses of investigational product and were followed for ≥ 7 months after the last dose
[b] Subjects who discontinued treatment after receiving 1 dose of investigational product or receiving ≥ 2 doses of investigational product and were followed for < 7 months after the last dose
[c] Subjects who completed 6 doses of investigational product

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Question 4

Currently, the data does not support a conclusion that justifies a warning for increased MVF incidence following treatment discontinuation, see section 2. The Applicant should comment how they plan to communicate these conclusions in light of the contradictory information that they have previously circulated.

Response:

Amgen acknowledges that the identification of the new risk of multiple vertebral fracture (MVF) following discontinuation of Prolia treatment is based on data that are inherently limited: the original report is a case series with a subsequent expansion of cases (Lamy et al, 2017; Aubry-Rozier et al, 2016), the Amgen analyses are derived from ad hoc analyses of a completed clinical trial that was not prospectively designed to assess long-term off-treatment follow-up. The findings of the submitted analyses indicate that (1) discontinuation of Prolia treatment is associated with an increased risk for vertebral fracture, which rapidly returns to levels comparable to those observed in subjects who received placebo (Brown et al, 2016a), and (2) among subjects who sustained a new vertebral fracture after discontinuing denosumab, the incidence of multiple new vertebral fractures was higher than in subjects who discontinued placebo (Brown et al, 2016a).

Amgen has reached out to scientific experts from several regions to seek advice on the analyses. Furthermore, several of these scientific experts have worked independently on data analyses from Studies 20030216 and 20060289 to further characterise the risk; their findings and conclusions are reported in a manuscript submitted for publication and currently under review (Cummings et al, unpublished data, 2017). The advice and conclusions corroborated Amgen's point of view that MVF following Prolia discontinuation is a risk for patients, particularly in those with a history of vertebral fracture.

As a result, Amgen believes it is important to communicate this information to healthcare professionals (HCPs) to help ensure that prescribers have all available information to help inform management decisions in patients with osteoporosis at increased risk for fracture. Therefore, Amgen has updated Prolia's Core Data Sheet (CDS) to indicate that (1) just like the decision to initiate treatment, the decision to discontinue treatment should be made under a physician's supervision, and (2) transition to an alternative antiresorptive therapy should be considered for patients who discontinue treatment with Prolia. The latter (# 2) precaution for use is consistent with the recommendation provided by an independent medical advisor in the expert review contained in the analysis on the risk of MVF (Period Benefit-Risk Evaluation Report/Periodic Safety Update Report Number 10 Section 16.2.3.1) and in publications presented at multiple international scientific congresses (Brown et al, 2017; Ferrari et al, 2017; Brown et al, 2016a; Brown et al, 2016b).

Information on this risk and recommended mitigation strategy has entailed a comprehensive communication plan, which included:

- A Dear Investigator Letter (DIL), issued on 13 May 2016 to all investigators involved in ongoing clinical trials of denosumab to inform them of the newly identified risk and provide advice on mitigation strategies.

- Regional prescribing information updates, consistent with the updated Section 4.4 Special Warnings and Precautions for Use of Prolia's CDS version 18 (27 May 2016). Regions where this update is already approved include:

  - Australia (approved 11 October 2016)
  - Brazil (approved 26 October 2016)
  - Canada (approved 25 August 2016)
  - Japan (approved 20 April 2017)
  - New Zealand (approved 03 November 2016)
  - United States (approved 31 January 2017)

- Dear Health Care Professional (DHCP) communications, imposed in 1 region (Swissmedic) at the request of the local regulatory authorities.

- Scientific publications detailing the results of the ad hoc analyses conducted on the available data from subjects who discontinued investigational product (placebo or denosumab 60 mg subcutaneously every 6 months) from the 3-year FREEDOM trial or its 7-year Extension, which have been presented at international scientific congresses (Brown et al, 2017; Ferrari et al, 2017; Brown et al, 2016a; Brown et al, 2016b) and are summarized in a manuscript authored by independent scientific experts, currently submitted for publication.

Amgen believes that this comprehensive communication strategy will help enable fulfilment of its duty to inform HCPs and patients of this newly identified risk and ensure patients who discontinue Prolia are adequately assessed, followed up, and treated (as appropriate). Amgen will continue to monitor this important identified risk through routine pharmacovigilance as included in the Risk Management Plan.

Assessment of the MAH's responses:

The data does not support a conclusion that justifies a warning for increased MVF incidence following treatment discontinuation. The fact that these ad hoc analyses have been published does not change the fact that the rate of new vertebral fractures following discontinuation of Prolia and placebo were similar. The MAH seems not willing to communicate this information. Therefore, a detailed EPAR is important in order to communicate the outcome of the variation and the rationale of rejecting the proposed changes.

Conclusion:

The Assessment report and conclusions have been updated accordingly.