26 April 2018
EMA/CHMP/406583/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prolia

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/001120/II/0068

Note

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

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List of abbreviations

Abbreviation or Term	Definition/Explanation
ANCOVA	analysis of covariance
AUC_{last}	area under the curve from time zero to time of last quantifiable concentration
BMD	bone mineral density
BTM	bone turnover marker
CRF	case report form
C_{max}	maximum concentration
CRO	contract research organization
DMC	Data Monitoring Committee
DXA	dual X-ray absorptiometry
eCRF	electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
GC-C	glucocorticoid-continuing
GCP	Good Clinical Practice
GC-I	glucocorticoid-initiating
GIOP	glucocorticoid-induced osteoporosis
HR-pQCT	high-resolution peripheral quantitative computed tomography
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IU	international units
IVRS	interactive voice response system
ONJ	osteonecrosis of the jaw
PFS	prefilled syringe
P1NP	procollagen type 1 N-telopeptide
PFS	prefilled syringe
PK	pharmacokinetic(s)
Q6M	every 6 months
QD	once daily
RANKL	RANK ligand
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
sCTX	serum type 1 collagen C-telopeptide
t_{max}	time of maximum concentration
ULN	upper limit of normal

1. Background information on the procedure

1.1. 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 8 March 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk of fracture and prevention of osteoporosis in women and men at increased risk of fracture who are starting or have recently started long-term glucocorticoid therapy for Prolia; as a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The Risk Management Plan version 19.0 has also been updated.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0058/2016 on the granting of a (product-specific) waiver and on the agreement of a Paediatric Investigation Plan (PIP).

At the time of the submission of the application, the PIP P/0058/2016 was not yet completed, as certain measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	8 March 2017
Start of procedure:	25 March 2017
CHMP Co-Rapporteur Assessment Report	16 May 2017
CHMP Rapporteur Assessment Report	19 May 2017
PRAC Rapporteur Assessment Report	19 May 2017
PRAC Outcome	9 June 2017
CHMP members comments	12 June 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 June 2017
Request for supplementary information (RSI)	22 June 2017
CHMP Rapporteur Assessment Report	6 October 2017
PRAC Rapporteur Assessment Report	6 October 2017
PRAC Outcome	26 October 2017
CHMP members comments	30 October 2017
Updated CHMP Rapporteur Assessment Report	2 November 2017
Request for supplementary information (RSI)	9 November 2017
CHMP Rapporteur Assessment Report	27 March 2018
PRAC Rapporteur Assessment Report	27 March 2018
PRAC members comments	n/a
PRAC Outcome	12 April 2018
CHMP members comments	11 April 2018
Updated CHMP Rapporteur Assessment Report	19 April 2018
Opinion	26 April 2018

2. Scientific discussion

2.1. Introduction

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures. Primary osteoporosis is the more common form and is due to typical age-related loss of bone. Secondary osteoporosis results from the presence of other diseases or conditions that predispose to bone loss. The most common cause of secondary osteoporosis is GC use.

Pharmacologic therapies approved in many countries for the treatment of GIOP include teriparatide

(anabolic) and several bisphosphonate (antiresorptive) therapies, including alendronate (oral, once daily [QD]), risedronate (oral, QD), and zoledronic acid (intravenous, yearly)

Denosumab is approved under the trade name of Prolia® as a 60 mg/mL denosumab solution (dosing regimen 60 mg SC Q6M) for indications involving bone loss, including treatment of women with postmenopausal osteoporosis (PMO), men with osteoporosis, and bone loss due to hormone-ablative therapy (HALT) in men receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer.

2.2. Non-clinical aspects

2.2.1. Ecotoxicity / environmental risk assessment

Denosumab is a monoclonal antibody. According to the Guideline on the environmental risk assessment of medical products for human use, no environmental risk assessment is necessary for denosumab.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

GCP

The Clinical trial 20101217 was performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Glucocorticoid induced osteoporosis

The pivotal study, Study 20101217, is a phase 3, international, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study to compare the effects of denosumab 60 mg SC Q6M with those of oral risedronate 5 mg QD on lumbar spine BMD in 795 subjects (556 women and 239 men) at high risk for fracture treated with GC. Two subpopulations of subjects who received GC therapy were studied: the glucocorticoid-continuing subpopulation (GC-C; n = 505) and the glucocorticoid-initiating subpopulation (GC-I; n = 290). This application presents data from the 12-month primary analysis period of the study. Subjects will continue blinded treatment and be evaluated through month 24 for assessment of additional safety and efficacy endpoints.

As the population in Study 20101217 has received GC, their disease is considered to be in the category of secondary osteoporosis. Supportive data are provided from the first 12 months of 4 pivotal clinical studies performed to support other bone loss indications in the following 2 categories:

1. Primary osteoporosis

Study 20030216 performed in 7808 women with postmenopausal osteoporosis (PMO), which is the basis for bridging antifracture efficacy to the proposed indication for GIOP

Study 20080098 performed in 242 men with osteoporosis

2. Bone loss in subjects undergoing HALT

Study 20040138 performed in 1468 men with bone loss due to ADT for prostate cancer

Study 20040135 in 252 women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer

Efficacy in subjects with GIOP is established based on clinically significant positive results for BMD in Study 20101217 in combination with antifracture efficacy demonstrated in Study 20030216, along with additional supportive efficacy information from Studies 20040138, 20080098, and 20040135. Change from baseline in lumbar spine BMD has been previously accepted by regulatory authorities as the primary efficacy assessment in clinical trials for GIOP in men and women after antifracture efficacy has been established in women with PMO (Reid et al, 2009; Saag et al, 2007; Reid et al, 2000; Cohen et al, 1999; Saag et al, 1998).

In addition to the above mentioned studies the MAH has previously conducted study 20040144, a Randomized, Double-blind, Placebo-controlled, Multi-dose Phase 2 Study to Determine the Efficacy, Safety and Tolerability of Denosumab in the Treatment of Rheumatoid Arthritis. RA is not a labelled indication for denosumab. A total of 227 subjects were enrolled and randomized and 203 (89%) completed the 12-month treatment period, last visit occurred in 2007. Safety results from this study were reviewed during this procedure, no new safety signal was identified.

2.3.1. Pharmacokinetics

118 subjects were included in the pharmacokinetic analysis from study 20101217 (glucocorticoid-initiating (GC-I) 44 subjects; glucocorticoid-continuing (GC-C), 74 subjects). Following the first 60 mg SC dose of denosumab, denosumab exposures (maximum concentration [Cmax] and area under the curve from time zero to time of last quantifiable concentration [AUClast]) were similar in the GC-I and GC-C subpopulations, Table 1. Further, the exposure in study 20101217 was consistent with that observed previously without concomitant glucocorticoids, Table 2.

Table 1

Descriptive Statistics of Denosumab Pharmacokinetic Parameter Estimates (12-month Primary Analysis)

Cohort	Descriptive Statistics	t_{max} (day)	C_{max} (µg/mL)	AUC_{last} (day•µg/mL)	$t_{1/2}$ (day)
GC-C	N	74	74	74	30
	Mean (SD)	NR	6.13 (2.88)	314 (192)	17.4 (7.36)
	Median (min, max)	9.9 (6.8, 98)	5.96 (0.557, 12.2)	306 (14.0, 767)	14.4 (9.41, 43.7)
	CV%	NR	47.1	61.1	42.3
GC-I	N	44	44	44	23
	Mean (SD)	NR	6.01 (2.04)	344 (182)	17.6 (4.95)
	Median (min, max)	9.9 (6.8, 91)	5.71 (1.42, 10.6)	325 (27.7, 983)	17.3 (11.2, 29.2)
	CV%	NR	34.0	52.8	28.1
Combined cohorts	N	118	118	118	53
	Mean (SD)	NR	6.08 (2.59)	325 (188)	17.5 (6.37)
	Median (min, max)	9.9 (6.8, 98)	5.90 (0.557, 12.2)	314 (14.0, 983)	15.4 (9.41, 43.7)
	CV%	NR	42.6	57.8	36.4

AUC_{last} = AUC from time zero to time of last quantifiable concentration; C_{max} = maximum concentration; CV% = percent coefficient of variation; GC-C = glucocorticoid-continuing population; GC-I = glucocorticoid-initiating population; NR = not reported; $t_{1/2}$ = terminal half-life; t_{max} = time of C_{max}

Table 2 Comparison of median Tmax, Cmax and t1/2.

Population	Tmax	Cmax	T1/2
Study 20101217 combined cohorts	9,9 days (7-98)	5,9 µg/ml (1-12)	15 days (9-44)
Previously reported	10 days (2-28)	6 µg/ml (1-17)	26 days (6-52)

The PK for denosumab looks similar in the GC-I and GC-C subpopulations in study 20101217. Also, the PK of denosumab appears similar for the combined cohort from study 20101217 to previosly reported pharmacokinetics for subjects without glucocorticoid as cocomitant medication.

Additional pharmacokinetic data was reported at the end of study. Majority of the data (98/106 samples) were collected at early termination, unscheduled time points or at 24 months and are therefore not anticipated to impact the month 12 primary analysis results. The serum denosumab C_{trough} concentrations at month 24 were consistent with those reported at month 12 (table 3 and table 4).

Table 3. Denosumab C_{trough} after SC 60 mg Q6M for Glucocorticoid Continuing patients

GC-C patients	Month 12	Month 24
N	57	48
Mean	0,029	0,023
SD	0,089	0,094
Min	0	0
Median	0	0
Max	0,56	0,64
CV%	303	403

LLOQ 20 ng/mL (values below LOQ set to 0)

Table 4. Denosumab C_{trough} after SC 60 mg Q6M for Glucocorticoid Initiating patients

GC-I patients	Month 12	Month 24
N	38	32
Mean	0,057	0,80
SD	0,18	0,19
Min	0	0
Median	0	0
Max	1,07	1,04
CV%	320	240

LLOQ 20 ng/mL (values below LOQ set to 0)

The applicants conclusion that the additional data is not anticipated to impact the 12 month primary analysis results is accepted since only 8 of the 106 new samples could impact the primary analysis.

Many of the C_{trough} samples are below LOQ and were set to 0. The median C_{trough} for 12 and 24 months both for GC-C and GC-I subjects was thus 0. Overall the Ctrough at 12 and 24 months for both GC-C and GC-I subject appear similar.

2.4. Clinical efficacy

2.4.1. Main study (study 20101217)

Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy and Safety of Denosumab Compared With Risedronate in Glucocorticoid-treated Individuals.

This active-controlled, double-blind, double-dummy study compares the effects of denosumab (60 mg every 6 months) and risedronate (5 mg once daily) treatment on glucocorticoid-induced osteoporosis in

(a) subjects initiating glucocorticoid treatment and (b) subjects continuing glucocorticoid treatment. The submitted clinical study report summarizes the 12-month primary analysis (Data cutoff date: 29 June 2016.) Subjects will continue to receive treatment for a further 12 months.

Methods

Study participants

Key inclusion criteria were:

- men and women ⩾ 18 years of age who were receiving prednisone ⩾ 7.5 mg daily or its equivalent and were expected to be treated with oral glucocorticoids for a total of at least 6 months
- at least 2 lumbar vertebrae and 1 hip had to be evaluable by DXA
- Subjects < 50 years of age at the time of screening were required to have a history of osteoporotic fracture.

Subjects who had initiated administration of prednisone within 3 months or ⩾ 3 months before screening were part of the GC-I subpopulation or GC-C subpopulation, respectively.

In the GC-C subpopulation, subjects who were ⩾ 50 years of age at screening were required to have a BMD value equivalent to a T-score ⩽ -2.0 at the lumbar spine, total hip, or femoral neck; or a BMD value equivalent to a T-score ⩽ -1.0 at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture.

Subjects excluded from the study included those who had received other osteoporosis or bone-active treatment, certain hormone-derived treatments, or certain biologic agents within defined time limits.

Other exclusion criteria:

Subject has an active infection or history of infections as follows:

- any active infection for which systemic anti-infectives were used within 4 weeks prior to screening
- a serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to screening
- recurrent or chronic infections or other active infection that, in the opinion of the investigator, might compromise the safety of the subject.

Evidence of any of the following:

- History of hyperthyroidism (stable on antithyroid therapy is allowed), History of hypothyroidism (stable on thyroid replacement therapy is allowed),
- History of hypo- or hyperparathyroidism
- History of Addison disease
- History of osteomalacia
- History of osteonecrosis of the jaw
- History of tooth extraction or other dental surgery within the prior 6 months
- Invasive dental work planned in the next 2 years
- Significantly impaired renal function as determined by a derived glomerular filtration rate (GFR) using Cockcroft-Gault formula of ⩽ 30 mL/min/1.73 m2 calculated by the central laboratory

It is noted that the exclusion criteria are more extensive than the SmPC in force at time of this application. For example, there are no warnings regarding infections in the EU SmPC.

Corticosteroids are a risk factor for ONJ. Patients with a history of tooth extraction or other dental surgery within the prior 6 months or invasive dental work planned in the next 2 years were excluded from the current study.

Treatments, Randomisation, Blinding

Subjects were randomized in a 1:1 ratio in a double-blind manner to receive double-dummy investigational product consisting either of SC injection of denosumab 60 mg every 6 months and oral placebo for risedronate or oral risedronate 5mg daily and SC injection of placebo for denosumab. An interactive voice response system was used. Randomization was stratified by sex within each subpopulation. Enrollment of men was restricted to between 30% and 40% within each subpopulation.

To maintain the blind, a double-dummy procedure was used: subjects randomized to receive SC denosumab injections also received oral placebo capsules for risedronate and subjects randomized to receive oral risedronate capsules also received SC placebo injections.

Placebo for denosumab was presented in identical containers and stored/packaged the in the same way as denosumab. Placebo for risedronate was presented in identical containers and stored/packaged in the same way as risedronate.

No dosage adjustments were permitted. Denosumab and denosumab placebo were injected by study center staff. Subjects were instructed to bring back the remaining capsules at the next visit for assessment of treatment compliance (total capsules taken = capsules dispensed – capsules returned).

All subjects are required to take daily supplements of at least 1000 mg elemental calcium and at least 800 IU vitamin D during the study. If a subject should become hypercalcaemic over the course of the study, the calcium and/or vitamin D supplementation may be discontinued until the serum calcium concentration has returned to the normal range.

Objectives

Outcomes / endpoints

Efficacy Endpoints

Endpoint	
Bone mineral density	
Percent change from baseline in lumbar spine BMD by DXA at 12 months (noninferiority)	Primary[a,b]
Percent change from baseline in lumbar spine BMD by DXA at 12 months	Secondary[a,b]
Percent change from baseline in total hip BMD by DXA at 12 months	Secondary[a,b]
Percent change from baseline in lumbar spine BMD by DXA at 24 months[c]	Secondary[a,b]
Percent change from baseline in total hip BMD by DXA at 24 months[c]	Secondary[a,b]
Percent change from baseline in femoral neck, trochanter, and 1/3 radius BMD by DXA at 12 and 24 months[c]	Exploratory[a]
Percent change from baseline in lumbar spine BMD by DXA at 6 and 18 months[c]	Exploratory[a]
Bone turnover markers	
Percent change from baseline in P1NP and sCTX at day 10 and at months 3, 4, 5, 6, 12, and 24[c,d]	Exploratory[e]
Fractures	
Subject incidence of clinical fractures and new vertebral fractures at 12 and 24 months[c]	Exploratory[e]
Bone quality	
Bone histology and histomorphometry parameters at 12 or 24 months[c,d]	Exploratory[e]
Percent change from baseline in distal radius and distal tibia parameters using HR-pQCT at 12 and 24 months[f]	Exploratory[e]
Subject preference and satisfaction	
PSQ at 12 and 24 months[c]	Exploratory[e]
Denosumab PK	
Serum denosumab concentrations at baseline, day 10, and month 3, 4, 5, 6, 12, and 24[c,d]	Exploratory[e]

BMD = bone mineral density; DXA = dual X-ray absorptiometry; HR-pQCT = high resolution peripheral quantitative computed tomography; P1NP = procollagen type 1 N-telopeptide; PK = pharmacokinetics; PSQ = Preference and Satisfaction Questionnaire; sCTX = serum C-telopeptide of type 1 collagen.
[a] Evaluated in each of the subpopulations separately.
[b] Part of fixed-sequence testing procedure to control the experiment-wise type 1 error rate within each subpopulation.
[c] This report includes results from data collected through month 12 (primary analysis period). Results for months 18 and 24 will be documented in a future report.
[d] Part of a substudy; not assessed for all subjects.
[e] Evaluated in the combined subpopulations.
[f] This report does not include 12-month data for HR pQCT because, per the statistical analysis plan for Study 20101217, HR pQCT parameters will only be analyzed at month 24. This change from the protocol-specified analyses was made based on advice from experts in the field of HR pQCT to assure consistency of the data for each subject over the course of the study.

Safety Endpoints

Safety endpoints evaluated in the combined subpopulations included the following:

- incidence of adverse events
- incidence of serious adverse events
- incidence of laboratory Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3
- incidence of antidenosumab antibodies
- vital signs

Sample size

The planned total sample size was 776 subjects with 248 per group in the GC-C subpopulation and 140 per group in the GC-I subpopulation.

The non-inferiority margins chosen for percent change from baseline in lumbar spine BMD at 12 months were based on results from two placebo-controlled studies with risedronate in the GIOP patient populations and the study with zoledronic acid in a similar population and risedronate as the active comparator (Cohen et al, 1999; Reid et al, 2000; Reid et al, 2009). Non-inferiority margins of -1.1 percentage points and -0.7 percentage points, representing a 50% preservation of the risedronate effect observed from these two studies were considered clinically relevant for the GC-I subpopulation and GC-C subpopulation, respectively.

Table 5 Sample Size Assumptions for Primary Endpoint Evaluation

Parameter	Glucocorticoid-continuing	Glucocorticoid initiating
NI margin ($\mu_{denosumab} - \mu_{risedronate}$) [percentage points]	-0.7	-1.1
Denosumab advantage (percentage points)	1.06	1.56
Standard deviation (percentage points)	3.4	3.4
Dropout (annual)	15%	15%
Number of subjects per group including dropouts	248	140
Power for achieving non-inferiority	> 99%	> 99%

In addition, each subpopulation was to have approximately at least a 90% power to detect a difference in

percent change in BMD by DXA at lumbar spine and total hip between the treatment groups (denosumab – risedronate) at month 12 (Table 6).

Table 6 Power Assumptions for Secondary Endpoints Evaluated at Month 12

	Subpopulation			
	Glucocorticoid-continuing N per group= 248 Dropout = 15%		Glucocorticoid-initiating N per group = 140 Dropout =15%	
	Lumbar Spine	Total Hip	Lumbar Spine	Total Hip
Denosumab advantage* (percentage points)	1.06	0.99	1.56	1.20
Standard deviation (percentage points)	3.4	2.5	3.4	2.5
Power for achieving superiority	89	98	94	95

* Denosumab advantage is based on the lower bound of a one-sided 80% confidence interval derived from the treatment differences observed between zoledronic acid and risedronate (Reid at el, 2009).

A larger NI margin was chosen for treatment with denosumab among patients initiating glucocorticoid therapy compared to those continuing. This is assumed to be explained by that a larger effect in the former subpopulation was expected and since both NI margins were chosen based on an idea of 50% preservation of risedronate efficacy against placebo and zoledronic acid versus risedronate/placebo as seen in earlier studies.

Statistical methods

The primary analysis was planned to occur after all subjects had had the opportunity to complete the 12-month study visit, the study was however to continue for another 12 months of blinded treatment, and there was no plan to allow stopping the trial due to efficacy or futility based on the 12-month analysis results.

Analyses of the primary and secondary efficacy endpoints and testing procedures were performed separately within the glucocorticoid-continuing and glucocorticoid-initiating subpopulations. The experiment-wise Type I error rate was controlled at a 5% significance level within each subpopulation using a fixed sequence testing procedure among the primary and secondary efficacy endpoints in the order presented below:

1. Primary efficacy endpoint: Lumbar spine BMD at month 12 (non-inferiority)
2. Secondary efficacy endpoint: Lumbar spine BMD at month 12
3. Secondary efficacy endpoint: Total hip BMD at month 12
4. Secondary efficacy endpoint: Lumbar spine BMD at month 24
5. Secondary efficacy endpoint: Total hip BMD at month 24

Endpoints not included in this testing procedure were to be considered exploratory.

The primary efficacy set included all randomised subjects who had a baseline measure and a post-baseline measure at the time point of interest. The per-protocol set included a subset of subjects from the Primary Efficacy Set who had minimum exposure to IP and did not significantly violate the inclusion/exclusion criteria nor significantly deviate from the protocol through month 12. Results based on the per-protocol subset set were to be used as a sensitivity analysis for the primary non-inferiority hypotheses.

For the primary and secondary endpoints, the DXA percent change from baseline at month 12 for each

skeletal site measured were analysed within the two subpopulations using an analysis of covariance (ANCOVA) model with main effects for treatment, sex, baseline BMD, machine type, and interaction effect for baseline BMD and machine type for each subpopulation, and addition of duration of prior glucocorticoid use (< 12 months versus ≥ 12 months) for GC-C subpopulation only.

Only subjects with observed BMD data at baseline and at the post-baseline time point of interest will be included in the primary analysis. Least-squares mean point estimates of the percent change from baseline for each arm were to be presented together with a two-sided 95% confidence interval and the associated p-value. A confidence interval will be constructed for the treatment contrast (denosumab - risedronate), and the lower bound were compared to the non-inferiority margin of the primary efficacy endpoint for the non-inferiority test within each subpopulation.

The following sensitivity analyses were to be provided for percent change from baseline at month 12 lumbar spine BMD (non-inferiority); the primary analysis was to be repeated using the per-protocol analysis set and the lumbar spine BMD percent changes from baseline at each time point analysed using a repeated measures model separately within each subpopulation.

The primary endpoint was also to be evaluated in glucocorticoid-continuing subjects who had a BMD value equivalent to a T-score ≤ -2.0 at the lumbar spine, total hip, or femoral neck; or a BMD value equivalent to a T-score ≤ -1.0 at the lumbar spine, total hip, or femoral neck and with a history of osteoporotic fracture using the same ANCOVA model as in the primary analysis.

Regarding exploratory endpoints, percent change from baseline in femoral neck, trochanter, and 1/3 radius BMD by DXA were to be analysed using the same methods as for secondary efficacy endpoints. For percent change from baseline in BTM a Wilcoxon rank sum test was to be used. Bone histology and histomorphometry and pharmacokinetic endpoints were to be analysed using descriptive statistics.

Subject incidence of new vertebral fractures was to be summarized over 12 and 24 months in combined glucocorticoid-continuing and glucocorticoid-initiating subpopulations. Subject incidence of clinical fractures in both subpopulations combined was also to be summarized over 12 and 24 months using Kaplan-Meier methodology. For the clinical fracture endpoint, the full analysis set (FAS) including all subjects randomised was used. For the new vertebral fracture endpoint the analysis set was to include all randomised subjects who had a baseline and ≥ 1 post baseline evaluation of vertebral fracture at or before the time point under consideration. Subjects in this analysis set were to be analysed according to their original treatment assignment, regardless of treatment received.

Within each treatment group, analyses of the proportions of patient preference and long term preference between the 6-month injection and daily pill were to be performed in which subjects with no preference and missing data were to be removed from the analysis.

All safety analyses were based on the subpopulations combined. The safety analysis set included all randomised subjects who received at least 1 dose of IP with subjects to be analysed according to their actual treatment received.

Before any analyses for this study report were conducted, the protocol-defined statistical analyses were detailed in the statistical analysis plan (SAP), which was amended once prior to the 12-month primary analysis. Version 1 of the SAP was dated 30 September 2011 and version 2 was dated 04 August 2016. The SAP was amended to match the Protocol Amendment 4 dated 30 June 2016 and to clarify which analyses were to be performed during the upcoming 12-month primary analysis (database snapshot planned on August 17, 2016) and final analysis for this study.

The study had two separate experimental aims; to assess denosumab efficacy in two different subpopulations, hence with main analyses to be performed separately for each subpopulation. The type I error rate was to be controlled at a 5% significance level within each subpopulation separately using a

fixed sequence testing procedure among primary and secondary endpoints. The multiplicity adjustment used implied that the study could be considered successful if the primary objective was met in either of the two subpopulations. This is acceptable with regard to that the study was planned with e.g. two separate primary objectives to support two new indications but should require that the two subpopulations can be considered to be mutually exclusive (i.e. that there is no overlap between them).

The primary and secondary endpoints, DXA percent change from baseline at month 12 for each skeletal site measured, were analysed using an analysis of covariance (ANCOVA) model. While the main effects for treatment, gender and baseline BMD is endorsed, main effect for e.g. machine type and the interaction effect for baseline BMD and machine type is not evidently. Although, importantly, the primary model was pre-specified (both in the study protocol and the SAP), no justification for including each of the covariates was found and was therefore requested. In their response the MAH justified the choice of primary analysis model including machine type and the interaction term by the different scales of baseline BMD between the two proprietary technologies (Lunar and Hologic machines) which is accepted. In addition, to investigate the robustness of the primary analysis, additional analyses were required based on an ANCOVA model with main effects for treatment, gender and baseline BMD. They had been provided during the procedure and show very similar outcomes hereby supporting the robustness of the primary analysis.

In the analysis of primary and secondary endpoints only subjects with observed BMD data at baseline and at the post-baseline time point of interest were included and hence no imputation if data missing were performed.

Given the definition of the primary efficacy set it corresponded to a completer analysis set. In addition to the primary efficacy set, a PP set was defined to be used for additional analyses of the primary endpoint. Considering the definition of the former and that the PP was to comprise a subset of the primary efficacy set, the difference between them tended to be small having an impact on the significance of the PP analysis as a measure of robustness. In a non-inferiority trial, the full analysis set and the per protocol analysis set should have equal importance and needs to provide consistent results. A Full Analysis Set was pre-defined but was not intended to be used for any analysis of the primary endpoint. Here, where not only non-inferiority but superiority has been shown an analysis based on the FAS is considered of (even more) importance.

No new amendments have been made to the statistical analysis plan. Hence the SAP submitted with the CSR for the 24-month final analysis is version 2 (dated 04 August 2016) that at the time had been revised to clarify which analyses were to be performed during the upcoming 12-month primary analysis (database snapshot planned on August 17, 2016) and final analysis for this study.

For the 24-month final analyses, two of the efficacy endpoints, lumbar spine BMD at month 24 and total hip BMD at month 24, were defined among the secondary endpoints included in the fixed sequence testing procedure used to control the Type I error rate at a 5% significance level (however separately for each subpopulation).

Results

Participant flow

Within the GC-I subpopulation, the study discontinuation rate was somewhat higher in the denosumab group (15.9%) than in the risedronate group (9.7%), which was related to a higher rate of withdrawal of consent in the denosumab group.

The applicant was asked to provide data on the progression of osteoporosis in these patients who discontinued. The Applicant considered that discontinuation rates compare with those reported in most

pivotal clinical trials of osteoporosis medications in GC-I osteoporosis, but has not provided an adequate explanation why there was such a significant difference in the discontinuation rate for the glucocorticoid-initiating population between denosumab (15.9%) and risedronate groups (9.7%).

According to the Applicant no information past study discontinuation is available and thus no data on the progression of osteoporosis in these patients has been provided. Issue was not further pursued as there appear to be no relevant data available.

Table 9-5. Subject Disposition, Glucocorticoid-initiating Subpopulation (Full Analysis Set) (12-month Primary Analysis)

	Risedronate 5 mg QD (N = 145) n (%)	Denosumab 60 mg Q6M (N = 145) n (%)
Subjects who completed first 12 months of study	131 (90.3)	122 (84.1)
Subjects who discontinued prior to first 12 months of study	14 (9.7)	23 (15.9)
Consent withdrawn	8 (5.5)	13 (9.0)
Adverse event	4 (2.8)	5 (3.4)
Administrative decision	1 (0.7)	1 (0.7)
Lost to follow-up	1 (0.7)	1 (0.7)
Death	0	1 (0.7)
Protocol deviation	0	1 (0.7)
Noncompliance	0	1 (0.7)

N = Number of subjects randomized; QD = once daily; Q6M = every 6 months
Source: Table 14-1.3.1

Table 9-5/2. Subject Disposition, Glucocorticoid-initiating Subpopulation (24 month Final analysis)

	Risedronate 5 mg QD (N = 145) n (%)	Denosumab 60 mg Q6M (N = 145) n (%)
Study completion accounting		
Completed study	117 (80.7)	109 (75.2)
Discontinued study	28 (19.3)	36 (24.8)
Consent withdrawn	15 (10.3)	20 (13.8)
Adverse event	7 (4.8)	7 (4.8)
Lost to follow-up	1 (0.7)	3 (2.1)
Death	3 (2.1)	2 (1.4)
Noncompliance	1 (0.7)	2 (1.4)
Administrative decision	1 (0.7)	1 (0.7)
Protocol deviation	0 (0.0)	1 (0.7)

N = Number of subjects randomized; QD = once daily; Q6M = every 6 months
Percentages based on number of subjects randomized

Within the GC-C subpopulation, the study discontinuation rate during the 12-month primary analysis period was more similar in the denosumab (14.2%) and risedronate (12.3%) groups. The rate of study discontinuations due to adverse events was also similar (denosumab 3.6%, risedronate 3.2%).

Table 9-6. Subject Disposition, Glucocorticoid-continuing Subpopulation (Full Analysis Set) (12-month Primary Analysis)

	Risedronate 5 mg QD (N = 252) n (%)	Denosumab 60 mg Q6M (N = 253) n (%)
Subjects who completed first 12 months of study	221 (87.7)	217 (85.8)
Subjects who discontinued prior to first 12 months of study	31 (12.3)	36 (14.2)
Consent withdrawn	12 (4.8)	19 (7.5)
Adverse event	8 (3.2)	9 (3.6)
Death	4 (1.6)	3 (1.2)
Lost to follow-up	4 (1.6)	2 (0.8)
Noncompliance	0	2 (0.8)
Protocol deviation	0	1 (0.4)
Other	2 (0.8)	0
Ineligibility determined	1 (0.4)	0

N = Number of subjects randomized; QD = once daily; Q6M = every 6 months.
Source: Table 14-1.3.2

Table 9-6/2. Subject Disposition, Glucocorticoid-continuing Subpopulation (24 month Final Analysis)

	Risedronate 5 mg QD (N = 252) n (%)	Denosumab 60 mg Q6M (N = 253) n (%)
Study completion accounting		
Completed study	178 (70.6)	186 (73.5)
Discontinued study	74 (29.4)	67 (26.5)
Consent withdrawn	34 (13.5)	34 (13.4)
Adverse event	9 (3.6)	12 (4.7)
Death	8 (3.2)	9 (3.6)
Lost to follow-up	13 (5.2)	5 (2.0)
Noncompliance	4 (1.6)	3 (1.2)
Other	4 (1.6)	2 (0.8)
Requirement for alternative therapy	1 (0.4)	1 (0.4)
Protocol deviation	0 (0.0)	1 (0.4)
Administrative decision	1 (0.4)	0 (0.0)

N = Number of subjects randomized; QD = once daily; Q6M = every 6 months
Percentages based on number of subjects randomized

Recruitment

This study was conducted at 79 centers in Europe, North America, Latin America, and Korea. The study initiation date was 28 March 2012 (first subject enrolled). The study is currently ongoing and treatment remains blinded. The data cutoff date for the 12-month Primary Analysis was 29 June 2016.

Conduct of the study

The study protocol was amended 4 times; major changes are documented in Table 8-10.

Table 8-10. Summary of Protocol Amendments

Amendment	Major Changes
Original Protocol 25 July 2011 (3 subjects enrolled)	Not applicable
Superseding version 06 December 2011 (18 subjects enrolled)	• Exploratory objectives clarified: HR-pQCT data to be collected in a subset of subjects only, and PK/BTM samples are only to be collected in subjects participating in the PK/BTM substudy • Added statement that subjects in the transiliac bone biopsy substudy are to receive tetracycline or tetracycline derivative prior to the bone biopsy procedure
Amendment 1 15 February 2012 (167 subjects enrolled)	• Entry criteria clarified: – Subjects less than 50 years old and without an osteoporotic fracture will not be eligible to enroll. – Subjects initiating biologics within 4 weeks prior to screening will not be eligible to enroll; however, administration of biologic medications will not be proscribed during the study – Subjects with a history of infection immediately prior to screening will not be eligible to enroll.
Amendment 2 29 June 2012 (127 subjects enrolled)	• Entry criteria clarified: – GC-C subjects ≥ 50 years of are required to have a BMD value equivalent to a T-score ≤ -2.0 at the lumbar spine, total hip, or femoral neck; or a BMD value equivalent to a T-score ≤ -1.0 at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture. – Subjects administering > 1 biologic agent for the treatment of underlying inflammatory disease to be excluded – Subjects with a history of Addison's disease to be excluded – Clarified the existing exclusion criterion of recent tooth extraction or dental surgery • Secondary objectives were separated with respect to lumbar spine and total hip. • Information on choice of noninferiority margins was updated. • Clarified that safety analyses would be done in the combined subpopulations • Added information regarding a DRT • Added criteria for permanent withholding of denosumab and risedronate due to serious infection • Added urine dipstick pregnancy tests at Day 10 and months 6, 12, and 18, and clarified that any female subject who becomes pregnant should permanently discontinue investigational product

Amendment	Major Changes
Amendment 3 22 February 2013 (480 subjects enrolled)	• Incorporated updated procedures of reporting adverse events and serious adverse events to IRB/IECs and regulatory authorities • Replaced the DRT with a DMC for ongoing monitoring of study data • Clarified that the noninferiority comparison will only be performed for the primary efficacy endpoint within each subpopulation
Amendment 4 30 June 2016 (0 subjects enrolled)	• Bone biopsy assessment added at 24 months for the bone biopsy substudy to bring the number of evaluable specimens closer to the protocol-indicated number (due to difficulties in recruitment to the substudy and some collected specimens being unevaluable) • Noted that analysis of HR-pQCT data will be performed at the end of the study (month 24) • Updated safety language

BMD = bone mineral density; BTM = bone turnover markers; DMC = Data Monitoring Committee; DRT = Data Review Team; GC-C = glucocorticoid-continuing; HR-pQCT = high-resolution peripheral quantitative computed tomography; IEC = independent ethics committee; IRB = investigational review board; PK = pharmacokinetic(s).

According to table 8-10 (above) it seemed as if the wrong number of enrolled subjects had been given at the time for amendment 1 and/or 2 (167 and 127 respectively). The dates were also considered to be somewhat confusing and the MAH was requested to clarify. The MAH explained that Table 8-10 showed the number of subjects who initially consented and enrolled under each specific protocol version over time and not the total number of subjects enrolled in the study on the date that a new protocol version was issued.

With amendment 3 it was clarified that the NI comparison was to be performed for the primary efficacy endpoint only within each subpopulation.

Baseline data

Table. Demographic Characteristics, Overall Study Population (Full Analysis Set)

	Risedronate 5 mg QD (N = 397)	Denosumab 60 mg Q6M (N = 398)
Sex, n (%)		
Men	119 (30.0)	120 (30.2)
Women	278 (70.0)	278 (69.8)
Ethnicity, n (%)		
Hispanic/Latino	72 (18.1)	63 (15.8)
Not Hispanic/Latino	325 (81.9)	335 (84.2)
Race, n (%)		
White	346 (87.2)	352 (88.4)
Other	22 (5.5)	25 (6.3)
Asian	21 (5.3)	15 (3.8)
Black or African-American	6 (1.5)	6 (1.5)
American Indian or Alaska Native	1 (0.3)	0
Multiple	1 (0.3)	0
Age (years)		
Mean (SD)	62.5 (10.8)	63.7 (11.4)
Median (minimum, maximum)	62 (28, 94)	64 (20, 90)
Age group, n (%)		
< 50 years	31 (7.8)	35 (8.8)
50 to 64 years	205 (51.6)	169 (42.5)
65 to 74 years	100 (25.2)	123 (30.9)
≥ 75 years	61 (15.4)	71 (17.8)
Geographic region, n (%)		
Europe	263 (66.2)	268 (67.3)
North American	51 (12.8)	61 (15.3)
Latin America	64 (16.1)	55 (13.8)
Asia	19 (4.8)	14 (3.5)

N = number of subjects randomized; QD = once daily; Q6M = every 6 months; SD = standard deviation.
Source: Table 14-2.10

Table. Baseline Characteristics, Glucocorticoid-initiating Subpopulation

	Risedronate 5 mg QD (N = 145)	Denosumab 60 mg Q6M (N = 145)
BMI (kg/m^2)		
Mean (SD)	27.73 (5.16)	27.50 (5.23)
Median (minimum, maximum)	26.98 (18.8, 46.7)	26.29 (17.5, 43.8)
Menopausal status (women only), n (%)		
Premenopause	7 (7.5)	10 (10.8)
Postmenopause	83 (89.2)	82 (88.2)
Unknown	3 (3.2)	1 (1.1)
Baseline daily oral prednisone-equivalent dose (mg)		
n	145	143
Mean (SD)	15.61 (10.25)	16.57 (13.01)
Median (minimum, maximum)	12.50 (7.5, 60.0)	12.50 (7.5, 70.0)
Duration of prior oral glucocorticoid use with ≥ 7.5 mg daily prednisone equivalent dose level, n (%)		
0 to < 3 months	129 (89.0)	133 (91.7)
≥ 3 months	16 (11.0)	10 (6.9)
3 to < 12 months	8 (5.5)	7 (4.8)
≥ 12 months	8 (5.5)	3 (2.1)
Missing	0	2 (1.4)
Secondary osteoporosis, n (%)		
Yes	20 (13.8)	9 (6.2)
No	125 (86.2)	136 (93.8)
Prevalent vertebral fracture, n (%)		
Yes	26 (17.9)	21 (14.5)
No	91 (62.8)	86 (59.3)
Unknown	12 (8.3)	13 (9.0)
Missing	16 (11.0)	25 (17.2)
Prior osteoporotic fracture,[a] n (%)		
Yes	51 (35.2)	49 (33.8)
No	94 (64.8)	96 (66.2)
10-year probability of major osteoporotic fracture calculated with BMD		
n	144	142
Mean (SD)	13.229 (8.312)	14.711 (10.923)
Median (minimum, maximum)	11.270 (2.34, 41.70)	11.510 (1.70, 65.53)
Lumbar spine BMD T-score		
n	143	144
Mean (SD)	-1.06 (1.57)	-0.92 (1.86)
Median (minimum, maximum)	-1.15 (-4.2, 3.4)	-1.08 (-5.9, 4.9)

BMD = bone mineral density; BMI = body mass index; N = number of subjects randomized; QD = once daily; Q6M = every 6 months; SD = standard deviation.

[a] Since age 18.

Table. Baseline Characteristics, Glucocorticoid-continuing Subpopulation

	Risedronate 5 mg QD (N = 252)	Denosumab 60 mg Q6M (N = 253)
BMI (kg/m^2)		
Mean (SD)	27.58 (5.86)	27.23 (5.14)
Median (minimum, maximum)	26.60 (16.3, 49.2)	26.59 (15.8, 45.3)
Menopausal status (women only), n (%)		
Premenopause	25 (13.5)	24 (13.0)
Postmenopause	157 (84.9)	159 (85.9)
Unknown	3 (1.6)	2 (1.1)
Baseline daily oral prednisone-equivalent dose (mg)		
n	252	252
Mean (SD)	11.13 (7.69)	12.29 (8.09)
Median (minimum, maximum)	10.00 (0.0, 100.0)	10.00 (7.5, 80.0)
Duration of prior oral glucocorticoid use with ≥ 7.5 mg daily prednisone equivalent dose level, n (%)		
0 to < 3 months	8 (3.2)	13 (5.1)
≥ 3 months	242 (96.0)	239 (94.5)
3 to < 12 months	75 (29.8)	81 (32.0)
≥ 12 months	167 (66.3)	158 (62.5)
Missing	2 (0.8)	1 (0.4)
Secondary osteoporosis, n (%)		
Yes	94 (37.3)	94 (37.2)
No	158 (62.7)	159 (62.8)
Prevalent vertebral fracture, n (%)		
Yes	80 (31.7)	67 (26.5)
No	121 (48.0)	137 (54.2)
Unknown	13 (5.2)	12 (4.7)
Missing	38 (15.1)	37 (14.6)
Prior osteoporotic fracture,[a] n (%)		
Yes	134 (53.2)	136 (53.8)
No	118 (46.8)	117 (46.2)
10-year probability of major osteoporotic fracture calculated with BMD		
n	250	249
Mean (SD)	17.063 (11.249)	17.655 (12.672)
Median (minimum, maximum)	14.020 (1.24, 53.55)	14.530 (2.55, 86.96)
Lumbar spine BMD T-score		
n	252	248
Mean (SD)	-1.96 (1.38)	-1.92 (1.39)
Median (minimum, maximum)	-2.20 (-5.7, 2.9)	-2.15 (-5.2, 3.1)

BMD = bone mineral density; BMI = body mass index; N = number of subjects randomized; QD = once daily; Q6M = every 6 months; SD = standard deviation.

[a] Since age 18

Table. Prior Medical Conditions Requiring Glucocorticoid Use Reported in ≥ 1% of Subjects in Either Treatment Group by Indication Preferred Term **Glucocorticoid-initiating Subpopulation**

MedDRA Indication Preferred Term	Risedronate 5 mg QD (N = 145) n (%)	Denosumab 60 mg Q6M (N = 145) n (%)
Polymyalgia rheumatica	52 (35.9)	50 (34.5)
Rheumatoid arthritis	43 (29.7)	48 (33.1)
Arthritis	9 (6.2)	11 (7.6)
Temporal arteritis	5 (3.4)	7 (4.8)
Asthma	2 (1.4)	3 (2.1)
Osteoarthritis	4 (2.8)	3 (2.1)
Polyarthritis	2 (1.4)	2 (1.4)
Systemic lupus erythematosus	4 (2.8)	2 (1.4)
Eosinophilic pneumonia	0 (0.0)	2 (1.4)
Interstitial lung disease	0 (0.0)	2 (1.4)
Arthralgia	1 (0.7)	2 (1.4)
Pemphigus	0 (0.0)	2 (1.4)
Autoimmune hepatitis	0 (0.0)	2 (1.4)
Myalgia	0 (0.0)	2 (1.4)
Ankylosing spondylitis	2 (1.4)	1 (0.7)
Granulomatosis with polyangiitis	3 (2.1)	0 (0.0)
Alveolitis allergic	2 (1.4)	0 (0.0)

MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified; QD = once daily; Q6M = every 6 months

Table. Prior Medical Conditions Requiring Glucocorticoid Use Reported in ≥ 1% of Subjects in Either Treatment Group by Indication Preferred Term **Glucocorticoid-continuing Subpopulation.**

MedDRA Indication Preferred Term	Risedronate 5 mg QD (N = 252) n (%)	Denosumab 60 mg Q6M (N = 253) n (%)
Rheumatoid arthritis	118 (46.8)	96 (37.9)
Polymyalgia rheumatica	18 (7.1)	20 (7.9)
Asthma	14 (5.6)	19 (7.5)
Systemic lupus erythematosus	16 (6.3)	15 (5.9)
Pulmonary fibrosis	3 (1.2)	7 (2.8)
Multiple sclerosis	9 (3.6)	7 (2.8)
Chronic obstructive pulmonary disease	4 (1.6)	6 (2.4)
Polymyositis	3 (1.2)	6 (2.4)
Interstitial lung disease	4 (1.6)	5 (2.0)
Temporal arteritis	3 (1.2)	5 (2.0)
Vasculitis	1 (0.4)	4 (1.6)
Sarcoidosis	5 (2.0)	4 (1.6)
Systemic sclerosis	0	3 (1.2)
Colitis ulcerative	2 (0.8)	3 (1.2)
Psoriatic arthropathy	4 (1.6)	3 (1.2)
Autoimmune hepatitis	1 (0.4)	3 (1.2)
Autoimmune haemolytic anaemia	0 (0.0)	3 (1.2)
Arthritis	3 (1.2)	2 (0.8)
Myalgia	3 (1.2)	2 (0.8)
Sjogren's syndrome	3 (1.2)	1 (0.4)
Myasthenia gravis	3 (1.2)	1 (0.4)
Crohn's disease	3 (1.2)	0 (0.0)

MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects randomized; QD = once daily; Q6M = every 6 months.

Table. Duration of Glucocorticoid Medications Use Between Baseline and 12 Months (Full Analysis Set in Combined Subpopulation) (20101217 12-month Primary Analysis)

	Risedronate 5 mg QD (N = 397)	Denosumab 60 mg Q6M (N = 398)	Overall (N = 795)
Duration of glucocorticoid medications use (days)			
n	397	397	794
Mean	334.0	325.3	329.7
SD	97.3	102.2	99.8
Median	366.0	365.0	366.0
Q1, Q3	358.0, 372.0	358.0, 370.0	358.0, 371.0
Min, Max	1, 768	6, 470	1, 768
Duration of glucocorticoid medications use - n (%)			
0 to < 3 months	23 (5.8)	32 (8.0)	55 (6.9)
≥ 3 months	374 (94.2)	365 (91.7)	739 (93.0)
3 to < 12 months	168 (42.3)	172 (43.2)	340 (42.8)
≥ 12 months	206 (51.9)	193 (48.5)	399 (50.2)
Missing	0 (0.0)	1 (0.3)	1 (0.1)

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N = Number of subjects randomized
Percentages based on number of subjects randomized

Numbers analysed

In the denosumab group, the full analysis set (N = 398) includes 5 subjects who were randomised to denosumab but did not receive any denosumab injections, and the safety analysis set (N = 394) includes 1 subject who was randomised to risedronate but received denosumab instead (Table below). In the risedronate group, the full analysis set (N = 397) includes 12 subjects who were randomised to risedronate but were not confirmed to have received any doses of investigational product; these 12 subjects and 1 subject who received denosumab erroneously were not included in the safety analysis set (N = 384).

Table. Number of Subjects by Analysis Set (12-month Primary Analysis)

	Risedronate 5 mg QD n	Denosumab 60 mg Q6M n
Full analysis set		
GC-I subpopulation	145	145
GC-C subpopulation	252	253
Total	397	398
Primary efficacy analysis set[a]		
GC-I subpopulation	126	119
GC-C subpopulation	211	209
Per protocol analysis set[b]		
GC-I subpopulation	108	101
GC-C subpopulation	173	177
Efficacy analysis set for new vertebral fracture endpoint	342	333
Safety analysis set[c]	384	394
Bone biopsy subset	13	8
PK/BTM subset	130	140

BTM = bone turnover markers; GC-C = glucocorticoid-continuing; GC-I = glucocorticoid-initiating; n = number of subjects in the analysis set of interest; Q6M = every 6 months; QD = once daily; PK = pharmacokinetics.

[a] Primary efficacy analysis set for primary endpoint.

[b] Per protocol analysis set for primary endpoint.

[c] Based on actual treatment received. One subject was randomized to risedronate but received denosumab in error; this subject was included in the denosumab group.

To be included in the primary analysis set a subject was required to have endpoint data month 12. Seemingly, not all who completed the first 12 months of the study had an evaluation/DXA at month 12.

In the GC-I subpopulation, the primary efficacy set included 82.1% (119/145) and 86.9% (126/145) of randomized subjects in the denosumab and risedronate treatment arm respectively. The corresponding PP set comprised 69.7% (101/145) of randomised subjects in the denosumab arm and 74.5% (108/145) of randomised subjects in the risedronate arm.

In the GC-C subpopulation, the primary efficacy set included 82.6% (209/253) and 83.7% (211/252) of randomized subjects in the denosumab and risedronate treatment arm respectively. The corresponding PP set comprised 70.0% (177/253) of randomised subjects in the denosumab arm and 68.7% (173/252) of randomised subjects in the risedronate arm.

This implies that in all analyses presented, a non-negligible proportion of randomised subjects were excluded; across subpopulations 13-18% in primary analyses and approximately 25-30% in analyses based on the PP set. No analyses of the primary or (key) secondary efficacy endpoints were planned or have been performed based on the Full Analysis set (including all randomised).

The vast majority (>90%) of the patients in the study were treated with GC for >6 months. Overall, 44% continued GC at month 24.

Most of the patients who discontinued GC treatment continued with the IP treatment. In contrast, antiresorptive treatment for GIOP is discontinued when GC treatment is discontinued in clinical practice. The increase in bone resorption in GIOP occurs early and is transient, which would implicate that the need of antiresorptive therapy is also limited in time. It is difficult to draw any conclusions regarding optimal treatment duration from the current study design. This needs to be based on individual patients BMD and other risk factors for fracture.

Table 9-4 Number of Subjects by Analysis Set (20101217 24-month Final Analysis)

	Risedronate 5 mg QD n	Denosumab 60 mg Q6M n	Overall n
Full analysis set			
GC-I subpopulation	145	145	290
GC-C subpopulation	252	253	505
Total	397	398	795
Primary efficacy analysis set[a]			
Lumbar spine			
GC-I subpopulation	113	107	220
GC-C subpopulation	174	183	357
Total hip			
GC-I subpopulation	111	104	215
GC-C subpopulation	176	181	357
Efficacy analysis set for new vertebral fracture endpoint	346	338	684
Safety analysis set[b]	385	394	779
Bone biopsy subset	13	11	24
PK/BTM subset	129	140	269
XtremeCT – GC-I subpopulation	24	32	56
XtremeCT – GC-C subpopulation	30	25	55

BTM = bone turnover markers; GC-C = glucocorticoid-continuing; GC-I = glucocorticoid-initiating; n = number of subjects in the analysis set of interest; Q6M = every 6 months; QD = once daily; PK = pharmacokinetics; XtremeCT = Xtreme computed tomography.
a Primary efficacy analysis set for secondary endpoints.
b Based on actual treatment received. One subject was randomized to risedronate but received denosumab in error; this subject was included in the denosumab group. Two additional deaths were reported in subjects randomized to risedronate (pneumonia bacterial and polymyositis). These subjects were not included in the safety analysis set, because it was not possible to confirm that they had taken at least 1 dose of oral investigational product. The 2 subjects died prior to their month-6 visit and oral investigational product accountability verification.

The primary efficacy set included all randomised subjects who had a baseline measure and a post-baseline measure at the time point of interest.

Analyses month 24 (analogous the primary analysis month 12) were hence based on observed data implying the exclusion of a rather high proportion of randomised subjects in each treatment arm in both the GC-I and the GC-C subpopulation.

In the GC-I subpopulation, the primary efficacy set (lumbar spine) included 73.8%% (107/145) and 77.9% (113/145) of randomised subjects in the denosumab and risedronate treatment arm respectively.

In the GC-C subpopulation, the primary efficacy set (lumbar spine) included 72.3% (183/253) and 69.0% (174/252) of randomised subjects in the denosumab and risedronate treatment arm respectively.

Outcomes and estimation

Primary Efficacy Analysis:

Table. Percent Change From Baseline in Lumbar Spine Bone Mineral Density at Month 12 (ANCOVA Model, *Non-inferiority*) (Primary Efficacy Analysis Set, Observed Data) (12-month Primary Analysis)

	Risedronate 5 mg QD	Denosumab 60 mg Q6M	Difference From Risedronate
GC-I subpopulation	(N = 133)	(N = 128)	
n	126	119	
LS mean (95% CI)[a,b]	0.8 (0.2, 1.5)	3.8 (3.1, 4.5)	2.9 (2.0, 3.9)
p-value (noninferiority)[c]			< 0.001
GC-C subpopulation	(N = 230)	(N = 228)	
n	211	209	
LS mean (95% CI)[a,b]	2.3 (1.7, 2.9)	4.4 (3.8, 5.0)	2.2 (1.4, 3.0)
p-value (noninferiority)[c]			< 0.001

ANCOVA = analysis of covariance; BMD = bone mineral density; CI = confidence interval; GC-C = glucocorticoid-continuing; GC-I = glucocorticoid-initiating; LS = least squares; N = number of subjects randomized with a baseline measurement and at least one postbaseline measurement for the lumbar spine BMD; n = number of subjects with observed values; QD = once daily; Q6M = every 6 months.

[a] Based on ANCOVA model adjusting for treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction. The duration of prior glucocorticoid use (< 12 months versus ≥ 12 months) was also added for the GC-C subpopulation only in the GC-I subpopulation and -0.7% for lumbar spine in the GC-C subpopulation.

[b] Two-sided confidence interval.

[c] One-sided p-value based on the prespecified noninferiority margins for lumbar spine of -1.1% in the GC-I subpopulation and -0.7% in the GC-C subpopulation.

Table. Primary Efficacy Analyses of Secondary Endpoints: Percent Change From Baseline in the Lumbar Spine and Total Hip Bone Mineral Density at Month 12 (Primary Efficacy Analysis Set, Observed Data, 12-month Primary Analysis)

	Risedronate 5 mg QD	Denosumab 60 mg Q6M	Difference From Risedronate
GC-I subpopulation	(N = 135)	(N = 128)	
Lumbar spine			
n	126	119	
Estimate (95% CI)[a]	0.8 (0.2, 1.5)	3.8 (3.1, 4.5)	2.9 (2.0, 3.9)
p-value			< 0.001
Total hip			
n	128	119	
Estimate (95% CI)[a]	0.2 (-0.2, 0.7)	1.7 (1.2, 2.2)	1.5 (0.8, 2.1)
p-value			< 0.001
GC-C subpopulation	(N = 230)	(N = 229)	
Lumbar spine			
n	211	209	
Estimate (95% CI)[a]	2.3 (1.7, 2.9)	4.4 (3.8, 5.0)	2.2 (1.4, 3.0)
p-value			< 0.001
Total hip			
n	215	217	
Estimate (95% CI)[a]	0.6 (0.2, 1.0)	2.1 (1.7, 2.5)	1.5 (1.0, 2.1)
p-value			< 0.001

CI = confidence interval; n = number of subjects with observed values; GC-C = glucocorticoid-continuing; GC-I = glucocorticoid-initiating; N = number of subjects randomized with a baseline measurement and at least one postbaseline measurement for the lumbar spine or total hip BMD; QD = once daily; Q6M = every 6 months.

[a] Based on ANCOVA model adjusting for treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction; additionally includes duration of prior glucocorticoid use (< 12 months versus ≥ 12 months) for GC-C subpopulation. Includes subjects with observed percent change data (both baseline and month 12 BMD).

Subgroups were explored for the percent change from baseline in lumbar spine BMD at month 12 separately within each subpopulation. Each analysis was performed by subpopulation (GC-I and GC-C). The subgroup results consistently demonstrated a greater increase in BMD at the lumbar spine at month 12 in the denosumab group compared with the risedronate group. A significant quantitative interaction was observed only in the analysis by sex (men versus women) in the GC-I subpopulation (1.2% for men and 3.7% for women).

However, non-significant qualitative interaction testing indicated that there was no evidence that the direction of the denosumab effect differed by gender in the GC-I subpopulation.

With both treatments, the BMD increased both in GC-I and GC-C populations. For the denosumab treated patients, the mean baseline T-score at lumbar spine was -1.92 for the GC-C Subpopulation and -0.92 for the GC-I Subpopulation. At 12 month (applying the results from table above), the lumbar spine T-scores

would end up to approximately -1.64 for the GC-C Subpopulation and -0.63 for the GC-I Subpopulation. This means that the majority of GC-I Subpopulation had normal T-score at 12 months.

It seems that denosumab increases the T-score irrespectively of the baseline values. The clinical benefits of increasing BMD in patients with T-score at normal range in GIOP was discussed further at the ad-hoc expert meeting, see section "additional expert advice" in the efficacy discussion.

In the analyses of the primary endpoint, not only non-inferiority but superiority was shown for denosumab versus risedronate and in each subpopulation. Analyses had however only been performed on the primary analysis set corresponding to a completers set and a PP analysis set comprising a subset of the primary efficacy set. Since superiority has been shown, the PP analyses are of lesser value. Instead, analyses based on the Full Analysis Set (all randomised) were requested to confirm the conclusions of denosumab being superior to risedronate. In these analyses, missing data should not be ignored but handled using methods that could be considered conservative in analyses with the aim to show superiority. Several analyses were welcomed using different methods and, in at least one analysis, missing data were to be handled as treatment failures. The analyses were to be performed for each subpopulation separately.

Secondary endpoints aimed at superiority and have also been shown. Analogous requested additional analyses of the primary endpoint, analyses based on FAS were requested also for the secondary endpoint; percent change from baseline in Total Hip BMD at month 12 (separately for each subpopulation).

In response to the analyses as requested above, the MAH performed two different sensitivity analyses of the percent change from baseline in lumbar spine BMD and total hip BMD respectively separately in the GC-I and GC-C subpopulations; one based on a baseline-observation-carried-forward imputation approach, according to the MAH, corresponding to "treatment failure" and, one based on a multiple imputation approach *within* each treatment group. Whilst the former implies more conservative estimates the latter is based on an assumption of missing at random in that subjects with missing data is assumed to perform as those within the same treatment group who completed/had data month 12.

Considering the claim that denosumab is superior to risedronate, estimates of treatment efficacy and the difference between the treatments should be from an analysis based on all randomised according to the intention-to-treat principle; here FAS. Although the use of BOCF implies a decreased variability and it may be discussed whether baseline-observation-carried-forward really implies treatment failure in the prevention setting, it is considered to offer a more conservative analysis approach than the one used in the primary analysis based on observed data excluding those with missing data month 12.

Secondary endpoints assessed at 24 months

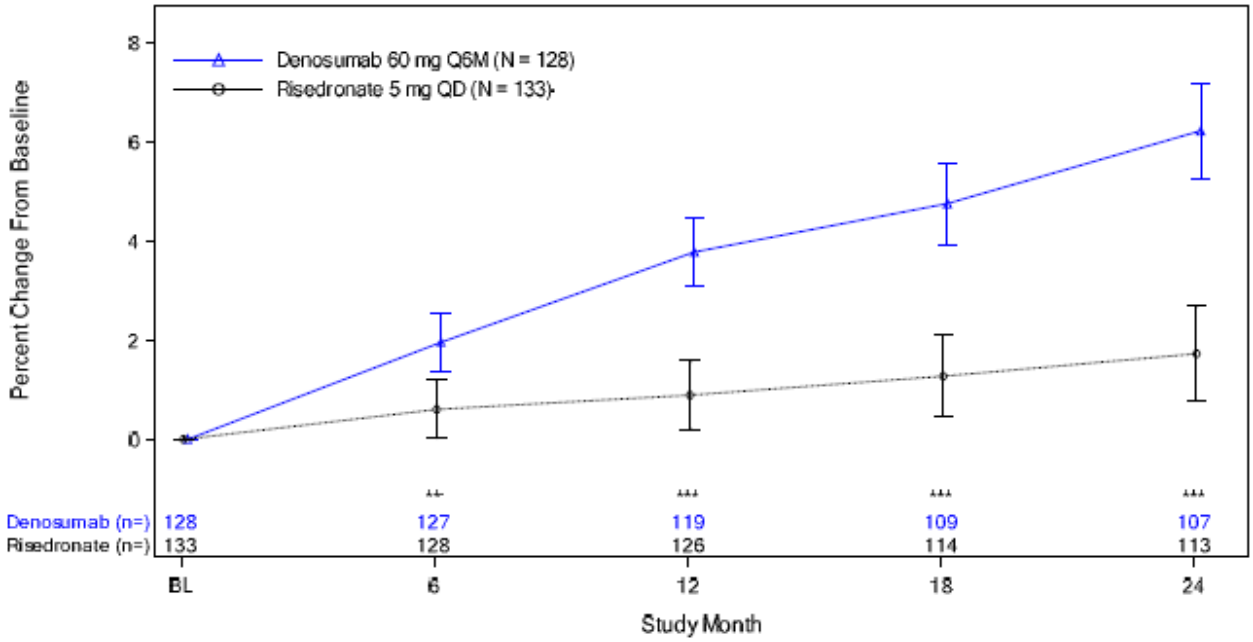
Table. Primary Efficacy Analyses of Secondary Endpoints: Percent Change From Baseline in the Lumbar Spine and Total Hip Bone Mineral Density at Month 24 (Primary Efficacy Analysis Set, Observed Data)(20101217 Final Analysis)

	Risedronate 5 mg QD	Denosumab 60 mg Q6M	Difference From Risedronate
GC-I subpopulation	(N = 145)	(N = 145)	
Lumbar spine			
N1	133	128	
n	113	107	
Estimate (95% CI)[a]	1.7 (0.8, 2.7)	6.2 (5.3, 7.2)	4.5 (3.2, 5.8)
p-value			< 0.001
Total hip			
N1	128	120	
n	111	104	
Estimate (95% CI)[a]	-0.0 (-0.6, 0.6)	3.1 (2.4, 3.7)	3.1 ((2.2, 3.9)
p-value			< 0.001
GC-C subpopulation	(N = 252)	(N = 253)	
Lumbar spine			
N1	230	228	
n	174	183	
Estimate (95% CI)[a]	3.2 (2.3, 4.1)	6.4 (5.5, 7.2)	3.2 (2.0, 4.3)
p-value			< 0.001
Total hip			
N1	216	218	
n	176	181	
Estimate (95% CI)[a]	0.5 (-0.1, 1.0)	2.9 (2.4, 3.5)	2.5 (1.7, 3.2)
p-value			< 0.001

ANCOVA = analysis of covariance; BMD = bone mineral density; CI = confidence interval; n = number of subjects with observed values; GC-C = glucocorticoid-continuing; GC-I = glucocorticoid-initiating; N = number of subjects randomized; N1 = number of subjects randomized with a baseline measurement and at least one postbaseline measurement for the bone location of interest; QD = once daily; Q6M = every 6 months.

[a] Based on ANCOVA model adjusting for treatment, baseline BMD value, sex, machine type, and baseline BMD value-by-machine type interaction; additionally includes duration of prior glucocorticoid use (< 12 months versus ≥ 12 months) for GC-C subpopulation.

Figure. Percent Change From Baseline Through Month 24 in Lumbar Spine Bone Mineral Density by Visit and Treatment in the Glucocorticoid-initiating Subpopulation (ANCOVA Model), Least Squares Means and 95% Confidence Intervals (Primary Efficacy Analysis Set, Observed Data)(20101217 Final Analysis)



N = Number of subjects randomized with a baseline measurement and at least one postbaseline measurement for the lumbar spine BMD

n = Number of subjects with observed data

Point estimates and nominal 95% confidence intervals are based on ANCOVA model adjusting for treatment, baseline BMD value, gender, machine type, and baseline BMD value-by-machine type interaction.

* p-value ≤ 0.05; ** p-value ≤ 0.025; *** p-value ≤ 0.001

The percent change from baseline in lumbar spine and total hip BMD at 24 months was greater with denosumab treatment than with risedronate treatment in both subpopulations ($p < 0.001$ in all comparisons). The % difference from risendronate continued to increase from 12 to 24 months.

Of note, most of the patients in the Glucocorticoid-initiating Subpopulation did not have osteoporosis at baseline (mean T-score -1.0). Denosumab seemingly increases BMD without a therapeutic plateau in individuals treated with corticosteroids with non-osteoporotic BMD at baseline.

As planned and hence in accordance with the SAP and analogous the primary 12-month analysis, the final 24-month analyses were based on observed data implying the exclusion of a rather high proportion of randomised subjects in each treatment arm in both the GC-I and the GC-C subpopulation. For the claim that denosumab is superior to risedronate, estimates of treatment efficacy and the difference between the treatments should be from an analysis based on all randomised according to the intention-to-treat principle; here FAS. For the primary analyses of the primary endpoint, additional analyses based on the Full Analysis Set (all randomised) were requested. An analysis using baseline-observation-carried-forward (BOCF) were then considered to offer a more conservative analysis approach than the one used in the primary analysis based on observed data excluding those with missing data month 12 and the outcomes are presented in the SmPC (section 5.1) accordingly.

The finally accepted outcomes presented in the SmPC for percentage change from baseline in lumbar spine BMD year 1 and year 2 for denosumab and risedronate reflect outcomes from analyses based on FAS using baseline-observation-carried-forward.

Exploratory Endpoints

Other Bone mineral density endpoints

At month 6, the increase in lumbar spine BMD was significantly greater with denosumab treatment than with risedronate treatment in both subpopulations ($p < 0.001$ for the GC-I subpopulation, $p = 0.002$ for the GC-C subpopulation). Denosumab increased lumbar spine BMD more than did risedronate by 1.4 percentage points in the GC-I subpopulation and 1.1 percentage points in the GC-C subpopulation.

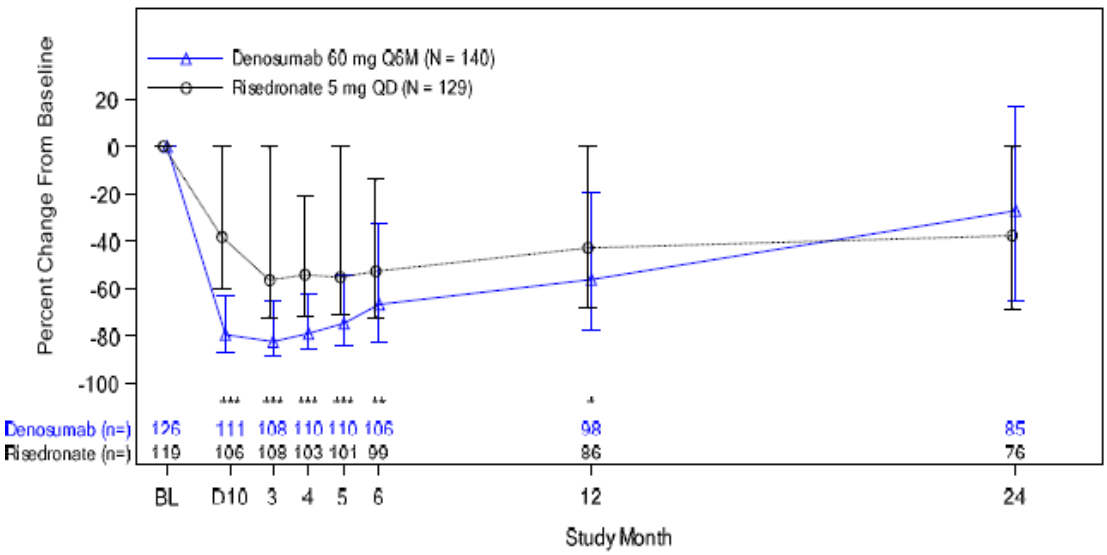
For the GC-I subpopulation, denosumab treatment led to significantly greater increases in BMD compared with risedronate at the femoral neck ($p = 0.02$) and the trochanter ($p < 0.001$).

In the GC-C subpopulation, denosumab treatment led to significantly greater increases in BMD compared with risedronate at the femoral neck ($p = 0.004$), trochanter ($p < 0.001$), and 1/3 radius ($p = 0.008$).

Bone Turnover Markers

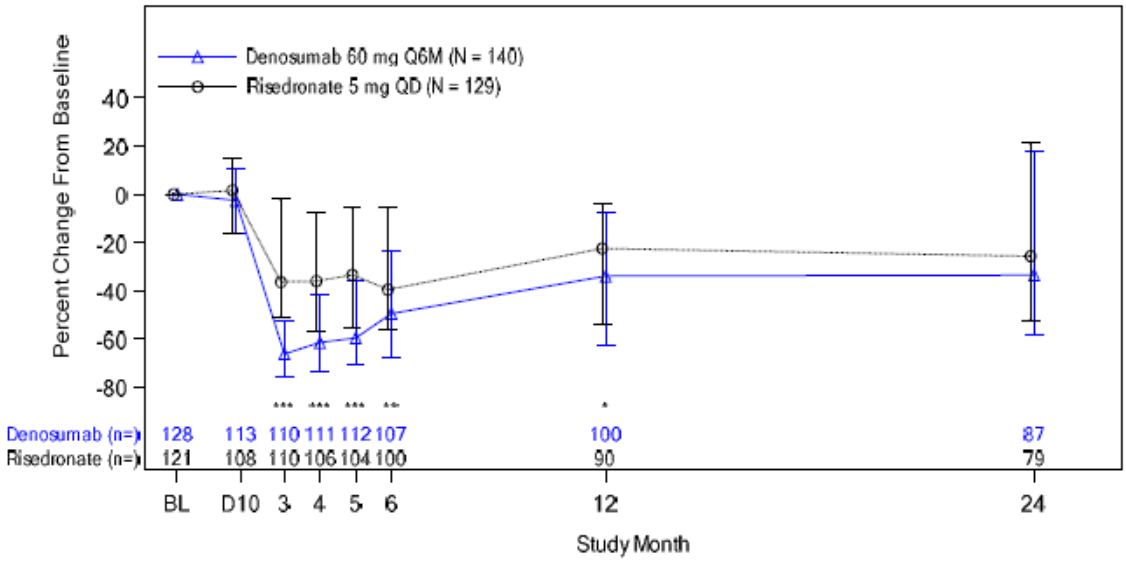
A At baseline, mean sCTX and P1NP values were similar between treatment groups. Levels of sCTX decreased significantly more with denosumab than with risedronate treatment at day 10 and months 3, 4, 5, 6, and 12; the difference between treatment groups in percent change from baseline to month 24 was not statistically significant. Levels of P1NP decreased significantly more with denosumab than with risedronate treatment at months 3, 4, 5, 6, and 12; the difference between treatment groups in percent change from baseline to day 10 and to month 24 was not statistically significant.

Figure. Percent Change From Baseline in Serum C telopeptide of Type 1 Collagen by Visit and Treatment, With Median and Inter-quartile Ranges (PK/BTM Subset) (Combined Subpopulations)(20101217 Final Analysis)



N = Number of subjects in the PK/BTM substudy
n = Number of subjects with observed data
P-value is based on the Wilcoxon rank sum test without adjusting for multiplicity.
* p-value ≤ 0.05; ** p-value ≤ 0.025; *** p-value ≤ 0.001

Figure. Percent Change From Baseline in Procollagen Type 1 N-telopeptide by Visit and Treatment, With Median and Inter-quartile Ranges (PK/BTM Subset) (Combined Subpopulations) (20101217 Final Analysis)



N = Number of subjects in the PK/BTM substudy
n = Number of subjects with observed data
P-value is based on the Wilcoxon rank sum test without adjusting for multiplicity.
* p-value ≤ 0.05; ** p-value ≤ 0.025; *** p-value ≤ 0.001

Both denosumab and risendronate show similar pattern of changes in bone-turnover markes over time with no significant difference at moth 24. This is in contrast to significant difference seen in BMD.

Bone biopsy

Table. Bone Biopsy Evaluability at Month 12 (Bone Biopsy Subset12-month Primary Analysis)

	Risedronate 5 mg QD n/N1 (%)	Denosumab 60 mg Q6M n/N1 (%)
Number of subjects who consented to the substudy	13	8
Number of subjects who withdrew consent after agreeing to participate	2	2
Number of subjects who had biopsies	11	6
Number of evaluable biopsies obtained at month 12	11	6
Evaluable for histology	11/11 (100.0)	6/6 (100.0)
Evaluable for histomorphometry[a]	7/11 (63.6)	3/6 (50.0)

N = number of subjects in the substudy; n = number of subjects with observed data; Q6M = every 6 months; QD = once daily.
[a] For 4 subjects (1 denosumab, 3 risedronate), the sample was not taken from the standard iliac crest site.

All subjects scheduled for biopsy followed a double tetracycline labeling procedure before undergoing the biopsy.

	Trabecular		Cortical		Trabecular or Cortical[a]	
	Risedronate 5 mg QD n (%)	Denosumab 60 mg Q6M n (%)	Risedronate 5 mg QD n (%)	Denosumab 60 mg Q6M n (%)	Risedronate 5 mg QD n (%)	Denosumab 60 mg Q6M n (%)
Number of evaluable biopsies obtained at month 12	11	5	10	6	11	6
Any label	8 (72.7)	1 (20.0)	8 (80.0)	0 (0.0)	11 (100.0)	1 (16.7)
Any double label	8 (72.7)	1 (20.0)	8 (80.0)	0 (0.0)	11 (100.0)	1 (16.7)
Only single label	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No label	3 (27.3)	4 (80.0)	2 (20.0)	6 (100.0)	0 (0.0)	5 (83.3)

n = Number of biopsies
Percentages based on the number of evaluable biopsies at the time point of interest
Any double label includes only double label or both single and double label.
[a] Any double label includes biopsies where double label was observed in trabecular or cortical compartment. Only single label includes biopsies where only single label was observed in trabecular and/or cortical compartments. No label includes biopsies where no label was observed in trabecular or cortical compartment

Biopsies from 10 subjects (3 denosumab, 7 risedronate) were evaluable for histomorphometry.

As expected, resorption and formation parameters were nominally lower in subjects treated with denosumab than risedronate, consistent with a lower rate of bone remodeling.

Wall thickness and width were slightly but statistically significantly higher in the denosumab-treated subjects compared with those treated with risedronate.

Due to difficulties in recruitment to the substudy and some collected specimens being unevaluable, Protocol Amendment 4 added a bone biopsy assessment at 24 months to bring the number of evaluable specimens closer to the protocol-indicated number of approximately 30 specimens.

At month 24, 1 additional biopsy had been obtained for a subject in the denosumab group The additional bone biopsy c showed normal bone histology. There was evidence of normal lamellar bone, normal mineralization, and normal osteoid. There was no evidence of osteomalacia, marrow fibrosis, woven bone, or other clinically significant marrow abnormality. Double label was observed in the trabecular compartment for this subject and histomorphometry was consistent with other denosumab-treated subjects.

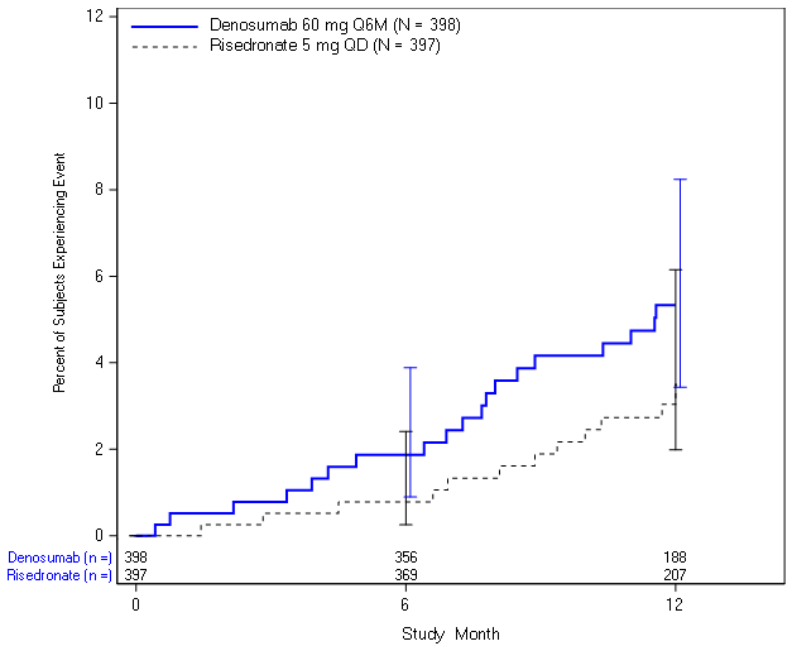
New Vertebral Fractures and non-vertebral fractures

Table. Subject Incidence of New Vertebral Fractures and Non-vertebral Fractures at Month 12 (Full Analysis Set) (Combined Subpopulations)(20101217 12-month Primary Analysis)

	Risedronate 5 mg QD	Denosumab 60 mg Q6M
New vertebral fracture		
n / N1	11 / 342	9 / 333
% (95% CI)	3.2 (1.6, 5.7)	2.7 (1.2, 5.1)
Non-vertebral fracture (low trauma)		
n / N	10 / 397	17 / 398
% (95% CI)	2.5 (1.2, 4.6)	4.3 (2.5, 6.8)

N1 = Number of subjects randomized with a baseline assessment and at least one postbaseline assessment of vertebral fracture at or before the time point of interest.
N = Number of subjects randomized
n = Number of subjects with at least one fracture
95% CI based on an exact method

Figure. Kaplan-Meier Curve of Time to First Clinical Fracture Through Month 12 for Combined Subpopulations (Full Analysis Set) (20101217 12-month Primary Analysis)



N = number of subjects randomized; n = number of subjects at risk for event at time point of interest; Q6M = every 6 months; QD = once daily
Vertical bars represent the 95% confidence interval.
Source: Figure 100-2.4.1

Table. Number of New Vertebral Fractures and Clinical Fractures by Skeletal Site at Month 12 (Full Analysis Set) (20101217 12-month Primary Analysis)

	Number of Fractures					
	GC-I Subpopulation		GC-C Subpopulation		Combined Subpopulations	
Skeletal Site Location	Risedronate 5 mg QD (N = 145)	Denosumab 60 mg Q6M (N = 145)	Risedronate 5 mg QD (N = 252)	Denosumab 60 mg Q6M (N = 253)	Risedronate 5 mg QD (N = 397)	Denosumab 60 mg Q6M (N = 398)
New vertebral fractures	3	1	14	13	17	14
Clinical fractures[a]	3	5	18	17	21	22
Thorax	0	3	2	3	2	6
Rib	0	3	2	3	2	6
Pelvis	-	-	1	4	1	4
Pubis	-	-	1	2	1	2
Acetabulum	-	-	0	1	0	1
Sacrum	-	-	0	1	0	1
Foot	0	1	1	2	1	3
Metatarsus	-	-	0	2	0	2
Foot	0	1	1	0	1	1
Shoulder	0	1	3	2	3	3
Humerus	0	1	3	2	3	3
Spine	1	0	10	2	11	2
Lumbar vertebra	-	-	2	1	2	1
Thoracic vertebra	1	0	8	1	9	1
Forearm	1	0	1	1	2	1
Radius	1	0	1	1	2	1
Hip	1	0	0	1	1	1
Femur subtrochanter	-	-	0	1	0	1
Femoral neck	1	0	-	-	1	0
Lower leg	-	-	0	1	0	1
Fibula	-	-	0	1	0	1
Thigh	-	-	0	1	0	1
Femur distal	-	-	0	1	0	1

GC-C = glucocorticoid-continuing; GC-I = glucocorticoid-initiating; Q6M = every 6 months; QD = once daily
Note: Locations sorted by descending order of frequency in the denosumab group of the combined subpopulations.
[a] Clinical fractures included clinical vertebral and nonvertebral fractures excluding skull, facial bones, mandible, metacarpus, finger phalanges, toe phalanges and cervical vertebrae and not associated with known high trauma severity (fall from higher than the height of stool, chair, first rung on a ladder or equivalent [> 20 inches] or severe trauma other than a fall) or pathological fractures.
Source: Table 100-2.1.1, Table 100-2.1.2, Table 100-2.1.3

Table. Subject Incidence of New Vertebral Fractures and Non-vertebral Fractures at Month 24 (Full Analysis Set) (Combined Subpopulations)(20101217 Final Analysis)

	Risedronate 5 mg QD	Denosumab 60 mg Q6M
New vertebral fracture		
n / N1	20 / 346	14 / 338
% (95% CI)	5.8 (3.6, 8.8)	4.1 (2.3, 6.9)
Non-vertebral fracture (low trauma)		
n / N	15 / 397	21 / 398
% (95% CI)	3.8 (2.1, 6.2)	5.3 (3.3, 8.0)

Table. Number of Nonvertebral Fractures by Skeletal Site at Month 24 (Full Analysis Set) (Combined Subpopulations) (20101217 Final Analysis)

Skeletal Site Location	Risedronate 5 mg QD (N = 397) n	Denosumab 60 mg Q6M (N = 398) n
Nonvertebral fractures [a]	16	24
Thorax	4	7
Rib	3	7
Sternum	1	0
Foot	1	5
Foot	1	3
Metatarsus	0	2
Pelvis	2	4
Pubis	1	2
Acetabulum	0	1
Sacrum	0	1
Ischium	1	0
Shoulder	3	3
Humerus	3	3
Hip	1	2

Femur intertrochanter	0	1
Femur subtrochanter	0	1
Femoral neck	1	0
Lower leg	3	1
Fibula	2	1
Tibia	1	0
Forearm	2	1
Radius	2	1
Thigh	0	1
Femur distal	0	1

= Number of subjects randomized
n = Number of fractures
Locations are sorted by descending order of frequency in the denosumab group.
[a] A nonvertebral fracture is defined as a fracture reported on the Clinical Fracture Summary eCRF excluding skull fracture, facial bones fracture, fractured mandible, fractured metacarpals, fractured finger, fractured toe, thoracic vertebrae, lumbar vertebrae, and cervical vertebra, and any fracture associated with high trauma severity or a pathologic fracture

Table. Number of Nonvertebral Fractures by Skeletal Site at Month 24 (Full Analysis Set) (Glucocorticoid-initiating Subpopulation)(20101217 Final Analysis)

Skeletal Site Location	Risedronate 5 mg QD (N = 145) n	Denosumab 60 mg Q6M (N = 145) n
Nonvertebral fractures [a]	5	6

Table. Number of Nonvertebral Fractures by Skeletal Site at Month 24 (Full Analysis Set) (Glucocorticoid-continuing Subpopulation)(20101217 Final Analysis)

Skeletal Site Location	Risedronate 5 mg QD (N = 252) n	Denosumab 60 mg Q6M (N = 253) n
Nonvertebral fractures [a]	11	18

The subject incidence of new radiological vertebral fracture was numerically lower for denosumab compared to risendronate, 4.1% vs 5.8%.

In contrast, both the total number (24 vs 16) and the subject incidence of non-vertebral fractures was higher for denosumab compared to risendronate, 5.3% vs 3.8%.

Most of the non-vertebral fractures occurred in the denosumab treated patients in the Glucocorticoid-continuing Subpopulation.

Denosumab was superior to risendronate in both subgroups in increasing BMD but there was no correlation with the fracture data and the BMD data in this study, especially regarding non-vertebral fractures.

Anti-denosumab Antibody Assays

One of 394 subjects who received denosumab (0.3%) tested positive for antidenosumab antibodies at month 12; the subject tested negative for neutralizing antibodies. This subject was in the GC-C subpopulation. No PK samples were collected for this subject so the potential impact on exposure could not be assessed.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table: Summary of Efficacy for trial 20101217 primary analysis

Title: Randomised, Double-blind, Active-controlled Study to Evaluate the Efficacy and Safety of Denosumab Compared with Risedronate in Glucocorticoid-treated Individuals					
Study identifier	20101217				
Design	Phase 3 international, multicentre, randomised, 24-month, double-blind, double-dummy, active-controlled, parallel-group				
	Duration of main phase:		24 months, 12 months predefined primary analysis period		
	Duration of Run-in phase:		not applicable		
	Duration of Extension phase:		not applicable		
Hypothesis	Primary endpoint: non-inferiority; secondary endpoint: superiority				
Treatments groups	Denosumab		60 mg Q6M SC; 24 months, n=398		
	Risedronate		5 mg QD oral; 24 months, n=397		
Endpoints and definitions	Primary endpoint	BMD	Percent change from baseline in lumbar spine BMD by DXA at 12 months		
	Secondary endpoint	BMD	Percent change from baseline in lumbar spine and total hip BMD by DXA at 12 and 24 months		
Database lock	Continuing; data cut-off 29 June 2016 for 12 months primary analysis				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Primary Efficacy Analysis Set, Observed Data; 12 months				
Descriptive statistics and estimate variability	Treatment group	Denosumab GC-I	Denosumab GC-C	Risedronate GC-I	Risedronate GC-C
	Number of subjects	119	209	126	211
	BMD lumbar spine (LS mean percent change from baseline)	3.8	4.4	0.8	2.3
	95% CI	3.1, 4.5	3.8, 5.0	0.2, 1.5	1.7, 2.9
Effect estimate per comparison	Primary endpoint	Comparison groups	GC-I subpopulation	GC-C subpopulation	
		Difference from risedronate (LS mean)	2.9	2.2	
		95% CI	2.0, 3.9	1.4, 3.0	

		Prespecified non-inferiority margin	-1.1%		-0.7%
		P-value (non-inferiority)	<0.001		<0.001
Notes	None				
Analysis description	**Secondary analysis**				
Analysis population and time point description	Primary Efficacy Analysis Set, Observed Data ; 12 months				
Descriptive statistics and estimate variability	Treatment group	Denosumab GC-I	Denosumab GC-C	Risedronate GC-I	Risedronate GC-C
	Number of subjects	119	209	126	211
	BMD lumbar spine (LS mean percent change from baseline)	3.8	4.4	0.8	2.3
	95% CI	3.1, 4.5	3.8, 5.0	0.2, 1.5	1.7, 2.9
	Number of subjects	119	217	128	215
	BMD total hip (LS mean percent change from baseline)	1.7	2.1	0.2	0.6
	95% CI	1.2, 2.2	1.7, 2.5	-0.2, 0.7	0.2, 1.0
Effect estimate per comparison	Secondary endpoint lumbar spine	Comparison groups	GC-I subpopulation		GC-C subpopulation
		Difference from risedronate (LS mean)	2.9		2.2
		95% CI	2.0, 3.9		1.4, 3.0
		P-value	<0.001		<0.001
	Secondary endpoint total hip	Difference from risedronate (LS mean)	1.5		1.5
		95% CI	0.8, 2.1		1.0, 2.1
		P-value (superiority)	<0.001		<0.001

Analysis performed across trials

Bone Mineral Density

The effect size of the BMD percentage increase at the lumbar spine compared to placebo for glucocorticoid induced osteoporosis is somewhat less that observed in the postmenopausal females (PMO) DXA substudy but comparable to study in bone loss associated with hormone ablation therapy (HALT) in men with prostate cancer.

The LS mean point estimate for the percent change from baseline in lumbar spine BMD at month 12 in the denosumab group was 3.8% in the GC-I subpopulation and 4.4% in the GC-C subpopulation, consistent with the LS mean point estimates at month 12 in Study 20030216 (5.5%) and the 3 supportive studies (4.3% to 5.7%).

Table. Lumbar Spine Bone Mineral Density by DXA Percent Change From Baseline at Month 12 (ANCOVA Model) (Efficacy Analysis Set, Integrated Analysis of Efficacy)

	LS Means[b]									Difference in LS Means[b]		
	Placebo			Risedronate 5 mg QD			Denosumab 60 mg Q6M			Denosumab - Control Group[a]		
	n	Pt Est	(95% CI)	n	Pt Est	(95% CI)	n	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
20101217 - Glucocorticoid-initiating				126	0.8	(0.2, 1.5)	119	3.8	(3.1, 4.5)	2.9	(2.0, 3.9)	<0.0001
20101217 - Glucocorticoid-continuing				211	2.3	(1.7, 2.9)	209	4.4	(3.8, 5.0)	2.2	(1.4, 3.0)	<0.0001
20030216	208	0.0	(-0.5, 0.5)				227	5.5	(5.0, 6.0)	5.5	(4.8, 6.2)	<0.0001
20080098	118	0.9	(0.3, 1.4)				117	5.7	(5.1, 6.2)	4.8	(4.0, 5.6)	<0.0001
20040138	715	-0.7	(-0.9, -0.4)				714	4.3	(4.0, 4.5)	4.9	(4.5, 5.3)	<0.0001
20040135	122	-0.7	(-1.3, -0.1)				123	4.8	(4.3, 5.4)	5.5	(4.8, 6.3)	<0.0001

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[a] Control group = risedronate 5 mg QD for Study 20101217 and placebo for Studies 20030216, 20080098, 20040138 and 20040135
Number of subjects randomized in 20101217 glucocorticoid-initiating subpopulation: 145 risedronate and 145 denosumab
Number of subjects randomized in 20101217 glucocorticoid-continuing subpopulation: 252 risedronate and 253 denosumab
Number of subjects enrolled in 20030216 DXA substudy: 209 placebo and 232 denosumab
Number of subjects randomized in Study 20080098: 121 placebo and 121 denosumab
Number of subjects randomized in Study 20040138: 734 placebo and 734 denosumab
Number of subjects randomized in Study 20040135: 125 placebo and 127 denosumab
n = Number of subjects with observed values at baseline and at ≥ 1 postbaseline visit at or before the time point of interest; LS = Least squares; For Study 20101217, post-baseline BMD values are as observed data, and for Studies 20030216, 20080098, 20040138 and 20040135, post-baseline BMD values are imputed using LOCF
[b] Based on an ANCOVA model adjusting for treatment, baseline BMD, gender, machine type, and baseline BMD-by-machine type interaction for 20101217 glucocorticoid-initiating subpopulation; treatment, baseline BMD, gender, machine type, baseline BMD-by-machine type interaction, and duration of prior glucocorticoid use for 20101217 glucocorticoid-continuing subpopulation; treatment, baseline BMD, machine type, and baseline BMD-by-machine type interaction for Study 20030216; treatment and baseline BMD T-score level for Study 20080098; treatment, age group, ADT duration at study entry, baseline BMD, machine type, and baseline BMD-by-machine type interaction for Study 20040138; and treatment, stratification variable, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction for Study 20040135

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal trial (2010217) to support the new indication glucocorticoid induced osteoporosis (GIOP) is a randomised, double-blind bridging study in patients treated with denosumab 60mg or risedronate Q6M for 24 months. The primary analysis at 12 months has been submitted.

Data from study 20101217 have been compared to results from the 4 pivotal clinical studies that supported the primary osteoporosis indication (study 20030216, 7808 women with PMO, basis for bridging; study 20080098, 242 men with OP) and the bone loss in subjects undergoing HALT indication (study 20040138, 1468 men with bone loss from ADT for nonmetastatic prostate cancer; study 20040135, 252 women with bone loss after adjuvant aromatase inhibitor therapy for nonmetastatic breast cancer); these trials have been assessed during previous procedures. Trial 20101217 is based on the pharmacodynamic endpoint change in BMD which is bridged to the results of the two supportive studies with anti-fracture efficacy data for denosumab (study 20030216, osteoporosis in postmenopausal women; study 20040138, bone loss associated with hormone ablation in men with prostate cancer).

The study 20101217 had two separate experimental aims; to assess denosumab efficacy in two different subpopulations, the glucocorticoid-initiating subpopulation and the glucocorticoid-continuing

subpopulation respectively. The primary objective in each population was to show non-inferiority in percent change from baseline in lumbar spine BMD by DXA at 12 months. The non-inferiority margins were -1.1 and -0.7 percentage points for the GC-I and GC-C subpopulation respectively.

Main analyses were performed separately for each subpopulation (GC-I and GC-C). The primary and secondary endpoints, DXA percent change from baseline at month 12 for each skeletal site measured, were analysed using an analysis of covariance (ANCOVA) model with main effects for treatment, gender, baseline BMD, machine type and the interaction effect for baseline BMD and machine type. Although, importantly, the primary model was pre-specified, no justification for including each of the covariates was found and was to be provided. In their response the MAH justified the choice of primary analysis model including machine type and the interaction term by the different scales of baseline BMD between the two proprietary technologies (Lunar and Hologic machines) which is accepted. To investigate the robustness of the primary analysis, additional analyses were required based on an ANCOVA model with main effects for treatment, gender and baseline BMD. They had been provided and showed very similar outcomes hereby supporting the robustness of the primary analysis. The definition of the primary efficacy set corresponded to a completer analysis set. In addition to the primary efficacy set a PP set was defined to be used for additional analyses of the primary endpoint. Considering the definition of the former and that the PP was to comprise a subset of the primary efficacy set, the difference between them tended to be small having an impact on the significance of the PP analysis as a measure of robustness. A Full Analysis Set was pre-defined but was not intended to be used for any analysis of the primary or key secondary endpoints.

The study protocol was amended 4 times; major changes have been summarized. In this summary, the wrong number of enrolled subjects was seemingly given at the time point for amendment 1 and/or 2 (167 and 127 respectively). The dates were also somewhat confusing. Although expected to be of minor importance, the MAH has as requested clarified how Table 8-10 (Study 20101217 12-month Primary Analysis Clinical Study Report) should be read and thus clarified the issue.

Within the GC-I subpopulation, the study discontinuation rate was somewhat higher in the denosumab group (15.9%) than in the risedronate group (9.7%), which was related to a higher rate of withdrawal of consent in the denosumab group. Within the GC-C subpopulation, the study discontinuation rate was similar in the denosumab (14.2%) and risedronate (12.3%) groups. The rate of study discontinuations due to adverse events was also similar (denosumab 3.6%, risedronate 3.2%).

Efficacy data and additional analyses

Non-inferiority on the primary endpoint has been demonstrated; the difference from risedronate in change of measured BMD at the lumbar spine from baseline was 2.9% in the patients with glucocorticoid treatment <3 months group and 2.2% in the placebo group (n=118).

Results from the secondary analyses on the change of femoral neck and hip BMD were in line with the primary outcome. The 12 months primary analysis of the glucocorticoid induced osteoporosis trial (2010217) was not powered to show a statistically significant difference between groups on the reduction of osteoporotic fractures.

The pharmacokinetic data provided in patients with corticosteroids induced osteoporosis do not suggest any differences in exposure that would necessitate a dose adjustment in the new proposed indication compared to postmenopausal females.

In the analysis of primary and secondary endpoints only subjects with observed BMD data at baseline and at the post-baseline time point of interest were included. In all analyses presented, a non-negligible proportion of randomised subjects were excluded; across subpopulations 13-18% in primary analyses and approximately 25-30% in analyses based on the PP set. Here, where not only non-inferiority but

superiority has been shown for denosumab versus risedronate and in each subpopulation, analyses based on the Full Analysis Set (FAS) comprising all randomised is considered of importance. Analyses based on the FAS were hence to be provided to confirm the conclusions of denosumab being superior to risedronate. In response the MAH performed two different sensitivity analyses of the percent change from baseline in lumbar spine BMD and total hip BMD respectively separately in the GC-I and GC-C subpopulations; one based on a baseline-observation-carried-forward imputation approach, that, according to the MAH, corresponded to "treatment failure" and, one based on a multiple imputation (MI) approach *within* each treatment group. Although the use of BOCF implies a decreased variability and it may be discussed whether baseline-carried-forward really implies treatment failure in the prevention setting, it is considered to offer a more conservative analysis approach than the one used in the primary analysis based on observed data excluding those with missing data month 12. Regarding the MI approach, it is based on an assumption of missing at random in that subjects with missing data is assumed to perform as those within the same treatment group who completed/had data month 12. These analyses are therefore not considered to provide sufficiently conservative estimates. In the MI analyses the outcomes were identical compared to the primary analysis. For the claim that denosumab is superior to risedronate, estimates of treatment efficacy and the difference between the treatments should be from an analysis based on all randomised subjects according to the intention-to-treat principle (FAS) using a method for handling of missing data that can be considered to be sufficiently conservative (e.g. treatment failure imputation). For the claim of denosumab being superior to risedronate with regard to increases in BMD, the MAH therefore performed on request of the CHMP additional analyses based on FAS and BOCF. Data based on these more conservative analyses are therefore provided in section 5.1 of the SmPC to reflect the outcomes (denosumab demonstrated a greater increase in lumbar spine BMD compared to risedronate in the glucocorticoid-continuing subpopulation at 1 year: denosumab 3.6 %, risedronate 2.0%; $p < 0.001$, and 2 years: denosumab 4.5%, risedronate 2.2%; $p < 0.001$, as well as in the glucocorticoid-initiating subpopulation at 1 year: denosumab 3.1 %, risedronate 0.8%; $p < 0.001$, and 2 years: denosumab 4.6%, risedronate 1.5%; $p < 0.001$).

Relationship between increase in bone mineral density and decrease in risk of fracture

Study 20030216 in postmenopausal women demonstrated that increases in BMD with denosumab 60 mg Q6M are associated with an absolute risk reduction of new radiological vertebral fractures: 1.4% at 1 year, 3.5% at 2 years and 4.8% at 3 years.

For clinical fractures, an absolute risk reduction of 2.9% over 3 years was seen in study 20030216.

Study 20040138 in bone loss associated with androgen deprivation demonstrated decreases in risk of radiological vertebral fracture; denosumab demonstrated a significant relative risk reduction of new radiological vertebral fractures: 1.6% absolute risk reduction at 1 year, 2.2% at 2 years and 2.4% at 3 years.

Additional expert consultation

CHMP requested an ad hoc expert meeting to obtain the opinion of experts in the field of bone metabolism and osteoporosis, as well as from a patient representative. Questions were addressed to the ad hoc expert group. The questions and the corresponding answers are presented below:

General questions

1. Please discuss how to identify the optimal study population for the assessment of a medicinal product intended for the prevention/treatment of GIOP

a. What is the minimum dose and duration of treatment with glucocorticoids that would warrant treatment with a medicinal product for the prevention/treatment of GIOP?

For the purpose of clinical trials seeking an approval for GIOP, the experts found the commonly used threshold of ≥ 7.5 mg prednisone equivalent per day and the intended or actual use over at least 3 months reasonable. As threshold for treatment intervention in clinical practice, however, daily doses below 7.5 mg prednisone equivalent may be relevant in certain patients. A start of treatment for GIOP once the patient is being exposed to glucocorticoids (GCs) was also seen as relevant.

b. Is there a need for pharmacological intervention in patients without osteoporosis and at low risk of fracture at baseline who initiate glucocorticoid therapy?

Inclusion of patients in such studies and start of treatment in practice needs to not only rely on absence or presence of osteoporosis (as defined by T-score) but on overall recognition of an increased risk of fracture of the patient; thresholds for such interventions are defined, with some variability, in various clinical treatment guidelines, which may also guide study designs. The risk for instance in premenopausal women starting on GCs without any other risk factors may be low and may not require treatment. In any case, treatment and determination of the fracture risk in premenopausal women in clinical practice is often done on an individual basis.

c. Is it possible and/or necessary to distinguish the prevention of GIOP from the treatment of GIOP?

It would appear that "prevention" (defined as e.g. GC exposure < 3 months) and "treatment" populations (e.g. GC exposure ≥ 3 months) may present different stages of a continuum and such a separation may not be necessary, as treatment intervention would be rather based on fracture risk and moreover should, when indicated, be initiated early. Rapid bone loss occurs mostly during first months after the start of GC therapy, which is of relevance when considering study designs for this indication.

2. Some products for the prevention/treatment of GIOP have relied on bridging strategies using active comparator-controlled trials. Can sufficient sensitivity of the studies be assumed obviating the need for a concurrent placebo control with regards to BMD as well as fracture efficacy?

The experts were of the view that placebo-controlled RCTs, while in principle preferable, are not feasible for GIOP trials and therefore comparator-controlled trials will be required.

3. From a safety point of view, is a clinical study in GIOP of one year duration sufficient? (two years required in PMO). Is it reasonable to require long-term safety follow-up in GIOP (3-5 years required for PMO) after approval?

While a one year study regarding efficacy might be sufficient, this was considered not long enough for safety purposes, as e.g. ONJ may manifest only after a couple of years; the experts therefore recommended that after completion of the study phase, a follow-up of the patients with regard to safety aspects should be strongly recommended.

Product-specific questions

1. Were the criteria for selecting patients for the denosumab glucocorticoid induced osteoporosis (GIOP) trial appropriate, in particular the proposed distinction between prevention and treatment of GIOP?

The experts found the patient selection for the pivotal study overall adequate (based on known relevant risk factors including previous fracture history, age, BMD) and close to, or more restrictive, compared with existing treatment intervention guidelines. The exception is the population of premenopausal women, as these represented only a very small group (7.5 – 13.5% in various treatment groups of the study population), included few women younger than 40 years, and overall might represent a population of heterogeneous fracture risk. The study population was more restrictively selected compared to earlier GIOP studies with risedronate, but that was found to be adequate. It was acknowledged that certain exclusion criteria (such as advanced stages of renal impairment due to limitations of the comparator

product) did restrict the study population compared to the currently approved SmPC for Prolia. As GCs are often used for certain renal diseases, a need for more data on denosumab use in in systemic steroid users (i.e. patients with GIOP) and severely impaired renal function was mentioned. Rapid bone loss occurs mostly during first months after the start of GC therapy. With regard to the distinction between "prevention" vs. "treatment" see response to general question 1 c.

2. Is it possible in the framework of a clinical trial to distinguish GIOP from other causes of osteoporosis in patients that have been treated with glucocorticoids for more than 3 months/6 months/12 months?

(see response to question 3, below)

3. Fracture risk in patients treated with glucocorticoids may not be as strongly correlated with bone mineral density as in postmenopausal osteoporosis (PMO). Can a given change in BMD in patients at risk for GIOP that is comparable to patients with established postmenopausal osteoporosis (PMO) inform on a reduced fracture risk in the population at risk of GIOP?

The extent to which maintenance or improvement of bone mineral density (BMD) can predict a reduction of fracture rates in patients with PMO cannot simply be assumed to be similar in patients with GIOP, for the following reasons: 1) Underlying pathomechanisms of osteoporosis in PMO and GIOP are largely different, e.g. GCs have distinct effects at different times of exposure on osteoclast, osteoblast and osteocyte activity, compared to the PMO setting; 2) changes of bone structure as compared to bone mineral density may contribute more to bone fragility in GIOP than in PMO; 3) while some data on the relationship of BMD changes and fracture rates are available from placebo-controlled therapeutic interventions e.g. with risedronate, those data may not be directly translateable for denosumab, due to the different mechanism of action and potency; and 4) experience from BMD/fracture relationship with teriparatide, as another product approved for GIOP, is also not comparable to denosumab, due to very different mechanisms of action.
In the experts' view, this makes any such extrapolation between different forms of osteoporosis and different agents with different mechanism of action not straight forward. On the other hand, the experts acknowledged the large size of trials which would be needed for a non-inferiority RCT with clinical fractures as primary outcome. It was also acknowledged, that osteoporosis in GIOP is rarely due to GC excess alone, as a number of other pathogenic components are also often important, in particular most patients are > 50 years with a postmenopausal scenario in women and some level of testosterone-deficiency in older men. Therefore, increased bone fragility in this setting often involves a mix of causes of osteoporosis other than GIOP alone, allowing the assumption that some extrapolation of BMD changes being associated with a reduced fracture rate in PMO to GIOP could be justified.

Of some concern were the fracture data from the pivotal study: While the number of vertebral fractures was balanced between treatment with denosumab (n=14) and risedronate (n=17), there was an unexpected numerical imbalance for non-vertebral fractures (n=20 for denosumab; n=10 for risedronate); it was acknowledged, that the study was not powered for fracture outcomes, the numbers are very small, and the imbalance may well be a chance finding in the view of some experts; however, it still was of some concern to some experts, potentially warranting a longer than 1 year observation of those fracture outcomes. Two-year data will be available in a few months' time, according to the MAH representatives present in the first half of the meeting.

4. Can BMD data generated in postmenopausal women that initiate treatment with glucocorticoids be extrapolated to premenopausal women and men in order to infer efficacy as regards fracture prevention?

The number of premenopausal women (and men < 50 years) in the pivotal trial was very small (participants < 50 years: 7.8 - 8.8 % in various groups). Even though there may have been a BMD

improvement in this subpopulation consistent with the group of postmenopausal women, the very small number in the study does not allow firm conclusions. The experts had also some concerns with the reliability of fracture risk estimates of this subpopulation of the study. It is acknowledged, that data on premenopausal women is also scarce in other GIOP studies, such as for risedronate. While it is therefore difficult to draw any conclusions for this subpopulation from this study, the experts pointed out, that there are cases of (unmet) need for treatment of premenopausal women on GCs considered at high risk of fracture.
Men did comprise ca. 30% of the participants of the pivotal study. The observed change in BMD in the study may support to some extent the assumption of efficacy with regard to fracture prevention in men, particularly older men (see also response to question 3, above), but cannot directly be deduced from the data. The experts pointed out that in men on hormone ablative therapy an association between BMD and the frequency of vertebral fractures has been shown with denosumab treatment, but such a comparison is limited by the different nature of the underlying mechanism of bone loss in the two scenarios.

5. and 6. Patients with long-term concomitant treatment with glucocorticoids may be at increased risk for certain safety concerns related to denosumab such as infections, atypical fractures, delayed fracture union and osteonecrosis of the jaw (ONJ). What would be the required study duration to exclude an increased risk?
ONJ is an identified risk for denosumab in PMO and concomitant corticosteroid use is an additional risk factor. Patients with a history of tooth extraction or other dental surgery within the prior 6 months or invasive dental work planned in the next 2 years were excluded from the current denosumab GIOP study. Is the current Prolia product information sufficient to minimise this risk in the GIOP population?

The experts pointed out that ONJ often develops only several years after initiation of anti-resorptive therapy in PMO setting. Therefore capturing these events only within 1 or 2 years of study time is considered insufficient and additional post study surveillance for this was advocated. In principle, underlying disease states and co-medication such as MTX might increase the risk for ONJ, increase the risk of predisposing infections and may mask them, etc. The experts noted one (positively adjudicated) case of atypical fracture of the femur, thus not allowing relevant conclusions. While some proposal for enhanced risk mitigation, such as dental examination before initiation of therapy, was made, others were of the view that there was too little data to justify that, in particular as the product might only be prescribed short term for temporary GC use, considering the importance of rapid intervention, and as ONJ is still a very low-frequency event with low dose denosumab use.

2.4.3. Conclusions on the clinical efficacy

Data from the 12-month primary analysis period of study 20101217 showed that at 12 months denosumab was non-inferior to risedronate in percent change of BMD from baseline at the lumbar spine in both the GC-I and the GC-C subpopulation of the study. Furthermore treatment with denosumab led to a significantly higher percent increase from baseline in BMD at the lumbar spine and total hip compared with risedronate. Subgroup analyses of the BMD change from baseline at the lumbar spine also indicated a greater increase in subjects on denosumab compared to risedronate; the effects were seen both in pre- and postmenopausal women. Exploratory analyses of BMD changes from baseline to month 6 at the lumbar spine and to month 12 at the femoral neck, trochanter, and 1/3 radius, each performed for GC-I and GC-C subpopulations, consistently showed that increases were higher in subjects treated with denosumab than with risedronate, except for 1/3 radius in the GC-I subpopulation.

Values of the bone turnover markers sCTX and P1NP decreased statistically significantly more with denosumab than with risedronate at months 3, 4, 5, and 6, but not at month 12. Serum CTX was also significantly decreased compared with risedronate on day 10.

The primary analysis of Study 20101217 conducted at 12 months showed that the subject incidence of new vertebral fracture was numerically lower (2.7% [95% CI: 1.2, 5.1] versus 3.2% [95% CI: 1.6, 5.7]), and the subject incidence of non-vertebral fracture was numerically higher (4.3% [95% CI: 2.5, 6.8] versus 2.5% [95% CI: 1.2, 4.6]), in the denosumab compared with the risedronate group.

The final analysis conducted at 24 months showed that the subject incidence of new vertebral fracture continued to be numerically lower in the denosumab group compared with the risedronate group (4.1% [95% CI: 2.3, 6.9] versus 5.8%. [95% CI: 3.6, 8.8]), and the subject incidence of non-vertebral fracture continued to be numerically higher between the 2 treatment groups (5.3% [95% CI: 3.3, 8.0] versus 3.8% [95% CI: 2.1, 6.2]). The number of non-vertebral fractures was 24 versus 16 in the denosumab versus risedronate group, respectively.

The vast majority (>90%) of the patients in the study were treated with GC for >6 months. Overall, 44% continued GC at month 24. Most of the patients who discontinued GC treatment continued with the IP treatment. In contrast, antiresorptive treatment for GIOP is discontinued when GC treatment is discontinued in clinical practice. The increase in bone resorption in GIOP occurs early and is transient, which would implicate that the need of antiresorptive therapy is also limited in time. It is difficult to draw any conclusions regarding optimal treatment duration from the current study design. This needs to be based on individual patients BMD and other risk factors for fracture.

For bridging the results of study 20101217 on the surrogate parameter change in BMD from baseline to 12 months with the anti-fracture efficacy of denosumab the applicant has provided a comparison with data from previous trials including studies with fracture endpoints. When compared, in all 5 studies denosumab led to significantly higher increases in BMD compared to the control groups at all skeletal sites investigated with the exception of the 1/3 radius in the GC-I subpopulation of the GIOP study 20101217. The effect of denosumab on mean increases in BMD observed in GC-C and GC-I subpopulations of study 20101217 are considered generally comparable to the effects seen in the previous trials. Since BMD increases were associated with fracture risk reduction in pivotal osteoporosis studies 20030216 and 20040138, and BMD increases within the same range of the above were observed in Study 20101217, it could be reasonable to extrapolate the antifracture efficacy of denosumab 60 mg Q6M to subjects with GIOP, at least regarding radiological vertebral fractures in patients at increased risk of fractures and who are treated with corticosteroids >1 years.

2.5. Clinical safety

Patient exposure

A total of 778 subjects comprised the safety analysis set (denosumab, 394; risedronate, 384). Overall, 85.0% of subjects in the denosumab group received both the day 1 and month 6 doses, and 80.5% of subjects randomized to risedronate received ≥ 80% of oral risedronate doses.

Adverse events

Subject Incidence of Treatment-emergent Adverse Events, Combined Subpopulations (Safety Analysis Set) (12-month Primary Analysis)

	Risedronate 5 mg QD (N = 384) n (%)	Denosumab 60 mg Q6M (N = 394) n (%)
All adverse events, n (%)	265 (69.0)	285 (72.3)
Serious adverse events	65 (16.9)	63 (16.0)
Leading to discontinuation of investigational product	29 (7.6)	25 (6.3)
Leading to discontinuation from study	14 (3.6)	15 (3.8)
Fatal adverse events	2 (0.5)	6 (1.5)
Treatment-related adverse events,[a] n (%)	50 (13.0)	52 (13.2)
Serious adverse events	2 (0.5)	5 (1.3)
Leading to discontinuation of investigational product	14 (3.6)	13 (3.3)
Leading to discontinuation from study	6 (1.6)	7 (1.8)
Fatal adverse events	0	0

N = number of subjects who received ≥ 1 dose of investigational product; n = number of subjects reporting ≥ 1 event; QD = once daily; Q6M = every 6 months.
[a] Includes only events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product

Table. Summary of Subject Incidence of Treatment-emergent Adverse Events (Safety Analysis Set) (20101217 – 24 month Final Analysis)

	Risedronate 5 mg QD (N = 385) n (%)	Denosumab 60 mg Q6M (N = 394) n (%)
All treatment-emergent adverse events - n (%)	300 (77.9)	324 (82.2)
Serious adverse events	98 (25.5)	92 (23.4)
Leading to discontinuation of investigational product	37 (9.6)	31 (7.9)
Leading to discontinuation from study	15 (3.9)	18 (4.6)
Fatal adverse events	9 (2.3)	13 (3.3)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event; Q6M = every 6 months; QD = once daily
[a] Includes only events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
Two additional deaths were reported in subjects randomized to risedronate (pneumonia bacterial and polymyositis). These subjects were not included in the safety analysis set, because it was not possible to confirm that they had taken at least 1 dose of oral investigational product. The 2 subjects died prior to their month-6 visit and oral investigational product accountability verification.

There were 4 more deaths in the denosumab-group compared to risendronate at month 12, additional 7 events occurred up to month 24 in both groups.

Table. Subject Incidence of Treatment-emergent Adverse Events Reported in ≥ 3% of Subjects in Either Treatment Group by Preferred Term, Combined Subpopulations (Safety Analysis Set, 12-month Primary Analysis)

Preferred Term	Risedronate 5 mg QD (N = 384) n (%)	Denosumab 60 mg Q6M (N = 394) n (%)
Number of subjects reporting adverse events	265 (69.0)	285 (72.3)
Back pain	17 (4.4)	18 (4.6)
Arthralgia	21 (5.5)	17 (4.3)
Hypertension	13 (3.4)	15 (3.8)
Bronchitis	11 (2.9)	15 (3.8)
Headache	7 (1.8)	14 (3.6)
Nasopharyngitis	17 (4.4)	12 (3.0)
Anaemia	13 (3.4)	12 (3.0)
Dyspepsia	10 (2.6)	12 (3.0)
Urinary tract infection	8 (2.1)	12 (3.0)
Abdominal pain upper	7 (1.8)	12 (3.0)
Diarrhoea	13 (3.4)	11 (2.8)
Cataract	15 (3.9)	5 (1.3)
Nausea	14 (3.6)	9 (2.3)
Osteoarthritis	13 (3.4)	8 (2.0)

IP = investigational product; n = number of subjects reporting ≥ 1 event; N = number of subjects who received ≥ 1 dose of IP; QD, once daily; Q6M, every 6 months.
[a] Adverse events were coded using MedDRA version 19.0.

Overall, adverse events that were considered related to investigational product were reported in approximately 13% of subjects in each treatment group. By system organ class and preferred term, treatment-related adverse events were reported at similar rates in the denosumab and risedronate groups.

Table. Subject Incidence of Treatment-emergent Adverse Events Considered Related to Investigational Product Reported in ≥ 1% of Subjects in Either Treatment Group, Combined Subpopulations (Safety Analysis Set, 12-month Primary Analysis)

Preferred Term	Risedronate 5 mg QD (N = 384) n (%)	Denosumab 60 mg Q6M (N = 394) n (%)
Number of subjects reporting adverse events related to investigational product	50 (13.0)	52 (13.2)
Nausea	8 (2.1)	7 (1.8)
Dyspepsia	7 (1.8)	7 (1.8)
Abdominal pain upper	5 (1.3)	5 (1.3)
Vomiting	0	5 (1.3)
Diarrhoea	5 (1.3)	4 (1.0)
Abdominal pain	1 (0.3)	4 (1.0)
Bone pain	0	4 (1.0)

N = number of subjects who received ≥ 1 dose of IP; n = number of subjects reporting ≥ 1 event; QD = once daily; Q6M = every 6 months.
[a] Adverse events were coded using MedDRA version 19.0.

Serious adverse event / deaths / other significant events

Table. Subject Incidence of Treatment-emergent Serious Adverse Events Reported in ≥ 0.5% of Subjects in Either Treatment Group by Preferred Term, Combined Subpopulations (Safety Analysis Set, 12-month Primary Analysis)

Preferred Term[a]	Risedronate 5 mg QD (N = 384) n (%)	Denosumab 60 mg Q6M (N = 394) n (%)
Number of subjects reporting SAEs	65 (16.9)	63 (16.0)
Pneumonia	6 (1.6)	5 (1.3)
Cardiac failure	0	3 (0.8)
Transient ischaemic attack	0	3 (0.8)
Osteoarthritis	4 (1.0)	2 (0.5)
Cardiac failure congestive	1 (0.3)	2 (0.5)
Cerebrovascular accident	1 (0.3)	2 (0.5)
Sciatica	1 (0.3)	2 (0.5)
Dehydration	0	2 (0.5)
Dyspepsia	0	2 (0.5)
Femur fracture	0	2 (0.5)
Back pain	3 (0.8)	1 (0.3)
Pulmonary embolism	4 (1.0)	0
Anaemia	2 (0.5)	0
Bronchitis	2 (0.5)	0
Deep vein thrombosis	2 (0.5)	0
Renal failure	2 (0.5)	0
Rheumatoid arthritis	2 (0.5)	0

N = number of subjects who received ≥ 1 dose of investigational product; n = number of subjects reporting ≥ 1 event; QD = once daily; Q6M = every 6 months; SAE = serious adverse event.
[a] Adverse events were coded using MedDRA version 19.0.

Serious adverse events considered related to investigational product were reported for 5 subjects (1.3%) in the denosumab group (diverticulitis/dehydration, diverticulum intestinal, lung abscess/pneumonia bacterial, erosive oesophagitis, and humerus fracture) and 2 subjects (0.5%) in the risedronate group (cataract/cataract operation and pneumonia).

Table. Subject Incidence of Treatment-emergent Fatal Adverse Events by Preferred Term, Combined Subpopulations (Safety Analysis Set, 12-month Primary Analysis)

Preferred Term[a]	Risedronate[b] 5 mg QD (N = 384) n (%)	Denosumab 60 mg Q6M (N = 394) n (%)
Number of subjects reporting treatment-emergent fatal adverse events	2 (0.5)	6 (1.5)
Alveolitis allergic	0	1 (0.3)
Cardiopulmonary failure	0	1 (0.3)
Cerebral ischaemia	0	1 (0.3)
Cerebrovascular accident	0	1 (0.3)
Neoplasm	0	1 (0.3)
Organising pneumonia	0	1 (0.3)
Cardio-respiratory arrest	1 (0.3)	0
Upper gastrointestinal haemorrhage	1 (0.3)	0

N = number of subjects who received ≥ 1 dose of investigational product; n = number of subjects reporting ≥ 1 event; QD, once daily; Q6M, every 6 months.

[a] Adverse events were coded using MedDRA version 19.0.

[b] Three additional deaths were reported in subjects randomized to risedronate (pneumonia bacterial, chronic respiratory failure, and polymyositis). These subjects were not included in the safety analysis set, because it was not possible to confirm that they had taken at least 1 dose of oral investigational product. The 3 subjects died prior to their month 6 visit and oral drug accountability verification.

None of the deaths in either treatment group was considered related to investigational product.

Table. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set, 20101217 12-month Primary Analysis)

System Organ Class Preferred Term	Risedronate 5 mg QD (N = 384) n (%)	Denosumab 60 mg Q6M (N = 394) n (%)
Nervous system disorders	4 (1.0)	9 (2.3)
Transient ischaemic attack	0 (0.0)	3 (0.8)
Cerebrovascular accident	1 (0.3)	2 (0.5)
Sciatica	1 (0.3)	2 (0.5)
Cerebral ischaemia	0 (0.0)	1 (0.3)
Headache	0 (0.0)	1 (0.3)
Hemiparesis	1 (0.3)	0 (0.0)
Multiple sclerosis	1 (0.3)	0 (0.0)

Adverse Events of Interest

Table. Subject Incidence of Treatment-emergent Adverse Events of Interest, Combined Subpopulations (Safety Analysis Set) (20101217 Final Analysis, 24 months)

Event of Interest	Risedronate 5 mg QD (N = 385) n (%)	Denosumab 60 mg Q6M (N = 394) n (%)
Hypocalcemia		
Adverse events	0 (0.0)	1 (0.3)
Serious adverse events	0 (0.0)	0 (0.0)
Adjudicated positive ONJ	0 (0.0)	0 (0.0)
Adverse events potentially related to hypersensitivity		
Adverse events	18 (4.7)	25 (6.3)
Serious adverse events	1 (0.3)	1 (0.3)
Infection		
Adverse events	140 (36.4)	143 (36.3)
Serious adverse events	25 (6.5)	23 (5.8)
Bacterial cellulitis (skin infections)		
Adverse events	2 (0.5)	7 (1.8)
Serious adverse events	2 (0.5)	2 (0.5)
Malignancy	7 (1.8)	12 (3.0)
Cardiac disorders		
Adverse events	29 (7.5)	26 (6.6)
Serious adverse events	9 (2.3)	12 (3.0)
Vascular disorders		
Adverse events	32 (8.3)	43 (10.9)
Serious adverse events	6 (1.6)	4 (1.0)
Adjudicated positive atypical femoral fracture	0 (0.0)	1 (0.3)
Eczema		
Adverse events	2 (0.5)	2 (0.5)
Serious adverse events	0 (0.0)	0 (0.0)
Acute pancreatitis		
Adverse events	2 (0.5)	0 (0.0)
Serious adverse events	2 (0.5)	0 (0.0)
Musculoskeletal pain		
Adverse events	73 (19.0)	71 (18.0)
Serious adverse events	6 (1.6)	3 (0.8)

N = Number of subjects who received ≥ 1 dose of investigational product; n = Number of subjects reporting ≥ 1 event; ONJ = osteonecrosis of the jaw; QD = once daily; Q6M = every 6 months
Includes only treatment-emergent adverse events

Hypocalcaemia, bacterial cellulitis, hypersensitivity and musculoskeletal pain are identified risks with denosumab also in the PMO population.

Atypical femoral fracture

One subject in the denosumab group and no subject in the risedronate group had positively adjudicated atypical femoral fracture (preferred term: femur fracture). The event occurred approximately 2 months after the second dose of SC investigational product and approximately 8 months into the QD oral investigational product administration in a subject with a long history of receiving glucocorticoid therapy. The subject had no history of bisphosphonate or proton pump inhibitor use and reported only 1 previous fracture. The MAH was asked to calculate the incidence of AFF in study 20101217 and compare the incidence with the number from previous clinical trials and from the literature. The exposure-adjusted subject incidence rate (IR) of atypical femoral fracture in study 20101217 (276.5 events per 100 000 patient-years) was higher than in previous denosumab osteoporosis studies in patients without previous antiresoptive treatment (< 100 events per 100 000 patient-years).

Higher incidence rates were seen in Study 20110153 that enrolled subjects with previous bisphosphate use (630.7 events per 100 000 patient-years) and bisphosphate (zoledronic acid) (314.1 events per 100 000 patient-years).

Hypocalcaemia

One subject (0.3%) in the denosumab group had hypocalcaemia with CTCAE grade ≥ 2 (corrected serum calcium < 2.0 mmol/L). This subject's corrected calcium had decreased from 2.25 mmol/L at day 1 to 1.60 mmol/L (grade 3 hypocalcaemia) on day 12.

Malignancies

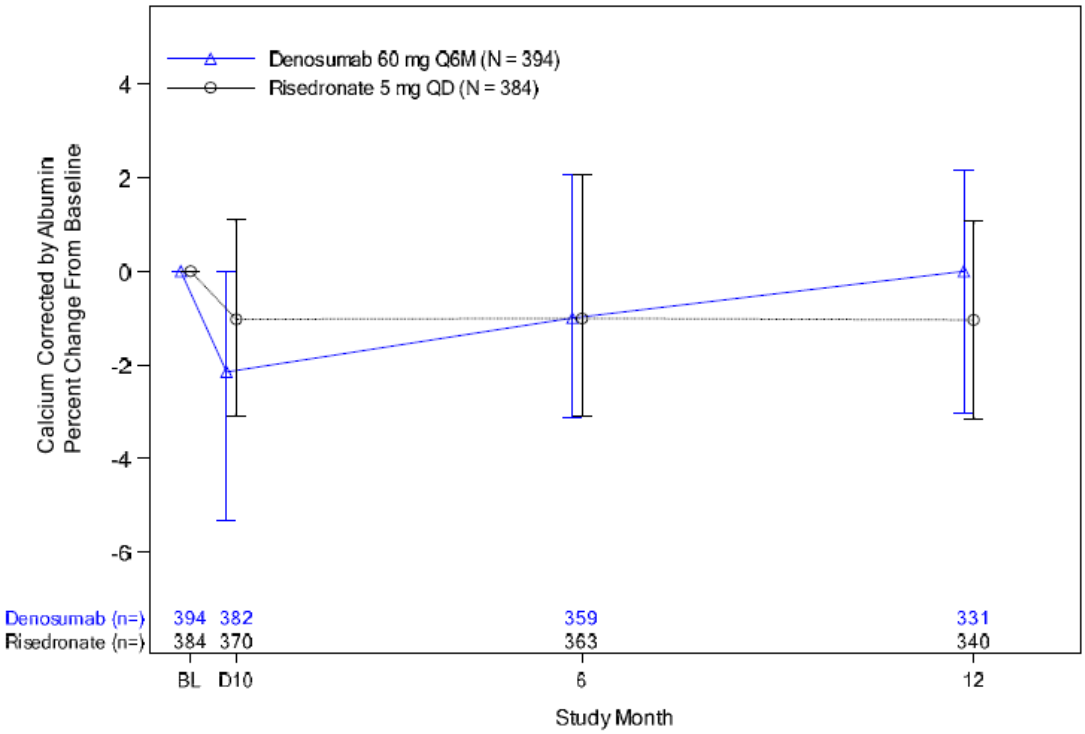
Recently, a small but statistically significant in new primary malignancies has been identified in populations with advanced cancer treated with higher doses of denosumab (xgeva vs zolendronic acid). No imbalances were seen in pivotal Prolia studies. A small numerical imbalance was noted in this study. Systemic glucocorticoids are potent immunosuppressants and these patients may have increased cancer risk. However, the number of cases from this study (12 vs 7) is small.

Laboratory findings

Albumin-corrected calcium

Mean calcium values decreased slightly in both treatment groups postbaseline; the mean decrease from baseline at day 10 was slightly more pronounced in the denosumab group (-2.51%) than in the risedronate group (-0.75%)

Table. Percent Change From Baseline in Calcium Corrected by Albumin by Visit, Median and Inter-quartile Ranges (Safety Analysis Set12-month Primary Analysis)



N = Number of subjects who received at least one dose of investigational product
n = Number of subjects with observed data

Slight mean decreases in serum phosphorus were observed that were more pronounced at day 10 in the denosumab group (-7.72%) than in the risedronate group (-0.99%).

Mean decreases from baseline in alkaline phosphatase were observed at month 6 and month 12 in both treatment groups, and were more pronounced in the denosumab group than in the risedronate group. Mean change from baseline to month 6 was -12.128% in the denosumab group, compared with -4.18% in the risedronate group; and mean change from baseline to month 12 was -8.51% in the denosumab group and -1.91% in the risedronate group.

Subject Incidence of Laboratory CTCAE Grade ≥ 3 During the Study (Safety Analysis Set 20101217 12-month Primary Analysis)

Laboratory Parameters	Relationship to Normal	Grade	Risedronate 5 mg QD (N = 384) n (%)	Denosumab 60 mg Q6M (N = 394) n (%)
Number of subjects with a laboratory CTCAE grade ≥ 3			34 (8.9)	44 (11.2)
Sodium	Below	Grade 3	2 (0.5)	3 (0.8)
Potassium	Above	Grade 4	1 (0.3)	0 (0.0)
	Below	Grade 3	1 (0.3)	2 (0.5)
Magnesium	Above	Grade 3	0 (0.0)	1 (0.3)
Calcium	Below	Grade 3	0 (0.0)	1 (0.3)
Calcium (Corrected)	Above	Grade 3	0 (0.0)	1 (0.3)
	Below	Grade 3	0 (0.0)	1 (0.3)
Phosphorus	Below	Grade 3	2 (0.5)	7 (1.8)
Aspartate Amino Transferase	Above	Grade 3	1 (0.3)	0 (0.0)
Alanine Amino Transferase	Above	Grade 3	2 (0.5)	2 (0.5)
Glucose	Above	Grade 3	3 (0.8)	6 (1.5)
	Below	Grade 3	1 (0.3)	0 (0.0)
Hemoglobin	Below	Grade 3	3 (0.8)	1 (0.3)
Platelets	Below	Grade 3	0 (0.0)	1 (0.3)
		Grade 4	0 (0.0)	2 (0.5)
White Blood Cells	Below	Grade 3	2 (0.5)	0 (0.0)
Total Neutrophils	Below	Grade 3	2 (0.5)	0 (0.0)
Lymphocytes	Below	Grade 3	5 (1.3)	7 (1.8)
Absolute Neutrophil Count	Below	Grade 3	2 (0.5)	0 (0.0)
International Normalized Ratio	Above	Grade 3	12 (3.1)	14 (3.6)

N = Number of subjects who received ≥ 1 dose of investigational product
The maximum toxicity grade experienced by each subject is based on the Common Terminology Criteria for Adverse Events, version 3.0.

Safety in special populations

Data on safety in special populations are limited to subgroup analyses by gender. Overall, the subject incidence of AEs and SAEs in the GIOP population in study 20101217 was consistent with that observed in the primary osteoporosis and HALT populations during the first 12 months of the studies in both women and men.

Safety in patients with renal impairment

Patients with severe renal impairment (Cockcroft-Gault formula of ⩽ 30 mL/min/1.73 m2) were not included in the trial. These patients are at increased risk of adverse events such as hypocalcaemia associated with denosumab, and the risk is likely increased in patients with concomitant glucocorticoid treatment. The MAH was asked to summarize safety data for patients with moderate renal impairment (GFR 30-60 mL/min/1.73 m2) in GIOP study 20101217:

Table. Most frequent Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term for Subjects with Baseline eGFR 30-60 mL/min/1.73 m2 (Safety Analysis Set) (20101217 Final Analysis)

System Organ Class Preferred Term	Risedronate 5 mg QD (N = 60) n (%)	Denosumab 60 mg Q6M (N = 74) n (%)
Number of subjects reporting treatment-emergent serious adverse events	16 (26.7)	24 (32.4)
Cardiac disorders	4 (6.7)	6 (8.1)
Infections and infestations	3 (5.0)	6 (8.1)
Musculoskeletal and connective tissue disorders	3 (5.0)	5 (6.8)
Nervous system disorders	2 (3.3)	4 (5.4)
Gastrointestinal disorders	1 (1.7)	4 (5.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	4 (5.4)

Table. Treatment-emergent Fatal Adverse Events by Preferred Term for Subjects with Baseline eGFR 30-60 mL/min/1.73 m2 (Safety Analysis Set) (20101217 Final Analysis)

Preferred Term	Risedronate 5 mg QD (N = 60) n (%)	Denosumab 60 mg Q6M (N = 74) n (%)
Number of subjects reporting treatment-emergent fatal adverse events	2 (3.3)	8 (10.8)
Alveolitis allergic	0 (0.0)	1 (1.4)
Cardiac arrest	0 (0.0)	1 (1.4)
Cerebrovascular accident	0 (0.0)	1 (1.4)
Death	0 (0.0)	1 (1.4)
Intestinal obstruction	0 (0.0)	1 (1.4)
Organising pneumonia	0 (0.0)	1 (1.4)
Rectal cancer metastatic	0 (0.0)	1 (1.4)
Subarachnoid haemorrhage	0 (0.0)	1 (1.4)
Blood pressure increased	1 (1.7)	0 (0.0)
Septic shock	1 (1.7)	0 (0.0)

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N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the denosumab group and coded using MedDRA version 20.0.

In the subgroup of patients with GFR 30-60 mL/min/1.73 m2 (N=135); the safety profile was numerically in favour of risendronate. Serious adverse events occurred with risendronate 27% vs denosumab 32%. Fatal events occurred with risendronate 3.3% vs denosumab 11%. Hypocalcaemia was not reported as a preferred term as a serious or fatal AE.

No data is available for patients with severe renal impairment (GFR ≤ 30) and concomitant denosumab and glucocorticoid treatment. Risendronate and other bisphosphonates are contraindicated in patients with GFR ≤ 30. In clinical practice, if approved for GIOP, denosumab could be considered to be the first-line treatment for these patients, although not studied. The absence of safety data in patiens with GFR ≤ 30 has been now included in the SmPC as well as an amendment to the 4.4: “Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia.”

Safety related to drug-drug interactions and other interactions

No relevant safety information related to drug-drug interactions and other interactions has been provided. This is considered acceptable based on the available data from previous trials.

Discontinuation due to adverse events

Overall, 25 subjects (6.3%) in the denosumab group and 29 subjects (7.6%) in the risedronate group discontinued investigational product due to adverse events

The most frequent events leading to investigational product discontinuation in the denosumab group were dyspepsia and abdominal distension.

A total of 13 subjects (3.3%) in the denosumab group and 14 subjects (3.6%) in the risedronate group discontinued investigational product due to adverse events considered related to investigational product. All of the cases of dyspepsia, abdominal pain upper and abdominal distension were considered related to investigational product.

Safety data compared to approved PMO and HALT indications

In the pivotal PMO study 20030216, 3 years duration:

Serious adverse events were reported for 25.8% of subjects in the denosumab group and 25.1% of subjects in the placebo group. SOCs with the highest subject incidences of adverse events in the denosumab group were cardiac disorders (5.0% denosumab, 4.1% placebo), musculoskeletal and connective tissue disorders (4.2% denosumab, 3.8% placebo), neoplasms benign, malignant and unspecified (incl cysts and polyps) (4.1% denosumab, 3.6% placebo), infections and infestations (4.1% denosumab, 3.4% placebo), and gastrointestinal disorders (3.7% denosumab, 2.7% placebo).

Pivotal HALT study:

In the Serious adverse events were reported for 34.6% of subjects in the denosumab group and 30.6% of subjects in the placebo group. The most commonly affected organ classes were denosumab, placebo) being cardiac disorders (9.4% denosumab, 10.3% placebo), nervous system disorders (6.8% denosumab, 4.8%), infections and infestations (5.9% denosumab, 4.6% placebo), and neoplasms (5.1% denosumab 5.8% placebo).

Of note, these studies had a placebo group, the current study 20101217 had risendronate as an active comparator.

Adverse events of hypocalcaemia do not show significant differences between groups and indications investigated. There was no case of adjudicated positive osteonecrosis of the jaw during the first 12 months of any of these studies. However, the risk of osteonecrosis of the jaw increases with denosumab treatment duration. There were cases of hypersensitivity related adverse events in study 20101217 and the incidence was higher in the denosumab than in the risedronate group. The incidence of hypersensitivity related adverse events with denosumab was comparable to that seen in previous trials. The analysis of adverse events of serious infection in study 20101217 indicated comparable subject incidences between denosumab and risedronate groups both for overall adverse events of infection and for serious infections; in both groups the incidence of serious infections was higher than in the two other indications which is considered in line with underlying medical conditions and concomitant therapies. Safety data on adverse events of serious bacterial cellulitis did not indicate relevant differences between groups and are considered to be in line with previous findings. The subject incidence of adverse events of malignancies was comparable between groups and in line with previous findings. The subject incidences of adverse events of cardiac as well as vascular disorders in study 20101217 were comparable between groups; the incidence of cardiac disorders was in line with previous findings, while the incidence of vascular disorders (cerebrovascular disorders not included here) was higher in the previous osteoporosis and HALT studies than in the GIOP trial. There was 1 case of adjudicated positive atypical femoral fracture in the denosumab versus none in the risedronate group in the GIOP study. No atypical femoral fractures were reported during the first year in the previous studies. The analysis of adverse events of eczema or pancreatitis did not indicate relevant new findings in study 20101217. In study 20101217, the subject incidence of adverse events of musculoskeletal pain was comparable between groups, but lower than in previous trials in the primary osteoporosis and HALT populations. The incidence of subjects with a laboratory parameter with toxicity grade $\geqslant$3 abnormality was higher in the GIOP than the primary osteoporosis and HALT population, consistent with the underlying medical condition of the subjects. Safety data on albumin-adjusted serum calcium, phosphorus levels and alkaline phosphatase were in line with data from previous studies. In study 20101217 only 1 positive result for binding anti-denosumab antibodies was seen in a patients on denosumab. So far no neutralising antibodies have been reported in any denosumab clinical trial.

2.5.1. Discussion on clinical safety

In general, the safety profile for denosumab in the current glucocorticoid-induced osteoporosis study did not markedly differ from that in female (postmenopausal) osteoporosis studies, where safety evaluation is based on larger numbers and longer observation periods.

The total number of serious adverse events, treatment related adverse events and discontinuations were balanced between the treatment groups. Hypersensitivity and bacterial cellulitis were numerically more frequent in the denosumab arm. One hypocalcaemia and one adjudicated atypical femur fracture occurred in the denosumab arm compared to none in the risendronate group. All these are identified risks for denosumab.

The study was smaller and shorter (primary analysis at 12 months, final analysis at 24 months than PMO and HALT studies (three years) which is a limitation for the safety evaluation in the corticosteroid induced osteoporosis population. On the other hand, in clinical practice, the goal is to the scale down the GC exposure as soon as possible and concomitant antiresorptive treatment is also often limited in time.

Corticosteroid use is a known risk factor for ONJ and rigorous exclusion criteria regarding dental health were applied in the current study. “Corticosteroids” is included as a risk factor for ONJ in the current Prolia SmPC. No further SmPC changes are require at this time point. The risk will be closely monitored in subsequent PSURs.

Corticosteroid treatment is considered as a risk factor for atypical fractures. At the time of the latest PSUR, there had been 5 positively adjudicated atypical femoral fracture cases in clinical trials with Prolia.. In the current relatively small and short study 20101217, there were two femoral fractures in the safety analysis set reported for denosumab vs none in risendronate, indicating a possibly higher incidence in this population treated with denosumab. One of the cases was positively adjudicated as AFF.

In the study 20101217 12-month Primary Analysis, there were two deaths in the denosumab group due to cerebrovascular cause. While a numerically higher number of cerebrovascular SAEs were observed in denosumab treated subjects in the GIOP study, the number of cases was limited. The issue will be followed in PSURs.

The MAH has previously conducted a study in the Treatment of Rheumatoid Arthritis. A total of 227 subjects were enrolled and randomized and 203 (89%) completed the 12-month treatment period, last visit occurred in 2007. RA is not a labelled indication for denosumab. Safety results from study 20040144 (Multi-dose Phase 2 Study in the Treatment of Rheumatoid Arthritis) have been reviewed by the CHMP. No new signal was identified during the 12 month treatment period (two doses given at baseline and at month 6). The incidence of RA flares during the off-treatment period 12-24 months appeared to be higher in the denosumab-treated groups. This difference, however, was not considered to reflect a higher incidence of RA flares following denosumab discontinuation, but is the result of an unexpectedly lower incidence of RA flares in the off-treatment, as compared to the on-treatment, period among subjects previously exposed to placebo.

In the subgroup of patients with GFR 30-60 mL/min/1.73 m2 (N=135) serious adverse events occurred with risendronate in 27% vs denosumab in 32%. Fatal events occurred with risendronate in 3.3% vs denosumab in 11%. Hypocalcaemia was not reported as a preferred term as a serious or fatal AE. Patients with severe renal impairment (Cockcroft-Gault formula of $\leq$ 30 mL/min/1.73 m2) were not included in the trial. There was no available safety data for patients with severe renal impairment (eGFR $\leq$ 30 and concomitant glucocorticoid treatment) from other denosumab studies, as other denosumab studies have included too few patients with both renal impairment and concomitant glucocorticoid use. This vulnerable group may be at increased risk of adverse events. The absence of safety data in patients

with GFR ≤ 30 is included in the SmPC and section 4.4 has been amended in order to highlight an increased risk (eg, “Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia”)

Animal studies have shown reproductive toxicity. SmPC section 4.6 has been updated to include information on contraception and that women should be advised not to become pregnant for at least 5 months after treatment with Prolia, which is in line with the current recommendations for Xgeva.

2.5.2. Conclusions on clinical safety

In general, the safety profile for denosumab in the current GIOP study did not markedly differ from the previous studies; safety data up to 24 months has been evaluated and specific information added to the SmPC.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 24 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Important identified risks	hypocalcemia, skin infection leading to hospitalization, osteonecrosis of the jaw, hypersensitivity reactions, atypical femoral fracture, musculoskeletal pain
Important potential risks	fracture healing complications, infection, cataracts in men with prostate cancer receiving androgen deprivation therapy, cardiovascular events, malignancy, immunogenicity, osteonecrosis outside the jaw including external auditory canal, hypercalcemia following treatment discontinuation in patients with growing skeletons
Missing information	risks with pregnancy/lactation, use in pediatric patients, use in patients with hepatic impairment, potential adult off-label use

Pharmacovigilance plan

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20080560 Controlled clinical study A double-blind, placebo-controlled study to evaluate new or worsening lens opacifications in subjects with non-metastatic prostate cancer receiving denosumab for bone loss due to androgen deprivation therapy Category 3	To assess the effect of denosumab on cataract event development or progression by month 12 based on a change of ≥ 1.0 in posterior subcapsular (P), ≥ 1.0 in cortical, or ≥ 0.7 in nuclear opalescence (NO) using the Lens Opacities Classification System III (LOCS III) score. To assess the effect of denosumab on cataract event development or progression by month 12 based on a change of ≥ 1.5 in P, ≥ 1.5 in C, or ≥ 1.5 in NO using the LOCS III score To assess the effect of denosumab on cataract event development or progression by month 6 based on LOCS III scores To assess the effect of denosumab on confirmed cataract event development or progression by month 12 based on LOCS III scores To assess the effect of denosumab on the incidence of decreased best corrected visual acuity (BCVA) from the baseline BCVA on the Early Treatment Diabetic Retinopathy Study (ETDRS) charts To assess the effect of denosumab on change in refraction needed to achieve BCVA To describe the safety of denosumab administration as measured by adverse events and safety laboratory parameters	Cataract in men with prostate cancer receiving androgen deprivation therapy	Ongoing	Anticipated Q1 2017

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20090522 Postmarketing observational study Denosumab global safety assessment among women with postmenopausal osteoporosis (PMO) and men with osteoporosis in multiple observational databases Category 3	Determine incidence of AESI in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and among all women with PMO Describe characteristics, clinical features, and AESI risk factors in women with PMO exposed to denosumab, women with PMO exposed to bisphosphonates, and all women with PMO Compare the incidence of the AESI in women with PMO exposed to denosumab to that in women with PMO exposed to bisphosphonates Describe incidence of AESI in postmenopausal women Describe denosumab utilization patterns in patients who receive denosumab therapy for treatment of PMO. Describe denosumab utilization patterns in patients who receive denosumab therapy for unapproved indications In men with osteoporosis treated with denosumab, describe patient characteristics, clinical features, AESI risk factors, patient follow-up, incidences of AESI, and denosumab utilization patterns (US Medicare data system and United Healthcare data system)	Osteonecrosis of the jaw, atypical femoral fracture, fracture healing complications, hypocalcemia, Infection (including skin infection), hypersensitivity leading to hospitalization or emergency room visit, malignancy	Ongoing	Annually from 05 December 2014; final report Q2 2023

Study/Activity Type, title and category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20130173 Controlled clinical study Prospective, multicenter, single-arm study to evaluate efficacy, safety, and pharmacokinetics of denosumab in children with osteogenesis imperfecta Category 3	Evaluate the effect of denosumab on lumbar spine BMD Z-score at 12 months, as assessed by DXA, in children 2 to 17 years of age with OI.	Hypocalcemia, atypical femoral fracture, hypercalcemia following treatment discontinuation in patients with growing skeletons	Ongoing	Final report: 31 March 2022

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Hypocalcemia	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • What you need to know before you use Prolia • Warnings and precautions • Possible side effects	DHPC was distributed
Skin infection leading to hospitalization	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • Warnings and precautions • Possible side effects	None
Osteonecrosis of the jaw	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • Warnings and precautions • Possible side effects	• DHPC was distributed • Patient reminder card was distributed
Hypersensitivity reactions	Relevant text is provided in the following sections of the SmPC: • Section 4.3, Contraindications • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • What you need to know before you use Prolia • Possible side effects	None
Safety Concern	Routine Risk Minimization Measures	Additional

		Risk Minimization Measures
Important Identified Risks (continued)		
Atypical femoral fracture	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • What you need to know before you use Prolia Possible side effects	DHPC was distributed
Musculoskeletal pain	Relevant text is provided in the following sections of the SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: Possible side effects	None
Important Potential Risks		
Fracture healing complications	Relevant text is provided in the following sections of the SmPC: • Section 5.3, Preclinical safety data	None
Infection	Relevant text is provided in the following sections of the SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • Possible side effects	None
Cataracts in men with prostate cancer receiving androgen deprivation therapy	Relevant text is provided in the following sections of the SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • Possible side effects	None
Cardiovascular events	None	None
Malignancy	None	None
Immunogenicity	Relevant text is provided in the following sections of the SmPC: • Section 5.1, Pharmacodynamic properties	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Potential Risks (continued)		
Osteonecrosis outside the jaw including external auditory canal	None	None
Hypercalcemia following treatment discontinuation in patients with growing skeletons	None	None
Missing Information		
Risks during pregnancy and lactation	Relevant text is provided in the following sections of the SmPC: • Section 4.6 Fertility, pregnancy and lactation • Section 5.3 Preclinical safety data Relevant text is provided in the following sections of the PIL: Pregnancy and breastfeeding	None
Use in pediatric patients	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration, • Section 5.2, Pharmacokinetic properties • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the PIL: Children and adolescents	None
Use in patients with hepatic impairment	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 5.2, Pharmacokinetic properties	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.6 and 5.1 of the SmPC have been updated. In addition, changes related to section 4.4 of the SmPC have been updated with regard to warnings for excipients. The Package Leaflet has been updated accordingly.

SmPC section 4.1 has been revised as follows (new text in bold):

"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.

Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see section 5.1)."

For the other changes of the SmPC see Attachment 1.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Favourable effects

The pivotal trial (2010217) to support the new indication glucocorticoid induced osteoporosis (GIOP) is a randomised, double-blind bridging study in patients treated with denosumab 60mg (N=398) or risedronate Q6M (N=397) for 24 months. Subjects who had initiated administration of prednisone or equivalent within 3 months or ≥ 3 months before screening were part of the GC-I subpopulation (N=290) or GC-C subpopulation (N=505), respectively. The primary analysis was performed at 12 months.

Non-inferiority on the primary endpoint has been demonstrated; in the glucocorticoid-continuing subpopulation, denosumab demonstrated an increase in lumbar spine BMD compared to risedronate at 1 year (denosumab 4.4%, risedronate 2.3%; $p < 0.001$) and 2 years (denosumab 6.4%, risedronate 3.2%; $p < 0.001$). In the glucocorticoid-initiating subpopulation, denosumab demonstrated an increase in lumbar spine BMD compared to risedronate at 1 year (denosumab 3.8%, risedronate 0.8%; $p < 0.001$) and 2 years (denosumab 6.2%, risedronate 1.7%; $p < 0.001$).

For the claim of denosumab being superior to risedronate with regard to increases in BMD, the MAH performed on request of the CHMP additional analyses based on all randomised subjects according to the intention-to-treat principle (FAS) using a method for handling of missing data which ensures a sufficiently conservative estimate, based on FAS and BOCF. Data based on these more conservative analyses are therefore provided in section 5.1 of the SmPC to reflect the outcomes (denosumab demonstrated a greater increase in lumbar spine BMD compared to risedronate in the glucocorticoid-continuing subpopulation at 1 year: denosumab 3.6 %, risedronate 2.0%; $p < 0.001$, and 2 years: denosumab 4.5%, risedronate 2.2%; $p < 0.001$, as well as in the glucocorticoid-initiating subpopulation at 1 year: denosumab 3.1 %, risedronate 0.8%; $p < 0.001$, and 2 years: denosumab 4.6%, risedronate 1.5%; $p < 0.001$).

Results from the secondary analyses on the change of femoral neck and hip BMD were in line with the primary outcome.

The pharmacokinetic data provided in patients with GIOP do not suggest any differences in exposure that would necessitate a dose adjustment in the new proposed indication compared to postmenopausal females.

3.2. Uncertainties and limitations about favourable effects

The study was not powered in order to demonstrate non-inferiority/superiority in fracture endpoints. The primary analysis conducted at 12 months showed that the subject incidence of new vertebral fracture was numerically lower (2.7% [95% CI: 1.2, 5.1] versus 3.2% [95% CI: 1.6, 5.7]), and the subject incidence of non-vertebral fracture was numerically higher (4.3% [95% CI: 2.5, 6.8] versus 2.5% [95% CI: 1.2, 4.6]), in the denosumab group compared with the risedronate group. A total of 20 nonvertebral fractures occurred in the denosumab group vs 10 in the risendronate group. Most of the fractures occurred in the GC-C subpopulation, as expected.

The final analysis conducted at 24 months showed that the subject incidence of new vertebral fracture continued to be numerically lower in the denosumab group compared with the risedronate group (4.1% [95% CI: 2.3, 6.9] versus 5.8%. [95% CI: 3.6, 8.8]), and the subject incidence of non-vertebral fracture continued to be numerically higher between the 2 treatment groups (5.3% [95% CI: 3.3, 8.0] versus 3.8% [95% CI: 2.1, 6.2]). The number of non-vertebral fractures was 24 versus 16 in the denosumab versus risedronate group, respectively.

The number of premenopausal women (and men < 50 years) in the pivotal trial was very small (participants < 50 years: 7.8 - 8.8 % in various groups).

In clinical practice, the goal is to the scale down the GC exposure as soon as possible. The current study was not designed to investigate the optimal duration of treatment for GIOP and outcomes after GC discontinuation.

3.3. Unfavourable effects

In general, the safety profile for denosumab in the current corticoid-induced osteoporosis study did not markedly differ from that in the postmenopausal osteoporosis studies, where safety evaluation is based on larger numbers and longer observation periods.

The total number of serious adverse events, treatment related adverse events and discontinuations were balanced between the treatment groups. Hypersensitivity cases with 25 (6.3%) vs 18 (4.7%) and bacterial cellulitis with 7 (1.8%) vs 2 (0.5%) were numerically more frequent in the denosumab arm at both timepoints of 12 and 24 months. One hypocalcaemia event and one adjudicated atypical femur fracture occurred in the denosumab arm compared to none in the risendronate group. All these are already identified risks for denosumab.

3.4. Uncertainties and limitations about unfavourable effects

The study was smaller and shorter (primary analysis at 12 months, final analysis at 24 months) than PMO and HALT studies (three years) which is a limitation for the safety evaluation in the GIOP population. On the other hand, in clinical practice, the goal is to scale down the GC exposure as soon as possible and concomitant antiresorptive treatment is also often limited in time.

There is no available safety data for patients with severe renal impairment (eGFR $\leq$ 30) and concomitant glucocorticoid treatment.

Corticosteroid use is a known risk factor for ONJ and rigorous exclusion criteria regarding dental health were applied in the current study. “Corticosteroids” is included as a risk factor for ONJ in the current Prolia SmPC. No further SmPC changes are require at this time point. The risk will be closely monitored in subsequent PSURs.

Corticosteroid treatment is considered as a risk factor for atypical fractures. At the time of the latest PSUR, there had been 5 positively adjudicated atypical femoral fracture cases in clinical trials with Prolia. In the current relatively small and short study 20101217, there were two femoral fractures in the safety analysis set reported for denosumab vs none for risendronate, indicating a higher incidence in this population treated with denosumab. One of the cases was positively adjudicated as AFF.

In the 12-month Primary Analysis of study 20101217, there were two deaths in the denosumab group due to cerebrovascular cause. While a numerically higher number of cerebrovascular SAEs were observed in denosumab treated subjects in the GIOP study, the number of cases was limited. The issue will be followed in PSURs.

3.5. Effects Table

Table. Effects Table for trial 20101217 - primary analysis at 12 months

Effect	Unit	Denosumab GC-I	Denosumab GC-C	Risendronate GC-I	Risendronate GC-C	Strength of evidence
Favourable Effects						
BMD lumbar spine (LS mean change from baseline)	%	3.1	3.6	0.8	2.0	Superiority (FAS) P < 0.001
Radiological vertebral fractures	n/N (%)	9/333 (2.7)		11/342 (3.2)		
Non-vertebral fractures	n/N (%)	17/398 (4.3)		10/397 (2.5)		
Unfavourable Effects						
Discontinuations	N (%)	23 (15.9)		14 (9.7)		
Deaths	N (%)	6 (1.5)		2 (0.5)		
Hypersensitivity	N (%)	19 (4.8)		12 (3.1)		
Bacterial cellulitis	N (%)	4 (1.0)		1 (0.3)		

(GC-I, glucocorticoid-initiating subpopulation; GC-C, glucocorticoid-continuing subpopulation)

3.6. Benefit-risk assessment and discussion

3.6.1. Importance and balance of favourable and unfavourable effects

Although glucocorticoids are effectively being used in the management of many inflammatory conditions, their use is associated with significant adverse outcomes. Osteoporosis, with resultant fractures, constitutes one of these. A rapid decline in bone mineral density (BMD) begins typically within the first 3 months of glucocorticoid use and peaks at 6 months, followed by a slower phase. An increased risk of both vertebral and nonvertebral fractures has been reported. However, there has been some controversy regarding the dose of glucocorticoid treatment at which an increased risk of fracture occurs.

Postmenopausal women and elderly men are at a higher risk for developing glucocorticoid-induced bone loss and fractures.

Efficacy in fracture risk reduction is regarded as the most relevant endpoint for osteoporosis treatment trials. Changes in BMD correlate to the decrease in fracture risk. For men with osteoporosis, BMD measurement at 12 months is considered a valid surrogate endpoint in bridging studies according the Guideline of new medicinal products in the treatment of primary osteoporosis (CPMP/EWP/552/95 Rev.2). This guideline does not specifically describe requirements for an approval of treatment of glucocorticosteroid induced osteoporosis; however, similar indications have been approved based on this type of data extrapolation (for example with the centrally authorised product zoledronic acid). BMD increases with denosumab were associated with fracture risk reduction in the previous pivotal studies 20030216 and 20040138, and BMD increases within the same range were now observed in Study 20101217.

Treatment with denosumab increase BMD T-score in the studied population and in the pivotal study the effect was more pronounced compared to risedronate. However, the adequacy of extrapolating benefits with respect to reduction of fracture risk from the PMO population to the GIOP population may not be straight forward considering that underlying pathomechanisms of osteoporosis are to some extent different. However, GIOP and PMO also share a number of characteristics with respect to the cellular pathophysiology of bone loss. Increased bone turnover occurs in both conditions, even though it differs in its time course. This justification supports that the increase of BMD T-score is expected to translate into a reduced risk of fractures also in the GIOP scenario.

Some data on the relationship of BMD changes and vertebral fracture rates are also available from placebo-controlled therapeutic interventions in the target population e.g. with risedronate. Although it can be questioned if data for risendronate can be extrapolated to denosumab considering different mechanisms of action, both are anti-resorptive treatments and it is not plausible that that the different mechanisms would lead to substantial differences in the ability to prevent fractures.

One uncertainty with respect to the effect on prevention of fractures is the imbalance in non-vertebral fractures seen in the pivotal study with numerically more fractures occurring in the denosumab group compared to risendronate. However, the study was not designed with adequate statistical power to detect similarity/difference in the incidence of fractures between treatment groups. Further, denosumab was superior to risedorante concerning increase of BMD T-score and there was no imbalance in the incidence of vertebral fractures.

Start of treatment in practice does not only rely on absence or presence of osteoporosis (as defined by T-score) but on overall recognition of an increased risk of fracture of the patient. In order to start treatment, a commonly used threshold of ≥ 7.5 mg prednisone equivalent per day and the intended or actual use over at least 3 months is generally considered reasonable. An early and transient increase in bone resorption in GIOP occurs against a background of low bone turnover with reduced bone formation. A start of treatment for GIOP once the patient is being exposed to glucocorticoids (GCs) is therefore relevant as an early (and transient) increase in bone resorption occurs in patients that initiate glucocorticoid therapy. This treatment strategy was supported by the Ad Hoc Expert group.

In general, requirements for an indication “treatment of bone loss associated with glucocorticoid therapy” are not included in EU regulatory guidelines and are not part of approval of other anti-osteoporotic agent authorised in the EU. Some of these anti-osteoporosis agents are authorised for the indication “treatment of GIOP” based on similar study designs and results as in the current study with denosumab. However, similar in wording with approved indications for Prolia *(Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures),* CHMP considered the chosen wording of the new indication for Prolia as adequate as the target population treated with glucocorticoids does not

only include patients with established osteoporosis.

The number of premenopausal women (and men < 50 years) in the pivotal trial was very small which was discussed by the Ad Hoc Expert group who had some concerns with the reliability of fracture risk estimates of this subpopulation of the study. However, the experts pointed out, that there are cases of (unmet) need for treatment of premenopausal women on GCs considered at high risk of fracture. Based on the mechanism of both GIOP and denosumab, it is considered that the new indication should not be limited to post-menopausal women and elderly men only. As animal studies with denosumab have shown reproductive toxicity, SmPC section 4.6 has been updated to include information on contraception and that women should be advised not to become pregnant for at least 5 months after treatment with Prolia, which is in line with the current recommendations for Xgeva.

One other limitation is that there was no safety data available for patients with severe renal impairment (eGFR ≤ 30) and concomitant glucocorticoid treatment. This vulnerable group may be at increased risk of adverse events. The absence of safety data in patients with GFR ≤ 30 is included in the SmPC. SmPC section 4.4 has been amended in order to highlight an increased risk (e.g. "Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia").

Taking into account above considerations and available data, it is reasonable to extrapolate anti-fracture efficacy of denosumab from PMO to GIOP based on similar BMD changes, similar to the extrapolation of data with some other antiresorptive agents used in GIOP. The study results regarding BMD and vertebral and non-vertebral fractures are presented in section 5.1 of the SmPC.

3.7. Conclusions

The overall B/R of Prolia, including for treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture, is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture for Prolia; as a consequence, sections 4.1, 4.2, 4.4, 4.6 and 5.1 of the SmPC are updated. In addition, a minor change is made to the existing warning regarding sorbitol content in section 4.4 of the SmPC. The Package Leaflet is updated in accordance. The Risk Management Plan is also updated to version 24.

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture for Prolia; as a consequence, sections 4.1, 4.2, 4.4, 4.6 and 5.1 of the SmPC are updated. In addition, a minor change is made to the existing warning regarding sorbitol content in section 4.4 of the SmPC. The Package Leaflet is updated in accordance. The Risk Management Plan is also updated to version 24.

Summary

Please refer to the published assessment report Prolia-H-C-1120-II-0068.