25 April 2014
EMA/CHMP/267934/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prolia

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/001120/II/0030

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
ADT	androgen deprivation therapy
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMD	bone mineral density
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum serum concentration
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Effects
CTX1	C-telopeptide of type 1 collagen
DXA	dual X-ray absorptiometry
EMA	European Medicines Agency
ER	emergency room
FDA	Food and Drug Administration
GREES	Group for the Respect of Ethics and Excellence in Science
HALT	hormone ablation therapy
ICH	International Conference on Harmonisation
K_d	dissociation equilibrium constant
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
ONJ	osteonecrosis of the jaw
PMO	postmenopausal osteoporosis
Q6M	every 6 months
Q4W	once every 4 weeks
RANKL	RANK ligand
SC	subcutaneous(ly)
SOC	system organ class
WHO	World Health Organization

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 8 August 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Prolia	denosumab	See Annex A

The following variation was requested:

Variation requested		**Type**
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	II

The MAH proposed to add the following new therapeutic indication: treatment of osteoporosis in men at increased risk of fracture. As a consequence the MAH proposed to update sections 4.1 and 5.1 of the SmPC. The Package Leaflet was proposed to be updated accordingly. In addition, the MAH proposed to make an update to the statement in section 5.1 of the SmPC related to the paediatric investigation plan.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Kristina Dunder

Co-Rapporteur: Jan Mueller-Berghaus

1.2. Steps taken for the assessment

Submission date:	8 August 2013
Start of procedure:	23 August 2013
Rapporteur's preliminary assessment report circulated on:	18 October 2013
Co-Rapporteur's preliminary assessment report circulated on:	14 October 2013
Rapporteurs' joint updated assessment report circulated on:	15 November 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 November 2013
MAH's responses submitted to the CHMP on:	22 February 2014
Rapporteurs' assessment report on the MAH's responses circulated on:	25 March 2014
PRAC Rapporteur's RMP assessment report circulated on:	27 March 2014
CHMP opinion:	25 April 2014

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0086/2013 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

2. Scientific discussion

2.1. Introduction

Osteoporosis is a systemic skeletal disease characterized by a decrease in bone mass greater than expected for an individual's sex, age, and race. Age-related osteoporosis causes loss in both trabecular and cortical bone and microarchitectural deterioration. These changes increase bone fragility and susceptibility to fracture.

Denosumab is a fully human monoclonal IgG2 antibody that binds to and neutralizes the activity of RANKL. In blocking RANKL, denosumab inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. Denosumab, under the trade name Prolia, is currently approved for use in bone-loss conditions, including in women with postmenopausal osteoporosis, men with non-metastatic prostate cancer receiving androgen deprivation therapy (certain regions), and in women with breast cancer receiving adjuvant aromatase inhibitor therapy (certain regions). The approval of denosumab in women with postmenopausal osteoporosis was based on the demonstration of anti-fracture efficacy in this patient population.

The purpose of this application is to add the following new indication to the Prolia Summary of Product Characteristics (SmPC): "Treatment of osteoporosis in men at increased risk of fracture."

The pivotal study undertaken in support of the application was conducted to assess the efficacy and safety of denosumab in men with low bone mineral density (BMD). Comprising two 12-month periods, the study was designed to compare the effects of denosumab versus placebo on BMD, bone turnover markers, and various safety parameters over 1 year of double-blind treatment, and to thereafter assess the safety of denosumab at 24 months following the 12-month open-label period, where all subjects (regardless of randomization in the double-blind period) received denosumab.

Paediatic requirements

At the time of submission of the initial Prolia marketing authorisatio application (MAA) in 2009, EMA confirmed that the indication to treat postmenopausal osteoporosis (PMO) fell within the scope of the class waiver for the "Treatment of menopausal and other perimenopausal disorders". This class waiver has however subsequently been revoked and PMO now falls within the scope of PIP2 for denosumab (EMEA – 000145-PIP02-12, Condition Osteoporosis). A product specific waiver was granted for the condition: "treatment of bone loss associated with sex hormone ablative therapy" as part of PIP 1 for Denosumab (EMEA – 000145-PIP01-07).

The proposed new indication falls within the scope of PIP2 for denosumab (EMEA – 000145-PIP02-12, Condition Osteoporosis). Indications targeted by this PIP are "treatment of glucocorticoid-induced osteoporosis" and "treatment of osteogenesis imperfecta", both of which are deferred measures.

2.2. Non-clinical aspects

No safety concerns were identified that would necessitate further non-clinical evaluation in support of the use of denosumab in patients with male osteoporosis, and therefore no new non-clinical data or summary documents are included, which is acceptable.

2.3. Clinical Pharmacology aspects

2.3.1. Pharmacokinetics

The Pharmacokinetics of subcutaneously administered denosumab has been thoroughly characterized in healthy subjects and in patients with low BMD, osteoporosis, or bone loss associated with HALT. Pharmacokinetic analysis was not conducted in patients in the pivotal study 20080098, which is acceptable.

The proposed dosing regimen (60 mg SC Q6M) for men with osteoporosis is the same as the currently approved one for postmenopausal women with osteoporosis and for men with prostate cancer receiving androgen deprivation therapy.

Previous studies included in the application for the PMO and HALT indications have demonstrated that the pharmacokinetics of denosumab is not significantly affected by age, sex, race, weight, body mass index or disease state. A tendency of lower exposure in patients with higher bodyweight has been observed but was considered not to be of clinical relevance due to similar effect on pharmacodynamic markers over the weight range.

2.3.2. Pharmacodynamics

No new pharmacodynamic data has been submitted in this application, which is acceptable. The targeted dosing regimen for denosumab in men with osteoporosis is 60 mg Q6M administered by SC injection. A discussion of the pharmacodynamic properties supporting this dosing schedule was provided in the PMO/HALT submission.

Study 20010223, a phase 2 dose-ranging study in postmenopausal women with bone loss, was used to determine the dose and regimen for all denosumab studies in bone loss settings. Study 20010223 compared the efficacy and safety of denosumab with placebo and alendronate in postmenopausal women with osteoporosis or low bone mass (-4.0 ≤ T-score ≤ -1.8 for the lumbar spine or -3.5 ≤ T-score ≤ -1.8 for the total hip or femoral neck). In that study, doses of 6, 14, and 30 mg denosumab administered every 3 months (Q3M) and doses of 14, 60, 100, and 210 mg administered Q6M effectively increased BMD with a similar dose-response relationship in both the Q3M and Q6M groups. Evaluation of BMD data from all anatomic sites, serum CTX1, and urinary N-telopeptide (NTX)/creatinine indicated that no additional pharmacodynamic activity was observed at doses higher than 60 mg, and doses of 30 mg Q3M and 60 mg Q6M showed similar pharmacodynamic activity and tolerability. Since denosumab was similarly effective when dosed at Q3M or Q6M intervals, the Q6M interval was selected for convenience and potentially increased patient compliance. Therefore, the 60 mg Q6M dose regimen was chosen for the phase 3 Study 20080098 in men with low BMD. Because similar changes in BMD in men with low BMD (Study 20080098) and in women with PMO (Study 20030216) were observed, the 60 mg Q6M dose regimen was confirmed as appropriate in the male osteoporosis population. Thus, 60 mg Q6M SC is proposed as the marketed dose in this patient population.

2.4. Clinical Efficacy aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Introduction

According to the CHMP guideline Doc. Ref. CPMP/EWP/552/95 Rev. 2 from 2006, no WHO definition for osteoporosis exists for men. However, in clinical practice the same cut-off for the diagnosis of osteoporosis in men, i.e. T-score below –2.5 of the female reference range, has been used. Epidemiological studies have shown a similar relationship between BMD and fracture risk in men and in postmenopausal women. However, since the other independent risk factors for fractures have not been as extensively validated in men as in women it is the Applicant's responsibility to justify that the criteria chosen for the inclusion of men in the pivotal study, including BMD, will generate a fracture risk of a magnitude similar to that of postmenopausal osteoporotic women, especially if the indication "treatment of osteoporosis in men at increased risk of fracture" is to be granted based on bridging studies. Other potential risk factors for fractures could also be taken into account in men.

The guideline also states:

"Once an initial marketing authorisation has been granted to a NCE for the treatment of postmenopausal osteoporosis in women at high risk of fracture, a separate bridging study of the same NCE, using the same formulation, dose, and route of administration in male osteoporotic patients could be sufficient for being granted a marketing authorisation with the indication "treatment of osteoporosis in men at increased risk of fracture" provided that:

- the duration of the study is at least one year;

- the dosage is justified;

- the applicant justifies that the cut-off of BMD, age and any other risk factor chosen for the inclusion of men in the pivotal study will generate a fracture risk of a similar magnitude compared with postmenopausal women that were recruited in the studies used to obtain the indication "Treatment of postmenopausal osteoporosis in women at increased risk of fracture" the magnitude of the changes in BMD versus placebo is similar to that observed in postmenopausal osteoporotic women treated with the same compound and is proportional to the decreased incidence of fractures in treated women.

If these conditions are not fulfilled, bridging strategy will not be acceptable and a therapeutic study with fracture endpoints will be required in a separate trial in men.

The application for the use of denosumab in the treatment of osteoporosis in men is based on one pivotal trial together with data from previous trials for the treatment of osteoporosis in postmenopausal women (study 20030216) and of bone loss associated with hormone ablation in men with prostate cancer (study 20040138).

The pivotal trial 20080098 was a phase 3, randomized, double-blind, placebo controlled study in 242 men to compare the effects of denosumab 60 mg SC every six months (Q6M) with placebo on lumbar spine bone mineral density (BMD) in men with low BMD. Trial 20080098 is based on the pharmacodynamic (PD) endpoint BMD while anti-fracture efficacy has been established in the original licensing application for Prolia.

Table: Main study and Key Supportive Efficacy Studies

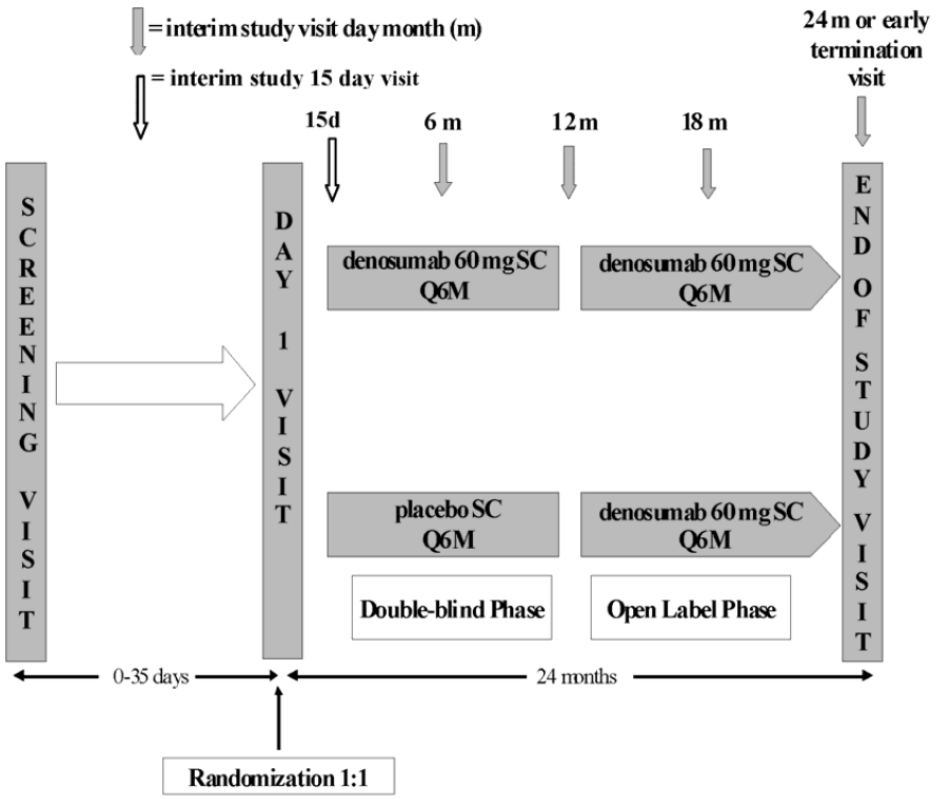
Study Design	Study Population	Primary and Secondary Endpoints	Region	Number of Randomized Subjects	Duration of Treatment
20080098					
Phase 3, randomized double-blind, placebo-controlled	Men aged 30 to 85 with low BMD at lumbar spine or femoral neck (BMD equivalent to T-score of ≤ -2 and ≥ -3.5 or ≤ -1 and ≥ -3.5 with history of major osteoporotic fracture)	Percent change from baseline in lumbar spine BMD at month 12 Percent change from baseline in BMD of the total hip, femoral neck, hip trochanter, and distal radius at month 12 Percent change from baseline in CTX at day 15	North America and Europe	242 (121 denosumab 60 mg Q6M, 121 placebo)	24 months (12-month double-blind treatment phase followed by 12-month open-label treatment phase in which all subjects received denosumab)
20030216					
Phase 3, randomized double-blind, placebo-controlled	Postmenopausal women aged 60 to 90 with BMD T-score < -2.5 at either the lumbar spine or the total hip and ≥ -4.0 at both locations	Subject incidence of new vertebral fractures (yes/no) during the entire 36-month treatment period Time to first nonvertebral fracture Time to first hip fracture	North America Europe, Latin America Australia, and New Zealand	7808 (3902 denosumab 60 mg Q6M, 3906 placebo)	36 months
20040138					
Phase 3, randomized double-blind, placebo-controlled	Men who have undergone bilateral orchiectomy or initiated ADT with GnRH agonists and are either: ≥ 70 years of age with histologically confirmed prostate cancer or ≥18 years of age and < 70 years of age, with histologically confirmed prostate cancer and a history of osteoporotic fracture or BMD T-score < -1 at lumbar spine, total hip, or femoral neck	Percentage change from baseline in lumbar spine BMD to month 24 Percent change of femoral neck BMD and total hip BMD from baseline to month 24 Subject incidence of any fracture over the 36-month evaluation period Percent change of lumbar spine BMD, femoral neck BMD, and total hip BMD from baseline to month 36 Time to first clinical fracture over the 24-month evaluation period Subject incidence of new vertebral fractures over the 36-month treatment period	North America and Europe	1468 (734 denosumab 60 mg Q6M, 734 placebo)	36 months

Main study

A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Compare the Efficacy and Safety of Denosumab versus Placebo in Males with Low Bone Mineral Density (the ADAMO Trial, 20080098)

This study is a multicenter, randomized, double-blind, placebo-controlled study in men with low bone mineral density (BMD) who were randomized (1:1) to receive single 60-mg subcutaneous (SC) administrations of denosumab or placebo on day 1 and month 6. Thereafter, all subjects (independent of randomization) received 60-mg SC injections of denosumab at month 12 and month 18 during the open-label phase of the study. End of study was month 24.

Methods



Abbreviations: d = day; m = month; Q6M = every 6 months; SC = subcutaneous(ly)

This study was designed to compare the effect of denosumab versus placebo on bone mineral density, bone turnover markers, and various safety parameters over 1 year. The duration of the treatment period, 12 months, is commensurate with regulatory guidance in male osteoporosis populations, once anti-fracture efficacy has been demonstrated in women with postmenopausal osteoporosis.

In order to evaluate the effect of denosumab on bone histology and histomorphometry, approximately 20 subjects were to be enrolled at selected sites in a transiliac bone biopsy substudy.

Study participants

Inclusion Criteria

Subjects who met all of the following criteria were eligible for participation in the study:

- Bone mineral density values (g/cm2) assessed by the local site at either the lumbar spine OR femoral neck that occurred within the following ranges, based on the particular scanner used:

	Scanner Type	
Region	GE Lunar	Hologic
Lumbar spine	0.800 ≤ BMD ≤ 0.980	0.706 ≤ BMD ≤ 0.871
Femoral neck	0.573 ≤ BMD ≤ 0.808	0.454 ≤ BMD ≤ 0.658

- OR -

Subjects with a history of a major osteoporotic fracture (eg, clinical vertebral, hip, humerus, and distal radius fractures) that occurred ≥ 6 months prior to screening were required to have BMD values within the following ranges:

	Scanner Type	
Region	GE Lunar	Hologic
Lumbar spine	0.800 ≤ BMD ≤ 1.100	0.706 ≤ BMD ≤ 0.981
Femoral neck	0.573 ≤ BMD ≤ 0.965	0.454 ≤ BMD ≤ 0.794

At least 2 lumbar vertebrae; it was required that ≥1 hip and ≥ 1 forearm be evaluable by DXA
- Ambulatory men 30 to 85 years of age inclusive at the start of screening
- Provided the appropriate written informed consent before any study-specific procedure

Main Exclusion Criteria

Subjects who met any of the following criteria or were diagnosed with any of the listed diseases or conditions were excluded from participation in the study:

- BMD values (g/cm2) in subjects with or without a history of major osteoporotic fractures, based on the particular scanner that is used:

	Scanner Type	
Region	GE Lunar	Hologic
Lumbar spine	BMD < 0.800	BMD < 0.706
Femoral neck	BMD < 0.573	BMD < 0.454

- Any severe or ≥ 1 moderate vertebral fractures on screening spinal x-ray;
- Any vertebral fracture diagnosed within the 6 months prior to screening;
- Any clinical fracture within the last 6 months prior to screening;
- Previous participation in clinical trials with denosumab or administration of commercial denosumab;

- Vitamin D deficiency (25[OH] vitamin D level < 20 ng/mL [< 49.9 nmol/L]); vitamin D replenishment was permitted and in such circumstances subjects could be re-screened;
- Hyper- or hypothyroidism; however, stable subjects (in the investigator's opinion) on thyroid hormone replacement therapy were allowed;
- Hyper- or hypoparathyroidism (intact parathyroid hormone [iPTH] values outside of the reference range as determined by the central laboratory);
- Elevated transaminases: serum aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT) > 2.5 x the upper limit of normal (ULN; both as determined by the central laboratory);
- Significantly impaired renal function as determined by a derived glomerular filtration rate (using the Modification of Diet in Renal Disease formula) of < 30 mL/min/1.73 m2 calculated by the central laboratory;
- Hypo- or hypercalcemia based on the central laboratory reference ranges for albumin-adjusted serum calcium;
- Malignancy (except fully resected cutaneous basal cell or squamous cell carcinoma) within the last 5 years;
- Any metabolic bone disease (eg, osteomalacia, osteogenesis imperfecta, rheumatoid arthritis, Paget's disease, Cushing's disease or hyperprolactinemia) that had the potential to interfere with the interpretation of the findings; or evidence of malabsorption syndromes that had the potential to interfere with absorption of vitamin D;
- Received any solid organ or bone marrow transplant or was on chronic immunosuppression for any reason;
- Administration of intravenous bisphosphonate, fluoride (except for dental treatment), or strontium ranelate;
- Oral bisphosphonate treatment: ≥3 months cumulatively in the past 2 years, OR ≥1 month in the past year, OR Any use during the 3-month period prior to randomization
- Administration of any of the following treatments within the 3 months prior to screening: Anabolic steroids or testosterone, Glucocorticosteroids (≥5 mg prednisone equivalent per day for more than 10 days or a total cumulative dose of ≥50 mg) Calcitonin Calcitriol or vitamin D derivatives (vitamin D contained in supplements or multivitamins was permitted)
- Other bone active drugs including anti-convulsives (except benzodiazepines) and heparin Chronic systemic ketoconazole, ACTH (adrenocorticotrophic hormone), cinacalcet, aluminum, lithium, protease inhibitors, methotrexate,
- gonadotropin-releasing hormone agonists
- Androgen deprivation therapy
- Bilateral hip replacements;
- Any physical or psychiatric disorder that, in the opinion of the investigator or Amgen, would prevent the subject from completing the study or would interfere with the interpretation of the study results;

All potential subjects attended a screening visit within the 35 days prior to first dose to establish eligibility; low BMD was confirmed at the screening visit by dual-energy x-ray absorptiometry (DXA)

scans of the lumbar spine (L1-L4) or femoral neck, with eligibility determined by BMD (g/cm2) values (as specified in Section 7.6.1) corresponding to BMD T-scores (based on male reference ranges)≤-2.0 and ≥-3.5 at the lumbar spine or femoral neck, OR a T-scores ≤-1.0 and ≥-3.5 at the lumbar spine or femoral neck in subjects with a history of major osteoporotic fracture.

Comment:

The current study included patients with somewhat lower fracture risk compared to inclusion criteria in PMO studies; please see discussion below.

Significantly impaired renal function as determined by a derived glomerular filtration rate of < 30 mL/min/1.73 m^2 was an exclusion criteria in the study. However, impaired renal function is not a current contraindication for denosumab. Impaired renal function is a common condition in the elderly osteoporosis patients. According to the MAH, there was no specific reason to exclude these patients from the study. The MAH proposal to clarify in the SmPC that subjects with an eGFR < 30 mL/min/1.73 m^2 were excluded from Study 20080098 is endorsed.

Treatments

During the 12-month double-blind phase, subjects were assigned treatment with 60-mg Q6M doses of denosumab or placebo by random assignment. All subjects received 60-mg Q6M doses of denosumab during the 12-month open-label phase.

Denosumab and the placebo for denosumab were administered as SC injections at the day 1, month 6, 12, and 18 visits as the last procedure after all other study visit procedures had been completed.

During the study, all subjects received daily supplements of calcium (≥1000 mg elemental calcium) and vitamin D (≥800 IU).

Objectives

Primary

To evaluate the effect of denosumab 60 mg administered once every 6 months (Q6M) compared with placebo on lumbar spine BMD at month 12 in men with low BMD.

Secondary

To evaluate the effects of denosumab in men with low BMD compared with placebo on:

- BMD at proximal femur (total hip, hip trochanter, femoral neck) and distal radius at month 12;
- Serum type-1 collagen C-telopeptide (CTX1) at day 15.

Exploratory

To evaluate the effects of denosumab in men with low BMD on:

- CTX1 at months 6 and 12 compared with placebo
- CTX1 change from baseline at months 18 and 24
- BMD for all skeletal sites at month 6 compared with placebo
- BMD change from baseline for all skeletal sites at month 24
- Bone histology and histomorphometry in a subset of subjects at month 12

Outcomes/endpoints

Efficacy	
Primary:	Percent change from baseline in the lumbar spine BMD at month 12

Secondary:	▪ Percent change from baseline to month 12 in BMD of:
	  ▪ Total hip
	  ▪ Femoral neck
	  ▪ Hip trochanter
	  ▪ Distal radius
	▪ Percent change from baseline in CTX1 at day 15

Exploratory:	▪ Percent change from baseline in BMD of the lumbar spine, total hip, femoral neck, trochanter, and distal radius at months 6 and 24 ▪ Percent change from baseline in CTX1 at months 6, 12, 18, and 24 ▪ Bone histology and histomorphometry in a subset of subjects at 12 months (Bone Biopsy Substudy)
Safety	
	▪ Incidence of adverse events at month 12 ▪ Changes from baseline in safety laboratory analytes (serum chemistry, hematology) at each visit and shifts between baseline and the worst on-study value ▪ Changes in vital signs at each visit

Additional exploratory analyses were performed to characterize the relationship between the primary and selected secondary efficacy endpoints and the following covariates: Age (continuous), Baseline lumbar spine T-scores (continuous), Previous clinical fractures, Race/ethnicity (Caucasian, non-Caucasian), Baseline CTX1 (continuous), Baseline testosterone levels (continuous), Geographic region, Baseline 10-year probability of major osteoporotic fracture with BMD (FRAXR) (continuous).

The significance of each covariate was evaluated in a univariate fashion; covariates were adjusted in the covariate analysis of the primary endpoint.

Comment: The endpoints are considered appropriate.

Sample size

Sample size considerations were taken with regard to both the primary and secondary endpoints and, to support a two-step sequential analysis strategy. While the Hochberg procedure was to be used in the actual analysis to control the overall type 1 error rate at 0.05, a more conservative method (Bonferroni) was applied in sample size calculation.

The assumptions on treatment differences between groups and standard deviations (SD) at different skeletal locations were based on the BMD results from Amgen previous clinical studies (in women with postmenopausal osteoporosis and in men with non-metastatic prostate cancer undergoing androgen deprivation therapy). The sample size was driven by the number of subjects needed to detect a difference at distal radius. A total of 232 subjects, 116 in each treatment arm, provided 99% power for other anatomical sites and 80% power for distal radius, the latter based on a difference between groups of 1.99%, a standard deviation (SD) of 4.2% and a two-sided type-1 error rate of 0.01. A 10% dropout rate for the 12-month treatment duration was assumed.

For the primary endpoint the sample size provided a minimum of 99% power to detect a 5.1% difference at lumbar spine between the treatment groups at month 12 assuming a SD of 3.8% and a 2-sided type-1 error rate of 0.05.

Comment: Due considerations seem to have been taken as regards the assumptions on key endpoints, the method to be used for multiplicity adjustment and expected dropout rate.

Randomisation

Approximately 232 subjects were to be randomized in a 1:1 ratio to either denosumab 60 mg SC or matching placebo at Day 1 and Month 6 based on a randomization schedule using randomly permuted blocks. The randomization schedule was stratified by minimum BMD value (≤-2.5, >-2.5) at either the lumbar spine or femoral neck whichever corresponded to a lower T-score. At least 116 subjects with a T-score ≤-2.5 were to be enrolled to ensure an adequate number for a subgroup analysis.

Comment: The randomisation procedure is acceptable.

Blinding (masking)

Denosumab or matching placebo doses were supplied in identical boxes containing a prefilled syringe (PFS) of 60 mg denosumab/mL or placebo solution. All DXA scans were submitted to the central imaging vendor for blinded analysis. Similarly, lateral spine x-ray films (for assessment of incident vertebral fracture) were scored at the central imaging vendor, with the radiologist being blinded to treatment. In addition, all post-baseline results of serum calcium, albumin-adjusted calcium, phosphorus, alkaline phosphatase, CTX1, BMD, bone histology and histomorphometry, and antidenosumab antibodies were concealed from investigators and sponsor personnel.

Comment: The procedures to blind study treatment and maintain blinding seem satisfactory.

Statistical methods

The primary analysis was performed after all on-study subjects have had an opportunity to complete their Month 12 visit. A two-step sequential analysis strategy was applied in order to maintain the overall type 1 error rate at 0.05. If the primary efficacy null hypothesis could be rejected (step 1), then all secondary hypotheses were to be simultaneously tested (step 2) using the Hochberg procedure. The primary analysis was performed using an analysis of covariance (ANCOVA) model with last-observation-carried-forward (LOCF) imputation. The ANCOVA model included treatment as the main effect and the level of baseline BMD T-score as a covariate (randomization stratification factor). Secondary BMD endpoints (i.e. percent change from baseline to month 12 in BMD of the other skeletal sites) were analysed using the same approach while the analysis of percent change from baseline to day 15 in CTX1 was analysed using the van Elteren stratified rank test adjusting for baseline BMD T-score.

The Primary Analysis Set comprised all randomized subjects who had a non-missing baseline and at least 1 non missing post baseline evaluation at or prior to the time point under consideration. The Per Protocol Set included subjects who were in the primary analysis set, received 2 doses of investigational product during the double-blind period, and satisfied all eligibility criteria.

Several sensitivity analyses were planned. These analyses included the primary analysis repeated based on the per protocol analysis set, an ANCOVA model (LOCF) incorporating baseline testosterone as an additional covariate, a likelihood-based repeated measures model without imputation of missing post baseline measurements of BMD, and the primary ANCOVA with missing post baseline BMD

imputed by baseline BMD for denosumab-treated subjects and by LOCF imputation for placebo-treated subjects. Sensitivity analyses for the BMD secondary endpoints were performed using the likelihood-based repeated measures model.

Additional exploratory analyses to characterize the relationship between a subset of key endpoints and a number of pre-defined covariates were planned. In addition a number of exploratory subgroups analyses were pre-defined.

Longer term safety and exploratory efficacy was to be assessed during the 12-month open-label phase once all on-study subjects have had an opportunity to complete their 24-month visit. Only descriptive statistics was to be provided for months 12-24 and was to be reported separately.

Comment:
Overall, the statistical analysis methods are acceptable. The stratification factor was taken into account in the analyses and the method to deal with multiple testing is considered adequate. Issues identified that may have led to a risk of overestimating the size of treatment efficacy with denosumab concerned the definition of the primary analysis population and primary method for handling missing data. In the light of this fact it can be questioned whether the sensitivity analyses are sufficiently conservative.

To be included in the primary efficacy population subjects were to have both baseline and at least one post-baseline assessment implying that subjects with missing data were to be ignored in the analyses. No analysis was planned based on all randomised subjects or planned to include patients without a post-baseline measurement. Regarding the imputation of missing data by using LOCF it is not fully clear whether appropriate in this setting since it is a less acceptable method in conditions expected to deteriorate over time.

While the performance of several sensitivity analyses is endorsed it can however be questioned whether any of the sensitivity analyses, besides the baseline-observation-carried-forward (BOCF)/LOCF imputation (meant to imply a worst case/best case imputation for denosumab and placebo respectively), is sufficiently conservative. An analysis based on the PP population is appropriate when offered as supportive evidence but is in general not considered conservative when the objective is to show superiority. In addition, sensitivity analyses based on a repeated measures model may neither be appropriate considering the potential risk for that treatment efficacy is overestimated. The use of this analysis method is in general only appropriate if missing data are negligible.

Regarding the potential concerns, the number of subjects with missing 12-month BMD data were however low and concerned 7-8 subjects in the denosumab arm and 3-4 in the placebo arm depending on BMD endpoint. Although there were more subjects in the denosumab than in the placebo arm that had missing data, it is not believed that another imputation method will change overall conclusions regarding BMD endpoints since both convincing and seemingly robust. In addition, although not evident that LOCF is appropriate in this setting, the sensitivity analysis of the primary endpoint using a BOCF/LOCF imputation provides the smallest difference between denosumab and placebo (the point estimate being 4.7, the 95% CI: 3.9, 5.5).

Results

Participant flow

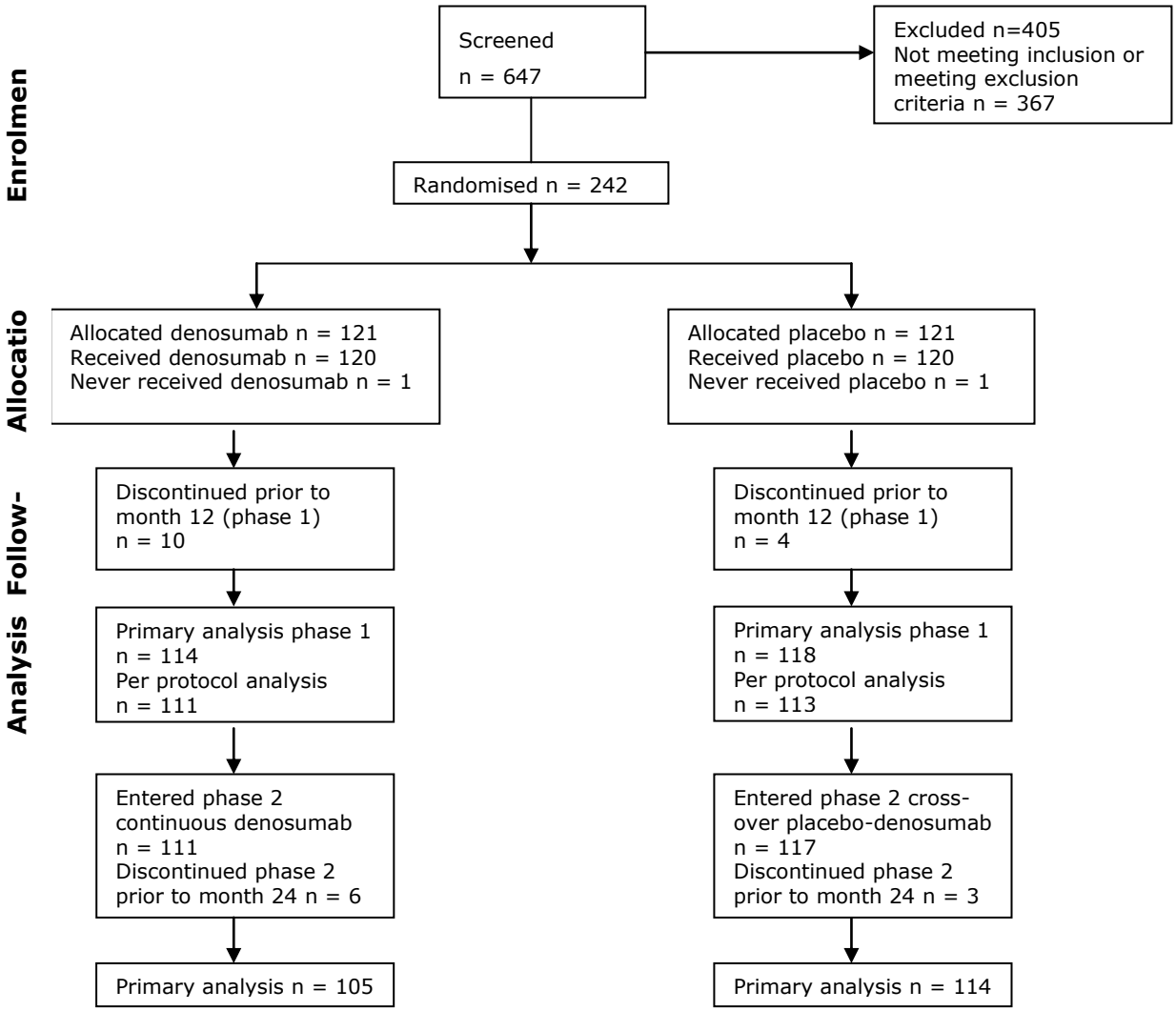


Table: Subject Disposition (Randomized Subjects) (20080098 Final 24 Months Analysis

	Placebo/ Denosumab 60 mg Q6M n (%)	Denosumab/ Denosumab 60 mg Q6M n (%)	All n (%)
Randomized	121	121	242
Entered open-label phase of study	117 (96.7)	111 (91.7)	228 (94.2)
Completed 24 months of study	114 (94.2)	105 (86.8)	219 (90.5)
Completed IP	111 (91.7)	104 (86.0)	215 (88.8)
Discontinued IP	2 (1.7)	1 (0.8)	3 (1.2)
Never received IP	1 (0.8)	0 (0.0)	1 (0.4)
Discontinued before completing 24 months of study	3 (2.5)	6 (5.0)	9 (3.7)
Completed IP	0 (0.0)	2 (1.7)	2 (0.8)
Discontinued IP	3 (2.5)	4 (3.3)	7 (2.9)
Never received IP	0 (0.0)	0 (0.0)	0 (0.0)

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Percentages based on number of randomized subjects
IP = investigational product; Q6M = once every 6 months

Recruitment

The first subject was screened on 10 September 2009 and the first subject was enrolled on 14 October 2009. The last subject completed month 12 on 21 June 2011 and month 24 on 23 May 2012. The CSRs for phase 1 and 2 are dated 01 November 2011 and 17 December 2012, respectively.

Conduct of the study

The original protocol (dated 22 June 2009) was not modified. There were no changes made to the protocol-specified analyses.

During phase 1 of the trial 10 subjects (4%) had important protocol deviations related to eligibility criteria (4 [3%] denosumab; 6 [5%] placebo). Of these, 3 subjects (1 denosumab, 2 placebo) were enrolled who did not fulfil the entry criterion of having BMD values within the study-specified range.

The overall subject incidence of important protocol deviations during the 12-month double-blind phase of the study was 10% (12 [10%] denosumab; 13 [11%] placebo). The most common deviations were characterized as ICH/GCP compliance issues (4% denosumab, 6% placebo), generally consisting of on-study DXA scans being analysed locally (3 denosumab, 4 placebo), failure to promptly obtain informed consent subsequent to the issuance of the protocol addendum (1 denosumab, 2 placebo), and the use of temperature-compromised investigational product (9 [4 denosumab, 5 placebo]; all centre 66008). Other eligibility criteria deviations occurred once only.

During the 12-month open-label phase 2 of the study, the overall subject incidence of important protocol deviations was 3.5% (3/111 [2.7%] long-term, 5/117 [4.3%] crossover). These deviations were use of temperature-compromised investigational product (4 subjects centre 22003; 2/111

[1.8%] long-term; 2/117 [1.7%] crossover), ICH/GCP compliance issues (1/111 [0.9%] long-term; 2/117 [1.7%] crossover) consisting of an on-study DXA scan being analysed locally (0 long-term; 1/117 [0.9%] crossover), failure to obtain informed consent subsequent to the issuance of a protocol addendum (1/111 [0.9%] long-term; 1/117 [0.9%] placebo), and a subject taking other medications affecting bone metabolism (0 long-term; 1/117 [0.9%] crossover).

None of the deviations were considered to have the potential to affect the conclusions of the study.

Comment: It is agreed that the protocol deviations reported for trial 20080098 are not considered to have an influence on the benefit/risk evaluation of this study.

Baseline data

All subjects were men, with a mean (SD) age of 65 (9.8) years (64.9 [10.5] years in the denosumab group and 65.0 [9.1] years in the placebo group); the majority of enrolled subjects were between the ages of 50 and 79 years. The overall mean body mass index (BMI) (SD) was 25.8 (3.6) kg/m2 (25.6 [3.6] in the denosumab group and 26.0 [3.6] in the placebo group).

All subjects in the denosumab group were white and 88.4% of subjects in the placebo group were white.

Baseline mean (SD) testosterone concentrations were similar between subjects in the denosumab (368.4 [121.0] ng/dL) and placebo (356.3 [116.7] ng/dL) treatment groups; 14.0% of subjects in the denosumab group and 16% of subjects in the placebo group were noted to be hypogonadal as defined by serum testosterone concentration < 250 ng/dL.

Most subjects (>97%) were categorized as not having underlying causes osteoporosis at baseline, including glucocorticoid use, rheumatoid arthritis or secondary osteoporosis.

Baseline bone turnover markers and laboratory parameters were similar across the treatment groups. Median baseline concentrations of the bone resorption marker serum CTX1 were 0.364 ng/mL in the denosumab group and 0.374 ng/mL in the placebo group.

Greater than 94% of subjects in each treatment group had no prior use of osteoporosis medications.

Baseline Bone Mineral Density by Densitometer Type (Descriptive Statistics)(Randomized Subjects) (20080098 First 12 Months Analysis)

	Densitometer Type	n	Mean	SD	Min	Q1	Median	Q3	Max
Lumbar spine (g/cm^2)									
Placebo (N = 121)	Lunar	25	0.9668	0.1180	0.784	0.8750	0.9600	1.0390	1.289
Denosumab 60 mg Q6M (N = 121)	Lunar	30	1.0237	0.1567	0.783	0.8920	1.0150	1.1220	1.318
All (N = 242)	Lunar	55	0.9978	0.1421	0.783	0.8760	0.9740	1.0900	1.318
Placebo (N = 121)	Hologic	95	0.8681	0.1110	0.711	0.7900	0.8460	0.9090	1.349
Denosumab 60 mg Q6M (N = 121)	Hologic	91	0.8636	0.1177	0.701	0.7830	0.8440	0.8820	1.325
All (N = 242)	Hologic	186	0.8659	0.1141	0.701	0.7860	0.8445	0.8910	1.349
Total hip (g/cm^2)									
Placebo (N = 121)	Lunar	25	0.8525	0.0671	0.732	0.8040	0.8530	0.8870	0.994
Denosumab 60 mg Q6M (N = 121)	Lunar	30	0.8581	0.0840	0.706	0.7940	0.8590	0.9040	1.034
All (N = 242)	Lunar	55	0.8555	0.0761	0.706	0.7970	0.8570	0.9040	1.034
Placebo (N = 121)	Hologic	96	0.8517	0.0982	0.644	0.7910	0.8555	0.9270	1.053
Denosumab 60 mg Q6M (N = 121)	Hologic	91	0.8382	0.0879	0.531	0.7760	0.8400	0.8930	1.070
All (N = 242)	Hologic	187	0.8451	0.0933	0.531	0.7770	0.8440	0.9100	1.070

N = Number of subjects randomized
n = Number of subjects who had nonmissing data at baseline
Lumbar spine includes L1 through L4.

Table. Baseline Demographics, Body Composition, and Geographic Region (Randomized Subjects) (20080098 Phase 1 First 12 Months Analysis)

	Placebo (N = 121)	Denosumab 60 mg Q6M (N = 121)
Gender - n (%)		
Male	121 (100)	121 (100)
Race - n (%)		
White or Caucasian	107 (88.4)	121 (100.0)
Hispanic or Latino	10 (8.3)	0 (0.0)
Asian	2 (1.7)	0 (0.0)
Black or African-American	1 (0.8)	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (0.8)	0 (0.0)
Age (years)		
Mean (SD)	65.0 (9.1)	64.9 (10.5)
Median	65.0	66.0
Q1, Q3	59.0, 70.0	59.0, 72.0
Min, Max	40, 84	31, 83
Age group (years) – n (%)		
< 50 years	5 (4.1)	9 (7.4)
50 - 59 years	26 (21.5)	22 (18.2)
60 - 69 years	49 (40.5)	44 (36.4)
70 - 79 years	35 (28.9)	39 (32.2)
≥ 80 years	6 (5.0)	7 (5.8)
Height (cm)		
Mean (SD)	172.9 (7.8)	172.7 (7.8)
Median	173.0	172.0
Min, Max	147, 194	157, 197
Weight (kg)		
Mean (SD)	77.73 (12.25)	76.32 (11.77)
Median	76.80	75.00
Min, Max	45.9, 114.6	55.0, 111.4
BMI (calculated as kg/m^2)		
Mean (SD)	26.0 (3.6)	25.6 (3.6)
Median	25.7	25.3
Min, Max	18, 36	17, 38
Geographic region – n (%)		
Europe	78 (64.5)	87 (71.9)
North America	43 (35.5)	34 (28.1)

Comment: Eligibility criteria for Study 20080098 were designed to include a subject population that was consistent with prior registration studies for the pharmacological treatment of male osteoporosis and encompassed a population with a significant risk of fracture as estimated using the FRAX algorithm. As regards baseline data there is very limited data on ethnicities for groups other than white.

As regards osteoporosis disease state although T-scores and the 10-year fracture risk calculated using the FRAX algorithm were comparable between groups, the proportion of subjects with prevalent vertebral fractures was numerically higher in the denosumab than in the placebo group probably indicating a slightly worse disease state in the denosumab group.

Numbers analysed

Two hundred forty-two (242) subjects were enrolled and randomized into the denosumab (n = 121) or placebo group (n = 121). A total of 240 subjects (120 denosumab, 120 placebo) received ≥ 1 dose. Of the enrolled subjects, 111 (91.7%) in the denosumab and 117 subjects (95.9%) in the placebo group

completed the primary analysis phase. Two hundred twenty-eight (228) subjects (94%) (111 denosumab / denosumab [long term], 117 placebo / denosumab [crossover]) entered the open-label phase, 1 of whom in the crossover group never received denosumab in this phase but remained on study and completed the study. Of the 228 subjects who entered the open-label phase, 105 (94.6%) in the long term and 114 (97.4%) in the crossover group completed this phase.

Comment: The number of dropouts was reasonable but higher in the denosumab group.

Outcomes and estimation

Primary Endpoint: percent Change From Baseline in Lumbar Spine BMD at 12 Months

Subjects treated with denosumab, as compared with placebo, showed significantly greater gains in mean percent change from baseline at month 12 in lumbar spine BMD.

Table. Lumbar Spine Bone Mineral Density by DXA Percent Change From Baseline by Visit (ANCOVA Model) (Primary Efficacy Subset, LOCF) (20080098 First 12 Months Analysis)

		% Change From Baseline [a]		Difference From Placebo [a]		
	n	LS Mean	95% CI	LS Mean	95% CI	p-value
Month 6						
Placebo (N = 118)	117	0.9	(0.4, 1.4)			
Denosumab 60 mg Q6M (N = 117)	117	4.3	(3.8, 4.8)	3.4	(2.7, 4.1)	<0.0001
Month 12						
Placebo (N = 118)	118	0.9	(0.3, 1.4)			
Denosumab 60 mg Q6M (N = 117)	117	5.7	(5.1, 6.2)	4.8	(4.0, 5.6)	<0.0001

N = Number of subjects with values at baseline and at ≥ 1 postbaseline visit
n = Number of subjects with values at baseline and at ≥ 1 postbaseline visit at or prior to the time point of interest
[a] Based on an ANCOVA model with treatment as main effect and level of baseline BMD T-score as covariate
P-value is not adjusted for multiple comparisons.

Denosumab significantly increased lumbar spine BMD, compared to placebo, in all of four sensitivity analyses that were conducted to evaluate the robustness of the results from the primary analysis of the primary endpoint.

In addition, after controlling for covariates (baseline age, race, baseline lumbar spine T-score, baseline serum CTX1, baseline testosterone level, previous osteoporotic fractures, geographic region, and baseline 10-year probability of major osteoporotic fracture [with BMD]) individually and simultaneously in the ANCOVA model, the effect of denosumab treatment on the primary endpoint remained both consistent and significant.

Comment: The study results demonstrated a significant increase in the primary endpoint: percent Change From Baseline in Lumbar Spine BMD at 12 Months.

Secondary Endpoints

As shown in the table below, subjects treated with denosumab showed greater gains at month 12 in BMD, as compared with placebo-treated subjects, at the total hip (2.4% vs 0.3%), femoral neck (2.1% vs 0%), trochanter (3.1% vs 0.8%), and distal radius (0.6% vs -0.3%); mean differences between the treatment groups ranged from 0.9% to 2.3%.

Table. Results of Secondary Endpoints(Primary Efficacy Subset, LOCF)(20080098 First 12 Months Analysis)

	Placebo n	Denosumab 60 mg Q6M n	Estimate	(95% CI)	p-value	Adjusted p-value [b]
Total hip BMD % change from baseline at month 12 [a]	119	117	2.0	(1.5, 2.6)	<0.0001	<0.0001
Femoral neck BMD % change from baseline at month 12 [a]	119	117	2.2	(1.3, 3.0)	<0.0001	<0.0001
Trochanter BMD % change from baseline at month 12 [a]	119	117	2.3	(1.4, 3.2)	<0.0001	<0.0001
Distal 1/3 radius BMD % change from baseline at month 12 [a]	118	116	0.9	(0.2, 1.6)	0.0144	0.0144

n= Number of subjects with values at baseline and at ≥ 1 postbaseline visit for BMD endpoints and at baseline and at day 15 visit for serum CTX1
[a.] Difference from placebo and p-value based on an ANCOVA model with treatment as main effect and level of baseline BMD T-score as covariate
[b.] Based on the Hochberg procedure for multiple comparisons

Serum CTX1

Treatment with denosumab significantly decreased mean serum CTX1 concentration, a marker of bone resorption, compared with placebo at day 15 (adjusted p <0.0001).

Median percent changes from baseline in serum CTX1 concentration at day 15 were -45% in the denosumab group and -2% in the placebo group.

Decreases in CTX1 were less than those observed in previous denosumab studies, which can be attributed to the CTX1 LLOQ defined by the central laboratory (0.2 ng/mL; Covance; Indianapolis, IN) being higher than the LLOQ defined in previous denosumab clinical studies (0.05 ng/mL) (PKPD, Amgen; Thousand Oaks, CA).

Comment: The study results demonstrated a significant increase in the secondary endpoints: percent Change from Baseline in total hip, femoral neck, trochanter and radius BMD at 12 Months as well as decrease in CTX at day 15.

Open label phase

In the open-label phase, for the efficacy analysis set of subjects who entered the open-label phase (N = 111 long-term, 117 crossover), BMD at the lumbar spine, total hip, femoral neck, hip trochanter, and distal radius continued to increase from month 12 to month 24 in the long-term group. In this group, mean percent increases from baseline were 8.0%, 3.4%, 3.4%, 4.6%, and 0.7% for lumbar spine, total hip, femoral neck, hip trochanter, and distal radius, respectively, at month 24 compared with 5.8%, 2.3%, 2.2%, 3.2%, and 0.6% at month 12.

In the crossover group, increases from month 12 to month 24 were similar to those observed in the long-term group from baseline to month 12 during the initial denosumab treatment. In this group, mean percent changes from baseline were 5.7%, 2.0%, 1.8%, 2.7%, and 0.6% for lumbar spine, total

hip, femoral neck, hip trochanter, and distal radius, respectively, at month 24 compared with 0.8%, 0.3%, -0.1%, 0.8%, and -0.3% at month 12.

In the open-label phase, the decrease in median percent change from baseline in CTX1 observed through month 12 (-60%) in the denosumab/long-term group was maintained through months 18 and 24 (-57% and -50%, respectively). Similar decreases were observed at month 18 and month 24 (-68% and -59%, respectively) in the placebo/crossover group after the first administration of denosumab for this group at month 12.

Fractures

During the 24-month study period, clinical fractures were reported by the investigators for 5 subjects (3 rib, 2 foot) in the denosumab/long-term group (5/120 = 4.2%) and 2 subjects (rib, humerus) in the placebo/cross-over group (2/120 = 1.7%, see table in the Safety section. Clinical osteoporotic fractures were reported in 3 subjects (3 rib) in the denosumab/long-term group (3/120 = 2.5%) and 2 subjects (rib, humerus) in the placebo/cross-over group (2/120 = 1.7%)

New (morphometric) vertebral fractures confirmed by the central imaging vendor were reported for 0 subjects in the denosumab/long-term group and 1 subject in the placebo/cross-over group (1/120 = 0.8%).

Comment: During the open label phase 2 of trial 20080098 the effects seen with denosumab on BMD as well as CTX1 were generally maintained, while in participants who were switched from the placebo arm in phase 1 to denosumab in phase 2 (crossover group) effects on BMD and CTX1 were comparable to those seen in the denosumab arm in phase 1.

The number of fracture events is too small for any meaningful analysis; study 20080098 was not powered to assess anti-fracture efficacy, but focussed on the surrogate parameter BMD.

Anti-denosumab antibodies

All subjects tested during the overall 24 months of the study (n = 239; 119 long-term, 120 crossover) were negative for anti-denosumab binding antibodies at all tested time points (baseline, months 12 and 24 [or at early termination where applicable]). Final post-baseline samples were not available for 7 subjects. No neutralizing antibodies were reported.

Comment: Since no anti-denosumab antibodies have been detected the influence of possible antibodies on efficacy could not be evaluated. In previous trials less than 1% of patients treated with denosumab for up to 5 years tested positive for non-neutralizing binding antibodies, with no evidence of altered pharmacokinetics, toxicity, or clinical response and no neutralizing antibodies had been observed.

Clinical studies in special populations

No separate studies in special populations have been conducted, but subgroups age, race, geographic region, baseline serum CTX1, minimum baseline BMD T-score, baseline testosterone, and baseline 10-year major osteoporotic fracture risk (with BMD) have been analysed for study 20080098. In all subgroups denosumab increased lumbar spine BMD at the primary assessment time point compared with placebo.

Comment: The applicant's strategy not to conduct separate studies in special populations but to bridge to previous results and to provide subgroup analyses for study 20080098 is endorsed.

Subgroup analyses

The primary endpoint was analyzed to assess the efficacy of denosumab within various subgroups: age, race, geographic region, baseline serum CTX1, minimum baseline BMD T-score, baseline testosterone, and baseline 10-year major osteoporotic fracture risk (with BMD). For all subgroups analyzed, denosumab increased lumbar spine BMD at the primary assessment time point compared with placebo. For the age subgroups, a significant quantitative interaction was observed: the percent change in lumbar spine BMD from baseline to month 12 for denosumab compared with placebo was 5.8% for subjects < 65 years of age and 4.1% for subjects ≥65 years of age. However, qualitative interaction testing indicates that, while some evidence exists that the magnitude of the treatment effect differs by age, there is no evidence that the direction of the effect differs by age.

Table. Lumbar Spine Bone Mineral Density by DXA Percent Change From Baseline at Month 12 by Age < 65 and ≥ 65 (ANCOVA Model) (Primary Efficacy Subset, LOCF) (Sensitivity Analysis) (20080098 First 12 Months Analysis)

		% Change From Baseline		Difference From Placebo		
	n	LS Mean	(95% CI)	LS Mean	(95% CI)	p-value
Primary analysis model[a]						
Placebo (N = 118)	118	0.9	(0.3, 1.4)			
Denosumab 60 mg Q6M (N = 117)	117	5.7	(5.1, 6.2)	4.8	(4.0, 5.6)	<0.0001
< 65 years[a]						
Placebo (N = 56)	56	0.5	(-0.4, 1.4)			
Denosumab 60 mg Q6M (N = 51)	51	6.3	(5.4, 7.2)	5.8	(4.5, 7.0)	<0.0001
≥ 65 years[a]						
Placebo (N = 62)	62	1.1	(0.4, 1.9)			
Denosumab 60 mg Q6M (N = 66)	66	5.2	(4.5, 6.0)	4.1	(3.0, 5.2)	<0.0001

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N = Number of subjects with values at baseline and at ≥ 1 postbaseline visit
n = Number of subjects with values at baseline and at ≥ 1 postbaseline visit at or prior to the time point of interest
[a] Based on an ANCOVA model with treatment as main effect and level of baseline BMD T-score as covariate
[b] Adding subgroup variable and treatment-by-subgroup interaction to the primary analysis model
P-value is not adjusted for multiple comparisons.

Comment: The percent change in lumbar spine BMD from baseline to month 12 for denosumab compared with placebo was 5.8% for subjects < 65 years of age and 4.1% for subjects ≥65 years of age.

The applicant has adequately discussed the difference seen in the percent change in lumbar spine BMD between subjects < 65 years and those ≥ 65 years of age in Study 20080098 including whether this finding might indicate a difference in efficacy between male and female patients. Contributing factors appear to be lower baseline BMD T-scores at the lumbar spine in the < 65-years subgroup compared to those ≥ 65-years and a higher than expected percent change from baseline in the placebo group in the ≥ 65-years subgroup compared with younger subjects. Also the treatment difference in the percent change from baseline in lumbar spine BMD at 12 months was consistent between age subgroups in Studies 20030216 (DXA substudy) and 20040138 and therefore does not indicate a difference in treatment efficacy between women and men. The treatment difference in the percent change from baseline in total hip BMD at 12 months was also consistent between age subgroups in Studies 20080098, 20030216 (DXA substudy), and 20040138.

The CHMP "Guideline on the Evaluation of Medicinal Products in the Treatment of Primary Osteoporosis" states that a bridging study in the male osteoporosis setting using the same dosing regimen may be sufficient for approval, provided that the eligibility criteria generate a similar fracture risk as in women with PMO.

The inclusion criteria of this male osteoporosis study resulted in an overall male population with higher BMD and a clearly lower fracture risk compared to PMO women.

The MAH states that factors independent of bone density contribute to susceptibility to fracture in men and that inclusion T-score criteria used are consistent with prior registration studies for the pharmacological treatment of male osteoporosis.

Furthermore the male study subgroup with a baseline 10-year fracture risk that overlapped with subjects from the PMO study included 222 of 242 subjects. In this subgroup, the effect of denosumab treatment on the percent change from baseline in BMD (4.7%) was consistent with that observed in the overall male study population (4.8%) and in the same range as observed in subjects enrolled in the PMO (DXA) substudy (5.5%).

The male osteoporosis subgroup that would have fulfilled the inclusion criteria for a PMO study in terms of age and baseline BMD criteria included only 59 of 242 subjects but the effect of denosumab treatment on the percent change from baseline in BMD (4.9%) was in the same range as observed in subjects enrolled in the PMO (DXA) substudy (5.5%).

Subjects with high fracture risk

Descriptive statistics are provided for percent change in BMD from baseline to month 12 at each skeletal site and for percent change from baseline in CTX1 for the subset of subjects with a baseline 10-year major osteoporotic fracture risk (with BMD [FRAX®]) in the highest tertile (> 11.2%). These results demonstrated similar increases in BMD at each skeletal site and similar decreases in CTX1 compared with the overall patient population.

Ethnicity

Limited data are available for non-white populations. The consistency of the effect of denosumab on BMD across ethnicities has been demonstrated in other studies, including Studies 20030216 and 20040138.

Comment: Data on the efficacy of denosumab in ethnicities other than white Caucasians is limited. The applicant has provided covariate analyses showing that the effect of denosumab on the percent change from baseline in lumbar spine BMD was comparable before and after adjusting for region. In addition a subgroup analysis of Study 20080098 comparing European and North American subjects did not show clinically relevant differences in the effect of denosumab on the percent change from baseline in lumbar spine BMD at month 12 between these subgroups. There were no clinically relevant differences in the incidence of adverse events between European and North American subgroups in Study 20080098.

Bone biopsy substudy

A total of 29 subjects (17 denosumab, 12 placebo) were enrolled at selected study sites to undergo a transiliac bone biopsy within 30 days prior to the month 12 visit.

Overall, bone biopsy results showed normal bone histology. After 12 months of denosumab treatment, there was evidence of normal lamellar bone, normal mineralization, and normal osteoid in both treatment groups. There was no evidence of osteomalacia, marrow fibrosis, woven bone, or abnormal osteoid. Denosumab did not impair matrix mineralization.

In accordance with denosumab's mechanism of action, evaluation of histomorphometric parameters showed changes consistent with decreased bone remodeling in subjects treated with denosumab compared with placebo. Decreased bone remodeling led to reductions in tetracycline uptake and therefore labeling. As a consequence, a reduction in single and double labels was observed in a number of biopsies in the denosumab group. Evaluation of dynamic bone histomorphometry in the subset of samples in which double or single labels were present showed changes consistent with decreased remodeling in subjects treated with denosumab.

Comment: The MAH has stated that the bone biopsy sub-study results did not differ from the bone biopsy studies in PMO women.

Ancillary analyses

Comparison and Analyses of Results Across Studies

This section provides a qualitative comparison of the results from:

- the actual phase 3 study in men with low BMD, **Study 20080098**
- the phase 3 study in PMO, **Study 20030216**
- the phase 3 study of denosumab in the treatment of bone loss associated with ADT in men with prostate cancer (HALT) Study **20040138**

The comparisons of efficacy results were based on data from the first 12 months of each study. For each BMD endpoint, the analysis set included all randomized subjects who had both a baseline measurement and at least 1 postbaseline evaluation at or before the timepoint under consideration. BMD information at the 12-month time point was not available for all subjects in Studies 20030216 and 20040138:

• In Study 20030216, BMD was measured at 12 months at all skeletal sites only in subjects in the DXA substudy. Thus, 12-month BMD results in Study 20080098 are compared with 12-month BMD results in subjects in the 20030216 DXA substudy.

• In Study 20040138, distal radius BMD was measured only in subjects enrolled in the DXA substudy; thus, distal radius BMD results for 20040138 were based on subjects in the DXA subtudy. Analyses for other BMD sites in Study 20040138 were based on all subjects.

Comment: BMD information at the 12-month time point was not available for all subjects in PMO study 20030216 and HALT study 20040138. The comparison of male osteoporosis BMD results are made with the DXA substudies of the pivotal studies.

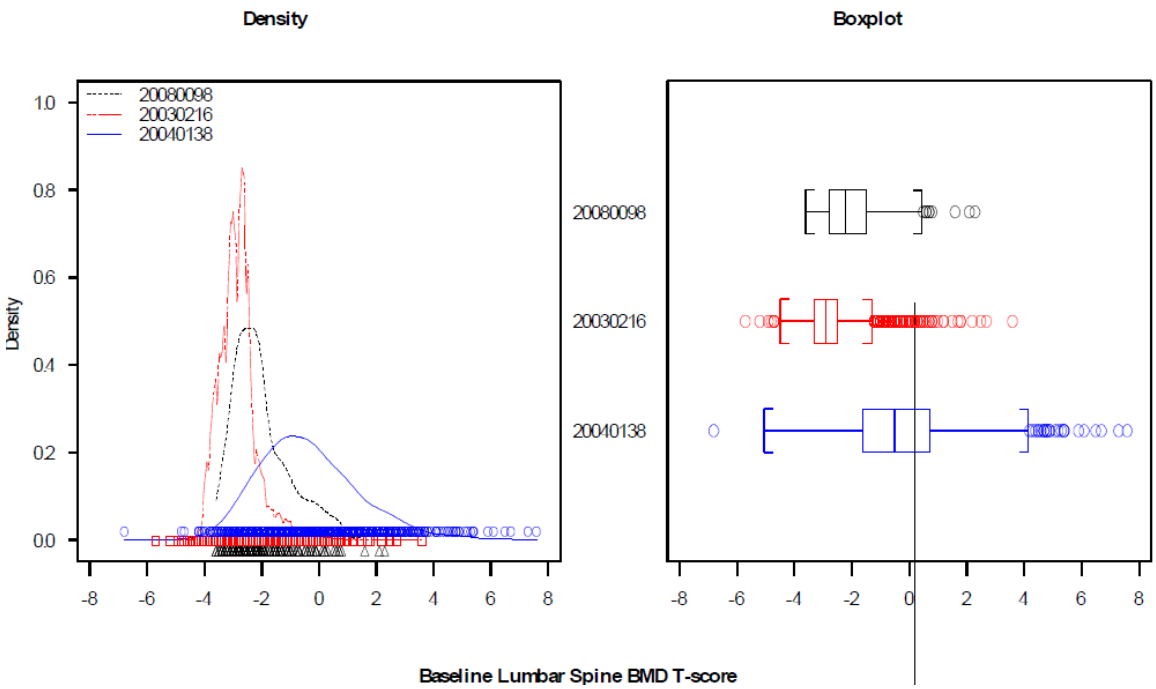
The MAH has adequately justified that the subjects in the DXA substudies were comparable with the total PMO and male HALT study populations in terms of baseline BMD, age, previous fractures and fracture risk.

Baseline demographics, BMD, fracture history, 10-year fracture risk

Overall, baseline subject demographic characteristics were well balanced between the denosumab and placebo groups in Studies 20080098, 20030216, and 20040138. As required by the inclusion criteria, all subjects were men in Studies 20080098 and 20040138 and all subjects were women in Study 20030216. Study 20080098 allowed enrollment of men as young as 30; therefore, the mean age in that study was lower (64.9 denosumab, 65.0 placebo) compared with Study 20030216 (72.3 denosumab, 72.3 placebo) and Study 20040138 (75.3 denosumab, 75.5 placebo).

Consistent with the eligibility criteria for these studies, the mean baseline BMD T-scores in Study 20030216 were lower than those in Study 20080098, which were generally lower than those in Study 20040138. For Study 20030216, BMD T-score at the lumbar spine or total hip had to be < -2.5 at either site and ≥ -4.0 at both sites. To be included in Study 20080098, subjects had to have BMD equivalent to a T-score of ≤ -2 and ≥ -3.5 at the lumbar spine or femoral neck or ≤ -1 and ≥ -3.5 at the lumbar spine or femoral neck with a history of major osteoporotic fracture. The criteria for Study 20080098 are similar to prior registrational studies for the pharmacologic treatment of male osteoporosis.

Figure. Distribution of Baseline Lumbar Spine BMD T-score for Studies 20080098, 20030216, and 20040138



The proportions of subjects with a history of any fracture (based on self-reported fractures recorded on the fracture history case report form [CRF]) were similar between treatment groups in each study, but were lower in Studies 20080098 and 20040138 (range 33.7% to 39.7%) than in Study 20030216 (range 53.3% to 53.7%).

Including femoral neck BMD in the calculation, the median (interquartile range) 10-year risks of major osteoporotic fracture and hip fracture in Study 20080098 (8.4% [5.3%, 12.7%] and 2.4% [1.1%, 4.5%], respectively) were similar to those in Study 20040138 (7.9% [5.3%, 11.2%] and 2.9% [1.6%, 4.8%]), and lower than those in Study 20030216 (15.1% [10.4%, 21.5%] and 4.8% [2.5%, 8.7%]).

The median level of serum CTX was lower in Study 20080098 than those in Study 20030216 or Study 20040138.

Comment: Overall, the subjects in the actual male osteoporosis study were younger, had higher BMD, less previous fractures and had a lower 10-year risk for fracture compared to the postmenopausal osteoporosis studies.

Comparison of Efficacy Results of All Studies

Cross-study comparisons are presented for both absolute change and percent change in BMD, as assessed by DXA, at each measured skeletal site. Statistically significant increases in BMD were observed at all skeletal sites measured.

Table. Summary of Bone Mineral Density by DXA Change From Baseline at Month 12 by Site (Descriptive Statistics, LOCF)

	Placebo			Denosumab 60 mg Q6M		
	n	Mean	SD	n	Mean	SD
Lumbar spine						
Study 20080098	118	0.0070	0.0279	117	0.0499	0.0281
Study 20030216	208	-0.0009	0.0281	227	0.0408	0.0259
Study 20040138	715	-0.0071	0.0409	714	0.0466	0.0395
Total hip						
Study 20080098	119	0.0025	0.0184	117	0.0197	0.0172
Study 20030216	207	-0.0010	0.0192	228	0.0230	0.0192
Study 20040138	706	-0.0099	0.0270	700	0.0186	0.0221
Femoral neck						
Study 20080098	119	-0.0005	0.0206	117	0.0148	0.0271
Study 20030216	207	-0.0010	0.0199	228	0.0167	0.0204
Study 20040138	706	-0.0073	0.0297	700	0.0142	0.0281
Trochanter						
Study 20080098	119	0.0044	0.0233	117	0.0201	0.0208
Study 20030216	207	0.0012	0.0228	228	0.0257	0.0206
Study 20040138	706	-0.0094	0.0302	700	0.0195	0.0252
Distal radius						
Study 20080098	118	-0.0026	0.0206	116	0.0045	0.0195
Study 20030216	191	-0.0014	0.0175	215	0.0042	0.0156
Study 20040138	120	-0.0151	0.0285	127	0.0053	0.0207

Number of subjects randomized in Study 20080098: 121 placebo and 121 denosumab Number of subjects enrolled in Study 20030216 DXA substudy: 209 placebo and 232 denosumab Number of subjects randomized in Study 20040138: 734 placebo and 734 denosumab; Number of subjects enrolled in DXA substudy: 148 placebo and 161 denosumab LS = Least squares; Pt Est = Point estimate; Difference = Denosumab - Placebo a Based on an ANCOVA model adjusting for treatment and baseline BMD T-score level for Study 20080098; treatment, baseline BMD, machine type, and baseline BMD-by-machine type interaction for Study 20030216; and treatment, age group, ADT duration at study entry, baseline BMD, machine type, and baseline BMD-by-machine type interaction for Study 20040138

Table. Summary of Bone Mineral Density by DXA Percent Change From Baseline at Month 12 by Site (ANCOVA Model With LOCF)

	Difference in LS Mean[a]		
	Pt Est	(95% CI)	p-value
Lumbar spine			
Study 20080098	4.8	(4.0, 5.6)	<0.0001
Study 20030216	5.5	(4.8, 6.2)	<0.0001
Study 20040138	4.9	(4.5, 5.3)	<0.0001
Total hip			
Study 20080098	2.0	(1.5, 2.6)	<0.0001
Study 20030216	3.4	(2.9, 3.9)	<0.0001
Study 20040138	3.1	(2.8, 3.4)	<0.0001
Femoral neck			
Study 20080098	2.2	(1.3, 3.0)	<0.0001
Study 20030216	2.9	(2.2, 3.5)	<0.0001
Study 20040138	2.7	(2.3, 3.0)	<0.0001
Trochanter			
Study 20080098	2.3	(1.4, 3.2)	<0.0001
Study 20030216	4.4	(3.7, 5.2)	<0.0001
Study 20040138	3.8	(3.4, 4.2)	<0.0001
Distal radius			
Study 20080098	0.9	(0.2, 1.6)	0.0144
Study 20030216	0.9	(0.3, 1.6)	0.0031
Study 20040138	3.0	(2.1, 3.9)	<0.0001

Number of subjects randomized in Study 20080098: 121 placebo and 121 denosumab Number of subjects enrolled in Study 20030216 DXA substudy: 209 placebo and 232 denosumab Number of subjects randomized in Study 20040138: 734 placebo and 734 denosumab; Number of subjects enrolled in DXA substudy: 148 placebo and 161 denosumab n = Number of subjects with observed data at baseline and at ≥ 1 postbaseline visit at or before the time point of interest

Comment: Overall, the placebo-subjects in the actual male osteoporosis study had a stable BMD during the 12 months talking against a rapid bone loss. The placebo-subjects had a decrease in BMD at 12 months especially in study 20040138.

Based on the differences in baseline absolute BMD levels between trials the applicant has presented both absolute and percent change in BMD, which is endorsed. The mean absolute changes between studies were comparable but the percent change in BMD was slightly lower in the actual study 20080098 due to higher baseline BMD.

Denosumab significantly reduced bone resorption, as assessed by decreases in serum CTX1 concentrations, in Studies 20080098, 20030216, and 20040138. The median decrease in serum CTX1 in the denosumab group in Study 20080098 was smaller than those estimated in previous denosumab clinical studies. This is due to a higher LLOQ of 0.2 ng/mL defined by the central laboratory of Study 20080098 compared with an LLOQ of 0.05 ng/mL defined in previous denosumab studies.

Comment: All studies consistently demonstrated a significant effect of denosumab on the marker of bone resorption serum CTX1, but the size of the effect in study 20080098 was lower than seen in the previous studies. The applicant argues that this is due to a higher LLOQ and imputation of the majority of CTX1 values at day 15 with this LLOQ and provided a recalculation using raw data for CTX1 from study 20080098. This recalculation showed a relative decrease in CTX1 comparable to that seen in the previous studies.

Summary of Results Across Studies by the MAH

The distribution of 10-year major osteoporotic fracture risk between Studies 20080098 and 20030216 have considerable overlap. The population studied in Study 20030216 is considered to be at increased fracture risk; the similarity in the risk distributions would indicate that the population in Study 20080098 is also at increased fracture risk. In addition, denosumab has consistent efficacy across the range of baseline fracture risk, further supporting the comparison of efficacy across the 3 studies. Covariate analyses demonstrated that the effect of denosumab was consistent across the range of baseline fracture risks in Study 20080098, and subgroup analysis in subjects with the highest baseline fracture risk demonstrated that denosumab increased BMD to a similar magnitude in these subjects.

In Studies 20030216 and 20040138, significant increases in BMD were observed at all skeletal sites measured (lumbar spine, proximal femur [total hip, femoral neck, trochanter], and distal radius). In Study 20030216, the primary efficacy analysis demonstrated the efficacy of denosumab at decreasing fracture risk, with relative risk reductions at month 36 for new vertebral, nonvertebral, and hip fractures of 68%, 20%, and 40%, respectively. A decrease in fracture risk was also observed in Study 20040138, with a 62% decrease in the incidence of new vertebral fractures in the denosumab group relative to the placebo group at month 36. Thus, Studies 20030216 and 20040138 demonstrated that increases in BMD with denosumab 60 mg Q6M are associated with decreases in the risk of fracture. Mean increases in BMD in Study 20080098 were similar to the mean increases in BMD in Studies 20030216 and 20040138 at month 12. Since increases in BMD were associated with fracture risk reduction in Studies 20030216 and 20040138, it is reasonable to extrapolate the anti-fracture efficacy of denosumab 60 mg Q6M to men with osteoporosis.

Comment: According to the MAH, baseline fracture risk between Studies 20080098 and 20030216 have considerable overlap. As discussed above, however, the subjects in the actual male osteoporosis study were younger, had higher BMD, less previous fractures and had a lower 10-year risk for fracture compared to the postmenopausal osteoporosis studies.

2.4.1. Discussion

It has previously been shown that the pharmacokinetics of denosumab is not significantly different depending on age, sex, race or disease state. A tendency of lower exposure in patients with higher bodyweight has been observed but was considered not to be of clinical relevance due to similar effect on pharmacodynamic markers over the weight range. Impaired renal function, which is a common condition in the elderly osteoporosis patients, is not a current contraindication for denosumab. Significantly impaired renal function as determined by a derived glomerular filtration rate of < 30 mL/min/1.73 m^2 was, however, an exclusion criteria in the study, according to the MAH without any apparent reason. This fact is specified in the SmPC.

Overall, the number of subjects that discontinued study and/or study treatment was low. Of the 240 subjects who received ≥ 1 dose of investigational product (120 in each group), 13 subjects (9 in the denosumab arm; 4 in the placebo arm) discontinued investigational product within the first 12 months of the study; the remaining 227 (94%) subjects completed the study (111 denosumab-treated subjects [92%]; 116 placebo-treated subjects [97%]).

A broad patient population of men with low BMD was enrolled, encompassing a wide age range (31 to 84 years) and range of baseline fracture risk. Denosumab increased BMD, as assessed by DXA at the lumbar spine, total hip, femoral neck, trochanter, and distal radius in men with low BMD. The mean change in primary endpoint, lumbar spine BMD after 12 months of treatment was large (5.7% in the denosumab group as compared with 0.9% in the placebo group [p < 0.0001]). The study results

demonstrated also a significant increase in the secondary endpoints: percent Change from Baseline in total hip, femoral neck, trochanter and radius BMD at 12 Months as well as decrease in CTX.

Using a bridging approach requires (besides a study of at least a one year duration and that the dosage is justified) that the risk factors chosen for inclusion in the pivotal study will generate a fracture risk of a magnitude similar to that of postmenopausal osteoporotic women. While acknowledged that independent risk factors for fractures have not been as extensively validated in men as in women, the relationship between BMD and fracture risk seems to be similar in men and postmenopausal women. The mean baseline BMD T-scores were however lower in Study 20030216 than in 20080098, consistent with and hence, depending on, the difference in eligibility criteria. In study 20030216, eligible subjects were postmenopausal women with osteoporosis (BMD T-score < -2.5 at the lumbar spine or the total hip and ≥ -4.0 at both sites). In study 20080098, eligible subjects were men 30 to 85 years of age, inclusive, with BMD T-score ≤-2 and ≥ -3.5 at the lumbar spine or femoral neck or ≤ -1 and ≥ -3.5 in subjects with a history of major osteoporotic fracture.

There is no reason to doubt the efficacy of treatment with denosumab in the studied population in increasing BMD T-score, irrespective of anatomic location. However, while there is a considerable overlap in the distribution of the 10-year major osteoporotic fracture risk between Study 20040138 (in men with non-metastatic prostate cancer undergoing ADT) and Study 20080098, the fracture risk distribution for Study 20080098 and Study 20030216 is not as overlapping. The median 10-year major osteoporotic fracture risk was 15.1% in Study 20030216 and 8.4% Study 20080098, respectively. Besides higher baseline BMD T-scores, the proportion of subjects with a history of any fracture was lower in Study 20080098 (<40%) than in Study 20030216 (>50%). There was also a difference in age. While 55% were 65 years or older in Study 20080098, the corresponding proportion in Study 20030216 was 95%.

2.4.1. Conclusions on the clinical efficacy

With reference to the EMA Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis (CPMP/EWP/552/95 Rev. 2) regarding bridging, the subjects for male osteoporosis studies in should include men with a similar risk for fracture as the PMO women for the substance. The MAH justification of the inclusion criteria of this male osteoporosis study that resulted in a male population with higher BMD and a clearly lower fracture risk compared to PMO women was considered acceptable by the CHMP.

Additional analyses comparing the treatment effect in a risk matched female and male population were required and confirmed that the effect on BMD was consistent.

The guideline further postulates that the magnitude of the BMD changes versus placebo should be similar to that observed in PMO women. BMD information at the 12-month time point was available only for a minority of subjects in the pivotal PMO study and HALT male studies. The comparison of male osteoporosis BMD results are therefore made with the small DXA substudies of the pivotal PMO study. The MAH has justified that the subjects in these DXA substudies were comparable with the total PMO population in terms of baseline BMD, age, previous fractures, and fracture risk.

Finally, the guideline states that the observed BMD changes should be proportional to the decreased incidence of fractures in treated women. This requirement has been fulfilled.

Treatment with denosumab in the studied male osteoporosis population increased BMD T-score, although no clinical benefit in terms of reduced fracture risk was observed in this small study and factors independent of bone density contribute to susceptibility to fracture in men to a greater extent than in women.

There was a numerical increase of total number of serious adverse events with active treatment in this study and denosumab is associated with previously identified risks such as ONJ and atypical femoral fractures that may occur at increasing frequencies in longer-term treatment duration. These issues need to be followed in the future PSURs.

2.5. Clinical Safety aspects

2.5.1. introduction

This application presents safety data from 242 men with osteoporosis (Study 20080098; n = 240 treated subjects) evaluated over 24 months. Supporting data are derived from 7808 women with PMO (Study 20030216; n = 7762 treated subjects) and 1468 men receiving ADT for prostate cancer (Study 20040138; n = 1456 treated subjects).

Safety results are presented by treatment group for the following 3 data sets and time periods:

1) All randomized subjects who received at least 1 dose of investigational product in the 12-month double-blind phase (120 denosumab, 120 placebo) - reporting time period = the 12 months constituting the double-blind phase of the study.

2) All subjects who entered the 12-month open-label phase and received at least 1 dose of denosumab during that phase (111 long-term, 116 crossover) - reporting time period = the 12 months constituting the open-label phase of the study.

3) All randomized subjects who received at least 1 dose of investigational product in the study (120 denosumab/long-term, 120 placebo/crossover) - reporting time period = the entire 24 months constituting the 12-month double-blind phase plus the 12-month open-label phase of the study.

A summary of the existing safety profile for Prolia:

Important identified risks	hypocalcemia, skin infection leading to hospitalization, ONJ, hypersensitivity reactions, atypical femoral fracture, musculoskeletal pain
Important potential risks	fracture healing complications, infection, cataracts in men with prostate cancer receiving ADT, cardiovascular events, malignancy, immunogenicity, osteonecrosis outside the jaw (avascular necrosis)
Important missing information	pregnant women, lactating women, pediatric patients, patients with hepatic impairment, potential adult off-label use

Musculoskeletal pain, osteonecrosis outside the jaw, QT-prolongation associated with hypocalcemia and increases in PTH have recently been identified a new important risks for Prolia based on adverse events reported in the post-marketing setting.

The incidence of ONJ was higher with longer duration of denosumab-exposure in XGEVA trials. The absence of ONJ in the PMO pivotal study but identification of up to this date approximately 203 reports of ONJ events from non-study sources suggest a similar pattern for Prolia.

Patient exposure

In the main study for this application, a total of 240 subjects received ≥1 dose of denosumab (n = 120) or placebo (n =120), constituting the Safety Analysis Set.

Cumulative exposure to denosumab in the bone loss program to date includes 13,476 subjects who received at least 1 dose of denosumab, 6318 subjects were treated with denosumab for ≥ 3 years, 3,537 subjects were treated with denosumab for ≥ 5 years, and 970 subjects were treated with denosumab for ≥ 8 years. Postmarketing exposure to Prolia through commercial distribution from the first marketing authorization (26 May 2010) through 26 May 2013 (data cutoff for the sixth denosumab Periodic Safety Update Report) has been estimated at 962,913 patient-years. In addition, cumulative exposure to denosumab administered at a dose of 120 mg Q4W (approved under the propriety name XGEVA) to date includes more than 20,000 subjects who have received at least 1 dose of denosumab. Postmarketing exposure to XGEVA through commercial distribution through 26 May 2013 has been estimated at 112,774 patient-years.

Adverse events

Table. Overall Summary of Adverse Events (Safety Analysis Set) (20080098 Final 24 Months Analysis)

	12-month double-blind		12-month open-label[a]		24 months	
	Placebo (N=120) n (%)	Denosumab (N=120) n (%)	Placebo/ Denosumab (N=116) n (%)	Denosumab/ Denosumab (N=111) n (%)	Placebo/ Denosumab (N=120) n (%)	Denosumab/ Denosumab (N=120) n (%)
Adverse events regardless of relationship						
All	87 (72.5)	87 (72.5)	60 (51.7)	70 (63.1)	100 (83.3)	100 (83.3)
Serious	11 (9.2)	13 (10.8)	5 (4.3)	9 (8.1)	16 (13.3)	20 (16.7)
Fatal	1 (0.8)	1 (0.8)	0 (0.0)	1 (0.9)	1 (0.8)	2 (1.7)
Leading to study discontinuation	0 (0.0)	4 (3.3)	0 (0.0)	1 (0.9)	0 (0.0)	5 (4.2)
Leading to investigational product discontinuation	0 (0.0)	5 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.2)
Adverse events related to investigational product[b]						
All	5 (4.2)	3 (2.5)	4 (3.4)	3 (2.7)	8 (6.7)	6 (5.0)
Serious	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.8)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to study discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to investigational product discontinuation	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

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Abbreviation: IP = investigational product
N = number of subjects who received ≥ 1 dose of IP
Includes only treatment-emergent adverse events
[a] Includes subjects who received at least 1 dose of IP in the open-label phase
[b] Includes only events for which the investigator indicated there was a reasonable possibility they may have been caused by IP

During the 12-month double-blind treatment period of Study 20080098, the most frequent adverse events (≥ 5% in either treatment group) by preferred term were back pain (8.3% denosumab, 6.7% placebo), arthralgia (6.7%, 5.8%), nasopharyngitis (6.7%, 5.8%), and constipation (0, 5.8%)

During the open-label treatment period of Study 20080098 the System organ classes with the highest subject incidences of adverse events were Musculoskeletal and Connective Tissue Disorders (22% long-term, 12% crossover) and infections and Infestations (21%, 20%).

By preferred term, the most frequent adverse events (subject incidence ≥5% in either treatment group) were back pain (5.4% long-term, 2.6% crossover), arthralgia (6.3%, 4.3%), and nasopharyngitis (4.5%, 6.0%).

Comment: The numbers of AEs were balanced in the first 12 months of the study. The percentages of AEs were generally lower under the open-label extension phase of the study which might be due to both selection to the extension study (9 discontinued the blinded phase in the denosumab group and 4 in the placebo group) and also some under-reporting of events due to the study open-label design and three study visits instead of four visits.
There were numerically more AEs and serious AEs in the long-term treatment group compared to crossover group.

Serious adverse events

During the 12-month double-blind treatment period of Study 20080098, the subject incidence of serious adverse events was 9.2% in the denosumab group and 8.3% in the placebo group. Two serious adverse events were reported in > 1 subject: prostate cancer for 3 subjects (2.5%) in the denosumab group and no subjects in the placebo group and arterial thrombosis limb for 2 subjects (1.7%) in the denosumab group and no subjects in the placebo group. Two of the 3 prostate cancer cases were likely present at baseline based on past medical history. Both subjects with arterial thrombosis limb had a past medical history of arterial insufficiency and prior vascular surgical intervention. No serious adverse events were considered by the investigator to be possibly related to investigational product.

During the open-label phase, subject incidences of serious adverse events were 8.1% in the long-term group and 4.3% in the crossover group.

The system organ class with the highest subject incidences of serious adverse events was Infections and Infestations: 5/111 subjects (4.5%) in the long-term group and 1/116 subjects (0.9%) in the crossover group.

Table. Subject-Year-Adjusted Serious Adverse Event Rates by System Organ Class in Descending Order of Frequency (Safety Subset) (20080098 Final 24 Months Analysis)

	12-month double-blind		12-month open-label[a]		24 months	
SYSTEM ORGAN CLASS Preferred Term	Placebo (N=120) (Subj-yr=118.9) e (r)	Denosumab 60 mg Q6M (N=120) (Subj-yr=118.9) e (r)	Placebo/ Denosumab (N=116) (Subj-yr=114.7) e (r)	Denosumab/ Denosumab (N=111) (Subj-yr=109.9) e (r)	Placebo/ Denosumab (N=120) (Subj-yr=234.3) e (r)	Denosumab/ Denosumab (N=120) (Subj-yr=228.6) e (r)
Total number of serious adverse events reported	14 (11.8)	19 (16.0)	6 (5.2)	12 (10.9)	20 (8.5)	31 (13.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (1.7)	4 (3.4)	0 (0.0)	2 (1.8)	2 (0.9)	6 (2.6)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.8)	3 (2.5)	3 (2.6)	2 (1.8)	4 (1.7)	5 (2.2)
INFECTIONS AND INFESTATIONS	1 (0.8)	0 (0.0)	1 (0.9)	5 (4.5)	2 (0.9)	5 (2.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (1.7)	4 (3.4)	0 (0.0)	0 (0.0)	2 (0.9)	4 (1.7)
CARDIAC DISORDERS	1 (0.8)	2 (1.7)	1 (0.9)	1 (0.9)	2 (0.9)	3 (1.3)
VASCULAR DISORDERS	1 (0.8)	3 (2.5)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.3)
HEPATOBILIARY DISORDERS	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.9)	0 (0.0)	2 (0.9)
NERVOUS SYSTEM DISORDERS	2 (1.7)	0 (0.0)	1 (0.9)	1 (0.9)	3 (1.3)	1 (0.4)
GASTROINTESTINAL DISORDERS	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
EYE DISORDERS	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

Includes only treatment-emergent adverse events.
Multiple occurrences of the same event for a subject are counted as multiple events.
Subj-yr = Total subject years of follow-uptime
N = Number of subjects who received at least 1 dose of IP
e = Number of events; r = Exposure-adjusted event rate per 100 subject-years (e / Subj-yr * 100)
System organ class and preferred terms are sorted by descending order of frequency in the denosumab/denosumab group in 24 months and coded using MedDRA version 15.0.
[a] Includes subjects who received at least 1 dose of IP in the open-label phase
[b] Percentage is based on N.

Comment:
During the double-blind phase, the (subject-year-adjusted) event rates per 100 subject years for all serious adverse events were 16.0 for the denosumab group and 11.8 for placebo.
The corresponding rates during the entire 24 months of study were 13.6 for the long term-denosumab group and 8.5 for the crossover group.
These numbers suggest that denosumab treatment might be associated with increase in serious AEs in this patient group. Numerical imbalances were seen in SOC serious musculoskeletal and connective tissue disorders and SOC serious infections.
However, the numbers of events are small in this study with limited number of participants. Of note, the subjects were of younger age in this study than in the other denosumab studies.

Deaths

Two deaths were reported during the 12-month double-blind treatment period of Study 20080098: myocardial infarction in a subject receiving denosumab and basilar artery thrombosis in a subject receiving placebo.

One additional subject died during the 12-month open-label treatment period of Study 20080098 in the long-term denosumab group: endocarditis

Fractures

Table. Adverse Events of Clinical Fracture by Preferred Term (Safety Analysis Set) (20080098 Final 24 Months Analysis)

	12-month double-blind		12-month open-label[a]		24 months	
Preferred Term	Placebo (N=120) n (%)	Denosumab 60 mg Q6M (N=120) n (%)	Placebo/ Denosumab (N=116) n (%)	Denosumab/ Denosumab (N=111) n (%)	Placebo/ Denosumab (N=120) n (%)	Denosumab/ Denosumab (N=120) n (%)
Number of subjects reporting adverse events of clinical fracture	2 (1.7)	1 (0.8)	0 (0.0)	4 (3.6)	2 (1.7)	5 (4.2)
Rib fracture	1 (0.8)	1 (0.8)	0 (0.0)	2 (1.8)	1 (0.8)	3 (2.5)
Foot fracture	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	2 (1.7)
Humerus fracture	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

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N = Number of subjects who received ≥ 1 dose of IP
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/denosumab group in 24 months and coded using MedDRA version 15.0.
[a] Includes subjects who received at least 1 dose of IP in the open-label phase.

Other significant events

Hypocalcemia, ONJ, fracture healing complications, atypical femoral fractures, osteonecrosis outside the jaw, and binding antidenosumab antibodies were not reported in the 12-month double-blind treatment period of Study 20080098, and no skin infections were reported in the denosumab group.

Rates of infection, acute pancreatitis, vascular disorders, cataracts, and adverse events potentially associated with hypersensitivity were similar between treatment groups.

In the 12-month double-blind treatment period of Study 20080098, malignancy adverse events were reported for 4 subjects (3.3%) in the denosumab group and no subjects in the placebo group. The events consisted of prostate cancer in 3 subjects (2.5%) and basal cell carcinoma in 1 subject (0.8%).

In the 12-month double-blind treatment period of Study 20080098, adverse events in the Medical Dictionary for Regulatory Activities (MedDRA) cardiac disorders system organ class (SOC) were reported for 8 subjects (6.7%) in the denosumab group and 3 subjects (2.5%) in the placebo group. Four subjects in the denosumab group reported events coded to the preferred term angina pectoris. Upon further clinical review, 2 of the cases of angina pectoris were identified as angina tonsillitis that had been incorrectly coded to angina pectoris due to differences in verbatim reporting across geographic regions. Serious adverse events in the cardiac disorders SOC were reported for 2 subjects (1.7%) in the denosumab group (acute myocardial infarction and myocardial infarction) and 1 subject (0.8%) in the placebo group (atrial fibrillation). The exposure-adjusted rate of events in the cardiac disorders SOC was lower in both treatment groups of Study 20080098 than in Studies 20030216 and 20040138. This observation may be due to the younger age of subjects in Study 20080098.

Table. AEs in the Cardiac Disorders SOC

SOC Preferred Term	Placebo (N=120) n (%)	Denosumab 60 mg Q6M (N=120) n (%)
CARDIAC DISORDERS	3 (2.5)	8 (6.7)
Angina pectoris	0 (0.0)	4 (3.3)
Arrhythmia	0 (0.0)	2 (1.7)
Acute myocardial infarction	0 (0.0)	1 (0.8)
Myocardial infarction	0 (0.0)	1 (0.8)
Atrial fibrillation	2 (1.7)	0 (0.0)
Palpitations	1 (0.8)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event, includes only treatment-emergent AEs

Comment: Adverse events in the MedDRA Cardiac Disorders SOC occurred in 8 subjects (6.7%) in the denosumab and 3 subjects (2.5%) in the placebo group during phase 1 of study 20080098. Of the 4 subjects reported with angina pectoris 2 were identified as angina tonsillitis after clinical review. Serious adverse events in the Cardiac Disorders SOC were reported for 2 subjects (1.7%) in the denosumab (acute myocardial infarction, myocardial infarction) and 1 subject (0.8%) in the placebo group (atrial fibrillation). Adverse events in the MedDRA Vascular Disorders SOC were reported for 6 subjects (5.0%) in the denosumab and 8 subjects (6.7%) in the placebo group. Currently cardiovascular risk is labelled as a potential risk with routine pharmacovigilance activities and "no risk minimization activities given the lack of evidence for cardiovascular risk. Expert adjudication of serious cardiovascular adverse events in the large long-term pivotal denosumab studies showed that denosumab did not increase the overall risk for cardiovascular serious adverse events. No difference between denosumab and placebo treatment groups was found in the change from baseline in aortic calcification score in a subset of subjects with high baseline cardiovascular risk. Results of clinical and nonclinical studies indicate that denosumab administration was not associated with clinically significant ECG abnormalities." The low absolute number of events (6 denosumab, 3 placebo) does not allow any firm conclusion. However, the population investigated in trial 20080098 was younger and therefore associated with a lower cardiovascular risk than that in the previous trials. The higher background cardiovascular risk could have masked a true difference in the risk of cardiovascular events between denosumab and placebo.

The applicant has discussed the discrepancy in the incidence of adverse events in the Cardiac Disorders SOC between denosumab and placebo (6 and 3 subjects, respectively) in study 20080098. The applicant argues that cardiac events occurred in the context of older age and past history of coronary disease and that analyses of cardiac events in the pivotal, placebo-controlled studies for PMO do not support an increased cardiovascular risk associated with denosumab. The applicant suggests to continue monitoring cardiovascular adverse events as a potential risk and to implement risk minimisation activities only if a safety risk for cardiovascular events has been identified. This approach is endorsed by the CHMP.

No denosumab-treated subjects tested positive for binding antidenosumab antibodies during Study 20080098, consistent with the low incidence of binding antibodies observed throughout the denosumab clinical development program.

Open-label phase:
There were no reports of hypocalcemia, osteonecrosis of the jaw (ONJ), fracture healing complications, or atypical femoral fractures during the open-label phase. Malignancy adverse events were reported for 1/111 subjects (0.9%) in the long-term group (gastric cancer plus metastases to the lung plus rectal neoplasm [benign]) and 2/116 subjects (1.7%) in the crossover group (bladder cancer; and malignant lung neoplasm plus metastases to central nervous system).

Laboratory findings

Consistent with previous studies, denosumab administration was associated with mild, transient decreases in serum calcium in the 12-month double-blind treatment period of Study 20080098. No Common Terminology Criteria for Adverse Effects (CTCAE) grade ≥3 decreased serum calcium values were reported during the study, and no adverse events of hypocalcemia were reported.
Denosumab administration also was associated with decreases in serum phosphorus the 12-month double-blind treatment period of Study 20080098. No CTCAE grade ≥3 decreased phosphorus values were reported in Study 20080098. Denosumab administration was not associated with trends in other serum chemistry or hematology parameters.
There were no clinically significant changes in mean and median on-study values for systolic and diastolic blood pressures, heart rate, body temperature, and body weight across the 3 studies.

Safety in special populations

Subgroup analyses of safety in special populations were not performed for study 20080098. For studies 20030216 and 20040138, clinical evaluations were performed to examine the impact of various intrinsic and extrinsic factors on the safety of denosumab. Intrinsic factors included demographics, disease or health-related characteristics, impaired renal function, and underlying disease (e.g., rheumatoid arthritis, metastatic cancer, and multiple myeloma). Extrinsic factors included geographic region and evaluations of safety in key active comparator studies, including subjects with PMO who transitioned from bisphosphonate therapy, and denosumab preparations from different manufacturing sites and dosage presentations.

Comment: Safety in special populations has been adequately assessed during the assessment of the initial marketing authorisation application for Prolia and thus it is acceptable that no further analyses have been provided.

Immunological events

Adverse Events Potentially Associated With Hypersensitivity

The incidence of AEs potentially associated with hypersensitivity was similar for both groups (3 subjects [2.5%]) in the 12-month double-blind phase 1 of study 20080098. Events in the denosumab group consisted of rash, allergic dermatitis, and eczema (1 subject each), while events in the placebo group consisted of rash (2 subjects) and eyelid oedema and allergic rhinitis (1 subject each). None of these cases was fatal or considered severe**.**

During the 12-month open-label phase 2 of study 20080098, 2 subjects had AEs potentially associated with hypersensitivity (1.8% long-term; 1.7% crossover). All events were nonserious.

Hypersensitivity reactions associated with Prolia have been observed in the postmarketing setting. Clinical features included rash, urticaria, facial oedema, erythema, and anaphylactic reaction.

Antibody Formation

No subject treated with denosumab tested positive for binding anti-denosumab antibodies during either phase 1 or 2 of study 20080098, consistent with the low incidence of binding antibodies observed throughout the denosumab clinical development program (< 1% of > 8000 subjects). In addition no neutralising antibodies have been reported in in any denosumab clinical study to date.

Comment: No new or unexpected findings occurred as regards hypersensitivity reactions and antibody formation. None of the subjects treated with denosumab during trial tested positive for binding anti-denosumab antibodies during study 20080098.

Safety related to drug-drug interactions and other interactions

No data on safety related to drug-drug interactions and other interactions specific to this variation application have been provided in the dossier, which is acceptable to the CHMP.

Study discontinuations

Reasons for Study Discontinuation (Randomized Subjects) (20080098 Final 24 Months Analysis)

	Placebo/ Denosumab 60 mg Q6M n (%)	Denosumab/ Denosumab 60 mg Q6M n (%)	All n (%)
Randomized	121	121	242
Entered open-label phase of study	117 (96.7)	111 (91.7)	228 (94.2)
Completed 24 months of study	114 (94.2)	105 (86.8)	219 (90.5)
Discontinued during open-label phase of study	3 (2.5)	6 (5.0)	9 (3.7)
Consent withdrawn	2 (1.7)	3 (2.5)	5 (2.1)
Adverse event	0 (0.0)	2 (1.7)	2 (0.8)
Death	0 (0.0)	1 (0.8)	1 (0.4)
Lost to follow-up	1 (0.8)	0 (0.0)	1 (0.4)

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Percentages based on number of randomized subjects

There were slightly more discontinuations in the denosumab group and long-term denosumab group compared to placebo and cross-over groups.

Comparison of safety data with 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.

The subject incidences of serious adverse events were balanced within system organ classes; 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).

HALT:

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 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).

No new safety concerns were identified in the male osteoporosis study.

In the current study, numerical imbalances were seen in SOC serious musculoskeletal and connective tissue disorders and AEs of serious infections. This is in line with previous finding from pooled pivotal studies for Prolia, where serious AEs of infection were more common in denosumab treated patients 213/4910 (4.3%) compared to placebo 168/4886 (3.4%), HR 1.25 (1.02-1.53).

Musculoskeletal pain has been observed with Prolia in the post-marketing setting and is now an identified risk, a type II variation has been submitted and is currently undergoing assessment by the CHMP.

Post marketing experience

Comment:

Osteonecrosis of the jaw (ONJ): No cases of ONJ were reported in the pooled pivotal studies for PMO and HALT or in the male osteoporosis study. Six cases were reported in the open-label extension to the pivotal PMO study. Cumulatively, 203 post-marketing reports of ONJ events have been received from non-study sources, with the number of positively adjudicated ONJ reports representing a reporting rate of 2.7 per 100,000 patient-years for Prolia. The incidence of ONJ was higher with longer duration of denosumab-exposure in pooled denosumab Xgeva trials, incidence up to 10% at three years.

The absence of ONJ in osteoporosis pivotal studies but identification of 203 reports of ONJ events from non-study sources suggest a similar pattern for Prolia. For patients treated for osteoporosis, this is of great concern as the treatment duration may theoretically be several decades. In an ongoing PSUR procedure for Prolia the MAH is requested to perform an analysis of time to adjudicated ONJ events in Prolia treated patients. An analysis of any of risk factors for ONJ in these cases will be presented as part of that procedure.

At present, no restrictions in the duration of Prolia treatment and no contraindications for patients with risk factors for ONJ have been implemented in the SmPC. The optimal treatment duration with Prolia, need of restrictions in terms of treatment duration and contraindications are currently assessed by the CHMP in an ongoing variation II-36.

Atypical femoral fracture: The number of reported atypical fractures is low but is expected to rise with increased duration of denosumab exposure in osteoporosis patients as it is the case for bisphosphonates. This identified risk has recently been added in the SmPC.

2.5.2. Discussion

No new safety concerns were identified in the male osteoporosis study. There were only a few clinical fractures in the study but numerically more in the long-term denosumab group (n=5) compared to cross over group (n=2). A proportion of the study population had probably baseline fracture risk not high enough to benefit from the treatment in terms of fracture prevention.

In principle, the need of pharmacological treatment for male osteoporosis should be defined according to the treatment guidelines in force and not according to the inclusion criteria of the study. This notion is considered important in light of the numerical increase of total number of serious adverse events in denosumab and denosumab/denosumab groups compared to placebo and placebo/cross-over groups, as well as the potential specific risks of serious adverse events of ONJ and atypical femoral fractures that may occur at increasing frequencies in longer-term treatment duration.

The applicant has discussed the discrepancy in the incidence of adverse events in the Cardiac Disorders SOC between denosumab and placebo (6 and 3 subjects, respectively) in study 20080098. The applicant argues that cardiac events occurred in the context of older age and past history of coronary disease and the fact that analyses of cardiac events in the pivotal, placebo-controlled studies for PMO do not support an increased cardiovascular risk associated with denosumab. The

applicant suggests to continue monitoring cardiovascular adverse events as a potential risk and to implement risk minimisation activities only if a safety risk for cardiovascular events has been identified. This approach is endorsed.

2.6. Risk management plan

PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table: Summary of safety concerns

Important identified risks	hypocalcemia, skin infection leading to hospitalization, ONJ, hypersensitivity reactions, atypical femoral fracture, musculoskeletal pain
Important potential risks	fracture healing complications, infection, cataracts in men with prostate cancer receiving ADT, cardiovascular events, malignancy, immunogenicity, osteonecrosis outside the jaw (avascular necrosis)
Important missing information	pregnant women, lactating women, pediatric patients, patients with hepatic impairment, potential adult off-label use

Pharmacovigilance plans

Table: Ongoing and planned studies in the PhV development 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 (C), 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 ETDRS ("Early Treatment Diabetic Retinopathy Study") 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 ADT	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 only)	ONJ, atypical femoral fracture, fracture healing complications, hypocalcemia, Infection, hypersensitivity leading to hospitalization or ER visit, malignancy	Ongoing	Next interim report Q3 2013; 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
20090695 Postmarketing observational study Estimation of off-label use of Prolia® (denosumab) in selected European countries using multiple observational databases Category 3	• Estimate the proportion of Prolia prescriptions that are off-label by country • Estimate the proportion of patients receiving Prolia that are for off-label use by country • Compare the frequency of off-label use in the first 6 months after product launch vs that in the second 6 months after product launch • Describe the indications for Prolia in each data source • Describe the proportion of prescriptions that derive from rheumatology, oncology, or other specialties with the potential to prescribe Prolia off label	Off-label use of Prolia	Ongoing	Anticipated Q1 2014

Risk minimisation measures

Table: Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Identified Risks		
Hypocalcemia	Text in SmPC • Section 4.2, Posology and method of administration, states that patients must be adequately supplemented with calcium and vitamin D (see Section 4.4). • Contraindicated in Section 4.3. • Section 4.4, Special warnings and precautions for use: - Adequate intake of calcium and vitamin D is important in all patients. - Precautions for use: Hypocalcemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcemia. Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcemia. In the post-marketing setting, severe symptomatic hypocalcemia has been reported (see section 4.8). • Section 4.8, Undesirable effects: - Listed as an adverse reaction and mentioned in the Summary of the Safety Profile - Under Description of selected adverse reactions, subheading Hypocalcemia: In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/l) following Prolia administration. Declines of serum calcium levels (less than 1.88 mmol/L) were not reported in the two phase III placebo-controlled clinical trials in patients receiving hormone ablation. In the postmarketing setting, rare cases of severe symptomatic hypocalcaemia have been reported in patients at increased risk of hypocalcaemia receiving Prolia.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Hypocalcemia (continued)	Text in SmPC (continued) - Under Other special populations: In clinical studies, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcaemia in the absence of calcium supplementation. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see section 4.4). Other routine risk minimization measures • Prescription only medicine • The following information is provided in PIL: - Under What you need to know before you use Prolia: Do not use Prolia if you have low calcium levels in the blood (hypocalcemia). - Under Warnings and Precautions: Tell your doctor if you have or have ever had severe kidney problems, kidney failure or have needed dialysis, which may increase your risk of getting low blood calcium if you do not take calcium supplements. You should also take calcium and vitamin D supplements while being on treatment with Prolia. Your doctor will discuss this with you. - Listed under Possible side effects: spasms, twitches, or cramps in your muscles, and/or numbness or tingling in your fingers, toes or around your mouth. These could be signs that you have low calcium levels in the blood (hypocalcaemia).	

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Skin infection leading to hospitalization	<u>Text in SmPC</u> • Section 4.4, Special warnings and precautions for use, under Precautions for use: Patients receiving Prolia may develop skin infections (predominantly cellulitis) leading to hospitalization (see section 4.8). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis. • Section 4.8, Undesirable effects: - Cellulitis is listed as an adverse reaction and mentioned in the Summary of the Safety Profile. - The following text is provided under Description of selected adverse reactions, subheading Skin infections: In phase III placebo-controlled clinical trials, the overall incidence of skin infections was similar in the placebo and the Prolia groups in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus Prolia [1.5%, 59 out of 4,050]) and in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus Prolia [1.4%, 12 out of 860]). Skin infections leading to hospitalization were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving Prolia. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the Prolia (0.6%, 5 out of 860) groups in the breast and prostate cancer studies. <u>Other routine risk minimization measures</u> • Prescription only medicine • The following text is provided in the PIL: - Under Warnings and precautions: Please tell your doctor immediately if you develop a swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis), and possibly with symptoms of fever while being on treatment with Prolia. - Under Possible side effects: Uncommonly, patients receiving Prolia may develop skin infections (predominantly cellulitis). Please tell your doctor immediately if you develop any of these symptoms while being on treatment with Prolia: swollen, red area of skin, most commonly in the lower leg, that feels hot and tender, and possibly with symptoms of fever.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
ONJ	Text in SmPC • Section 4.4, Special warnings and precautions for use, under Precautions for use: - Osteonecrosis of the jaw (ONJ) has been reported in patients treated with denosumab or bisphosphonates, another class of antiresorptive agents. Most cases have been in cancer patients; however some have occurred in patients with osteoporosis. - ONJ has been reported rarely in clinical studies in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis. - There have been reports of ONJ in clinical studies in patients with advanced cancer treated with denosumab at the studied dose of 120 mg administered monthly. Known risk factors for ONJ include a diagnosis of cancer with bone lesions, concomitant therapies (eg, chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, dental extractions, and comorbid disorders (eg, pre-existing dental disease, anemia, coagulopathy, infection) and previous treatment with bisphosphonates. - A dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia in patients with concomitant risk factors. While on treatment, these patients should avoid invasive dental procedures if possible. - Good oral hygiene practices should be maintained during treatment with Prolia. For patients who develop ONJ while on Prolia therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with Prolia, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation. • Section 4.8, Undesirable effects: - Listed as an adverse reaction and mentioned in the Summary of the Safety Profile. - Under Description of selected adverse reactions, subheading Osteonecrosis of the jaw: In the osteoporosis clinical trial program (8710 patients treated ≥ 1 year), ONJ was reported rarely with Prolia (see section 4.4).	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
ONJ (continued)	<u>Other routine risk minimization measures</u> • Prescription only medicine • The following text is provided in the PIL: - Under Warnings and precautions: A dental examination should be considered before you start treatment with Prolia if you have cancer, are undergoing chemotherapy or radiotherapy, are taking steroids, do not receive routine dental care or have gum disease. If you are under dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Prolia. It is important to maintain good oral hygiene when being on treatment with Prolia. - Under Possible side effects: persistent pain and/or non-healing sores of the mouth or jaw.	None
Hypersensitivity reactions	<u>Text in SmPC</u> • Under section 4.3, hypersensitivity to the active substance or to any of the excipients listed in section 6.1 is listed as a contraindication. • Section 4.8, Undesirable effects: - Hypersensitivity is mentioned in the Summary of the safety profile. - Drug hypersensitivity, rash, and anaphylactic reaction are listed as adverse reactions. - Under subheading Drug-related hypersensitivity reactions: In the postmarketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving Prolia. <u>Other routine risk minimization measures</u> • Prescription only medicine • The following text is provided in the PIL: - Under what you need to know before you use Prolia: do not use Prolia if you are allergic to denosumab or any of the other ingredients of this medicine (listed in section 6). - Under Possible side effects: allergic reactions (eg swelling of the face, lips, tongue, throat, or other parts of the body; rash, itching or hives on the skin; wheezing or difficulty breathing).	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Atypical femoral fracture	<u>Proposed Text in SmPC</u> • Section 4.4, Special warnings and precautions for use, under Precautions for use: Atypical femoral fractures have been reported in patients receiving Prolia (see section 4.8). Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterize these events. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (eg, bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore the contralateral femur should be examined in Prolia-treated patients who have sustained a femoral shaft fracture. Discontinuation of Prolia therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit risk assessment. During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture. • Section 4.8, Undesirable effects: - Atypical femoral fracture is mentioned in the Summary of the safety profile and listed as an adverse reactions. - Under Description of Selected adverse reactions, Subheading Atypical fractures of the femur: In the osteoporosis clinical trial program, atypical femoral fractures were reported very rarely in patients treated with Prolia (see section 4.4). <u>Other routine risk minimization measures</u> • Prescription only medicine • The following text is provided in the PIL: Under Possible side effects: Unusual fractures of the thigh bone may occur rarely. Contact your doctor if you experience new or unusual pain in your hip, groin or thigh while being on treatment with Prolia as this may be an early indication of a possible fracture of the thigh bone.	Per variation approved 12 February 2013: A Direct Healthcare Professional Communication ("Dear HCP letter") was distributed to accompany the inclusion of atypical femoral fracture in the SmPC.

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Musculoskeletal pain	Proposed Text in SmPC • Text will be added to Section 4.8, Undesirable effects: specific wording is pending.	None
Potential Risks		
Fracture healing complications	Text in SmPC • The following text is provided in section 5.3, Preclinical safety data: In male mice genetically engineered to express huRANKL (knock-in mice), which were subjected to a transcortical fracture, denosumab delayed the removal of cartilage and remodelling of the fracture callus compared to control, but biomechanical strength was not adversely affected. Other routine risk minimization measures • Prescription only medicine	None
Infection	Text in SmPC • In section 4.8, Undesirable effects: - Diverticulitis, upper respiratory tract infection, urinary tract infection, and ear infection are listed as adverse reactions. - The following text is provided under Description of selected adverse reactions, subheading Diverticulitis: In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving ADT an imbalance in diverticulitis adverse events was observed (1.2% denosumab, 0% placebo). The incidence of diverticulitis was comparable between treatment groups in postmenopausal women with osteoporosis and in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. Other routine risk minimization measures • Prescription only medicine • The PIL lists the following under Possible side effects: fever, vomiting and abdominal pain or discomfort (diverticulitis); ear infection.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Cataract in men with prostate cancer receiving ADT	Text in SmPC • Section 4.8, Undesirable effects: - Cataract is listed as an adverse reaction. - Under Description of selected adverse reactions, subheading Cataract: In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving androgen deprivation therapy (ADT) an imbalance in cataract adverse events was observed (4.7%) denosumab, 1.2% placebo). No imbalance was observed in postmenopausal women with osteoporosis or in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer. Other routine risk minimization measures • Prescription only medicine • The PIL lists the following under Possible side effects: cloudy area in the lens of the eye (cataracts).	None
Cardiovascular events	Text in SmPC: Not applicable Other routine risk minimization measures • Prescription only medicine	N/A
Malignancy	Text in SmPC: Not applicable Other routine risk minimization measures Prescription only medicine	N/A
Immunogenicity	Text in SmPC • In section 5.1, Pharmacodynamic properties, the following text is provided under subheading Immunogenicity: In clinical studies, neutralizing antibodies have not been observed for Prolia. Using a sensitive immunoassay < 1% of patients treated with denosumab for up to 5 years tested positive for non-neutralizing binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response. Other routine risk minimization measures • Prescription only medicine	N/A
Osteonecrosis outside the jaw (avascular necrosis)	Text in SmPC Not applicable Other routine risk minimization measures • Prescription only medicine	N/A

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Missing Information		
Pregnant women	<u>Text in SmPC</u> • The following text is provided in section 4.6 under subheading pregnancy: There are no adequate data from the use of Prolia in pregnant women. Reproductive toxicity was shown in a study of cynomolgus monkeys, dosed throughout pregnancy with denosumab at AUC exposures 119-fold higher than the human dose (see section 5.3). Prolia is not recommended for use in pregnant women. Women who become pregnant during Prolia treatment are encouraged to enroll in Amgen's Pregnancy Surveillance program. Contact details are provided in section 6 of the Package Leaflet–Information for the user. • The following text is provided in section 5.3, Preclinical safety data: In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (60 mg every 6 months), there was no evidence of maternal or fetal harm. In this study, fetal lymph nodes were not examined. In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 119-fold higher than the human dose (60 mg every 6 months), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced hematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. A no observed adverse effect level for reproductive effects was not established. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralization in multiple tissues was seen in one animal (relation to treatment uncertain). There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. <u>Other routine risk minimization measures</u> • Prescription only medicine • The following text is provided in the PIL under Pregnancy and breast-feeding: Prolia has not been tested in pregnant women. It is important to tell your doctor if you are pregnant; think you may be pregnant; or plan to get pregnant.	Not applicable

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Pregnant women (continued)	<u>Other routine risk minimization measures (continued)</u> Prolia is not recommended for use if you are pregnant. If you become pregnant during Prolia treatment, please inform your doctor. You may be encouraged to enroll in Amgen's Pregnancy Surveillance program. Local representative contact details are provided in section 6 of this leaflet.	
Lactating women	<u>Text in SmPC</u> • The following text is provided in section 4.6 under subheading Breastfeeding: It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL (the target of denosumab see section 5.1) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (see section 5.3). A decision on whether to abstain from breast-feeding or to abstain from therapy with Prolia should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Prolia therapy to the woman. Women who are nursing during Prolia treatment are encouraged to enroll in Amgen's Lactation Surveillance Program. Contact details are provided in section 6 of the Package Leaflet-Information for the user. <u>Other routine risk minimization measures</u> • Prescription only medicine • The following text is provided in the PIL under Pregnancy and breast-feeding: It is not known whether Prolia is excreted in breast milk. It is important to tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Prolia, considering the benefit of breast-feeding to the baby and the benefit of Prolia to the mother. If you are nursing during Prolia treatment, please inform your doctor. You may be encouraged to enrol in Amgen's Lactation Surveillance Program. Local representative contact details are provided in section 6 of this leaflet.	

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Pediatric Patients, including off-label pediatric use	Text in SmPC • Section 4.2, Posology and method of administration, under subheading Pediatric population: Prolia is not recommended in pediatric patients (age < 18) as the safety and efficacy of Prolia in these patients have not been established. Inhibition of RANK/RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption (see also section 5.3). • Section 5.2, Pharmacokinetic properties, under subheading Pediatric population: The pharmacokinetic profile in pediatric populations has not been assessed. • Section 5.3, Preclinical safety data: Knockout mice (see section 4.6) lacking RANK or RANKL exhibited decreased body weight, reduced bone growth and lack of tooth eruption. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with high doses of a construct of osteoprotegerin bound to Fc (OPG-Fc) was associated with inhibition of bone growth and tooth eruption. These changes were partially reversible in this model when dosing with RANKL inhibitors was discontinued. Adolescent primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. Other routine risk minimization measures • Prescription only medicine • The following text is provided in the PIL under Children and adolescents: Prolia is not recommended for children and adolescents under 18 years of age. The use of Prolia in children and adolescents has not been studied.	

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Patients With Hepatic Impairment	Text in SmPC • Section 4.2, Posology and method of administration, under subheading Patients with hepatic impairment: The safety and efficacy of denosumab have not been studied in patients with hepatic impairment (see section 5.2). • Section 5.2, Pharmacokinetic properties, under subheading Hepatic impairment: No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics of denosumab is not expected to be affected by hepatic impairment Other routine risk minimization measures Prescription only medicine	

The CHMP endorsed this RMP advice without changes.

2.7. Changes to the Product Information

The purpose of this application is to add the following new indication to the Prolia Summary of Product Characteristics (SmPC): "Treatment of osteoporosis in men at increased risk of fracture." As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the statement in section 5.1 of the SmPC related to the paediatric plan has been updated.

The following changes to the SmPC were agreed following the CHMP assessment of the data provided:

Summary of Product Characteristics

4.1 Therapeutic indications

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.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of Prolia was similar in ~~postmenopausal women~~ **patients** with osteoporosis and in breast or prostate cancer patients receiving hormone ablation in ~~four~~ **five** Phase III placebo-controlled clinical trials.

Uncommon cases of cellulitis; rare cases of hypocalcaemia, hypersensitivity**,** ~~and~~ osteonecrosis of the jaw and ~~rare cases of~~ atypical femoral fractures (see sections 4.4 and section 4.8 - description of selected adverse reactions) have been observed with Prolia.

……..

Table 1 Adverse reactions reported in ~~women~~ patients with ~~postmenopausal~~ osteoporosis and breast or prostate cancer patients receiving hormone ablation

MedDRA system organ class	Frequency category	Adverse reactions
Gastrointestinal disorders	Common **Common**	Constipation **Abdominal discomfort**

[1] See section Description of selected adverse reactions

……

Description of selected adverse reactions

Hypocalcaemia

In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/l) following Prolia administration. Declines of serum calcium levels (less than 1.88 mmol/l) were not reported in **either** the two phase III placebo-controlled clinical trials in patients receiving hormone ablation **or the phase III placebo-controlled clinical trial in men with osteoporosis.**

……

Skin infections

In phase III placebo-controlled clinical trials, the overall incidence of skin infections was similar in the placebo and the Prolia groups in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus Prolia [1.5%, 59 out of 4,050]); **in men with osteoporosis (placebo [0.8%, 1 out of 120] versus Prolia [0%, 0 out of 120])** and in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus Prolia [1.4%, 12 out of 860]). Skin infections leading to hospitalisation were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving Prolia. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the Prolia (0.6%, 5 out of 860) groups in the breast and prostate cancer studies.

Osteonecrosis of the jaw

In **clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation** ~~osteoporosis clinical trial program~~ (~~9768~~ **12347** patients, **9912** treated ≥ 1 year), ONJ was reported rarely with Prolia (see section 4.4).

……

Cataracts

In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving androgen deprivation therapy (ADT) an imbalance in cataract adverse events was observed (4.7% denosumab, 1.2% placebo). No imbalance was observed in postmenopausal women **or men** with osteoporosis or in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer.

Diverticulitis

In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving ADT an imbalance in diverticulitis adverse events was observed (1.2% denosumab, 0% placebo). The incidence of diverticulitis was comparable between treatment groups in postmenopausal women **or men** with osteoporosis and in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer.

……..

5.1 Pharmacodynamic properties

…….

~~Bone histology~~

~~Bone histology was evaluated in 62 postmenopausal women with osteoporosis or with low bone mass who were either naïve to osteoporosis therapies or had transitioned from previous alendronate therapy following 1-3 years treatment with Prolia. Bone biopsy results from both studies showed bone of normal architecture and quality with no evidence of mineralisation defects, woven bone or marrow fibrosis.~~

Treatment of osteoporosis in men

Efficacy and safety of Prolia once every 6 months for 1 year were investigated in 242 men aged 31-84 years. Patients with an eGFR < 30 ml/min/1.73 m^2 were excluded from the study. All men received calcium (at least 1,000 mg) and vitamin D (at least 800 IU) supplementation daily.

The primary efficacy variable was percent change in lumbar spine BMD, fracture efficacy was not evaluated. Prolia significantly increased BMD at all clinical sites measured, relative to placebo at 12 months: 4.8% at lumbar spine, 2.0% at total hip, 2.2% at femoral neck, 2.3% at hip trochanter, and 0.9% at distal 1/3 radius (all p < 0.05). Prolia increased lumbar spine BMD from baseline in 94.7% of men at 1 year. Significant increases in BMD at lumbar spine, total hip, femoral neck and hip trochanter were observed by 6 months (p < 0.0001).

Bone histology

Bone histology was evaluated in 62 postmenopausal women with osteoporosis or with low bone mass who were either naïve to osteoporosis therapies or had transitioned from previous alendronate therapy following 1-3 years treatment with Prolia. Bone histology was also evaluated in 17 men with osteoporosis following 1 year treatment with Prolia. Bone biopsy results from all studies showed bone of normal architecture and quality with no evidence of mineralisation defects, woven bone or marrow fibrosis.

……..

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Prolia in all subsets of the paediatric population ~~in the treatment of menopausal and other perimenopausal disorders, and~~ in the treatment of bone loss associated with sex hormone ablative therapy**, and in subsets of the paediatric population below the age of 2 in the treatment of osteoporosis.** See section 4.2 for information on paediatric use.

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

Benefits

Beneficial effects

The pivotal trial (20080098) to support the new indication is a randomised, double-blind bridging study in men with primary osteoporosis (n=242) treated with denosumab 60mg or placebo Q6M for 12 months. In the open-label phase of 12 months, all subjects received denosumab. Bone mineral density (BMD) at the lumbar spine after one year of treatment was the primary outcome.

Efficacy on the primary endpoint has been demonstrated; the relative change of measured BMD at the lumbar spine from baseline to last on treatment value was 5.7% in the denosumab group (n=117) versus 0.9%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.

Similar effect sizes for both genders were demonstrated for the absolute change in lumbar spine BMD. The effect size of the BMD percentage increase at the lumbar spine compared to placebo for male 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:

Male osteoporosis=study 20090098, Postmenopausal osteoporosis=study 20030216,

Bone loss associated hormone ablation therapy HALT in prostate cancer=study 20040138

	Difference in LS Mean[a]		
	Pt Est	(95% CI)	p-value
Lumbar spine			
Study 20080098	4.8	(4.0, 5.6)	<0.0001
Study 20030216	5.5	(4.8, 6.2)	<0.0001
Study 20040138	4.9	(4.5, 5.3)	<0.0001

The absolute risk reduction was 4.9% for new vertebral fractures, 1.4% for nonvertebral fractures and 0.4% for hip fractures in PMO study 2003016. The same fracture and BMD endpoints as in the PMO study were used for the HALT (bone loss associated hormone ablation therapy in patients with prostate cancer) indication. The absolute risk reduction was 1.4% for new radiological vertebral fractures but no risk reduction for nonvertebral and hip fractures in HALT study 20040138 was observed.

The pharmacokinetic data provided in males and the comparative population PK/PD data from osteoporotic males and females do not suggest any differences in exposure that would necessitate a dose adjustment in the male population compared to postmenopausal females.

Uncertainty in the knowledge about the beneficial effects

This male osteoporosis study was not powered to show a statistically significant difference between groups on the reduction of osteoporotic fractures. Overall, the number of new fractures observed in the study was low, with 5 patients (4.2%) clinical fractures in the denosumab/denosumab group compared to 2 (1.7%) in the placebo/crossover group.

Justification of inclusion criteria that will generate a fracture risk of a similar magnitude in the male study population as compared with the postmenopausal female population included in the phase III studies is essential for acceptance of the minimum requirement for granting the indication for treatment of osteoporosis in men based on bridging studies.

The baseline fracture risk was lower in male osteoporosis subjects in this study compared PMO study subjects. However, additional analyses comparing the treatment effect in a risk matched female and male population confirmed that the effect on BMD was consistent. The male study subgroup with a baseline 10-year fracture risk that overlapped with subjects from PMO study included 222 of 242 subjects. In this subgroup, the effect of denosumab treatment on the percent change from baseline in BMD (4.7%) was consistent with that observed in the overall male study population (4.8%) and in the same range as observed in subjects enrolled in the PMO (DXA) substudy (5.5%).

As regards baseline data there is a lack of data on ethnicities for groups other than white. In study 20080098 a larger proportion of Europeans were randomized to the denosumab group than the placebo group. However, additional analyses did not show an influence of region on efficacy or safety.

Consequently, granting the indication for treatment of osteoporosis in men need to be based on bridging study results to PMO women according to the CHMP guideline. Factors independent of bone density contribute to susceptibility to fracture in men. In the Rotterdam study, only 21% of all nonvertebral fractures in men occurred in men with BMD T-score < -2.5, while 44% of all nonvertebral fractures in women occurred in women with BMD T-score < -2.5 (Schuit et al, 2004). In the MINOS study, fracture incidence was comparable between men with a T-score < -2 (13.7% to 44.6%) and men with a T-score between -1 and -2 (27% to 45%) (Szulc et al, 2005).

Risks

Unfavourable effects

In general, the safety profile for denosumab in the male osteoporosis study did not markedly differ from that in female osteoporosis studies, where safety evaluation is based on much larger numbers and longer observation periods. The total number of serious adverse events was numerically higher in denosumab 19 (16%) and denosumab/denosumab groups 31(13.6%) compared to placebo 14 (11.8%) and placebo/cross-over 20(8.5%) groups. Numerical imbalances were seen in serious musculoskeletal disorders and serious infection SOC. These risks will be monitored in future PSURs.

Important identified risks with Prolia that did not occur in the male osteoporosis study include hypocalcaemia, skin infection leading to hospitalisation, osteonecrosis of the jaw, hypersensitivity reactions, atypical femoral fracture, and musculoskeletal pain.

Uncertainty in the knowledge about the unfavourable effects

The male osteoporosis study was considerably smaller and shorter than PMO and HALT studies which is a considerable limitation for the safety evaluation of this study. An ongoing Study 20090522 is a post-marketing safety study with a substudy to assess adverse events of special interest among men with osteoporosis treated with denosumab.

The male osteoporosis study patients were younger and had a lower fracture risk compared to the PMO women. The incidence of adverse events in this study might be different than for the men with a higher fracture risk.

No cases of ONJ were reported in the pooled pivotal studies for PMO and HALT or in the male osteoporosis study. Six cases were reported in the open-label extension to the pivotal PMO study. In addition, 203 post-marketing reports of ONJ events have cumulatively been received from non-study sources, with the number of positively adjudicated ONJ reports representing a reporting rate of 2.7 per 100,000 patient-years for Prolia. The incidence of ONJ is likely to be higher with longer duration of denosumab-exposure. For patients treated for osteoporosis, this is of great concern as the treatment duration may theoretically be several decades (the youngest patient in the actual study was 30 years).

There was a higher incidence of adverse events in the Cardiac Disorders SOC with 6 subjects in the denosumab versus 3 subjects in the placebo group during phase 1 of study 20080098. The low absolute number of events does not allow any firm conclusion.

Men with an estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 were excluded from male osteoporosis study. According to the MAH, there was no specific rationale for their exclusion. Patients with renal impairment are at increased risk of severe symptomatic hypocalcaemia under Prolia treatment. This safety issue and potential changes in the wording of SmPC warnings section will be addressed in the ongoing variation for Prolia EMEA/H/C/1120/II/37. The MAH proposal to clarify the fact that subjects with an eGFR < 30 mL/min/1.73 m^2 were excluded from Study 20080098 is endorsed.

Benefit-risk balance

Importance of favourable and unfavourable effects

BMD is a surrogate marker for osteoporosis severity and included in the osteoporosis definition by the WHO criteria. Radiological vertebral fractures are considered as important markers of osteoporosis severity but a common finding in elderly patients and usually asymptomatic (approximately 60%). Fractures that require surgery are the most dangerous aspect of osteoporosis. Hip fracture and the following surgery, in particular, are associated with serious risks, permanent disability, and increased mortality.

ONJ is a lesion occurring in the oral cavity as an area of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found. ONJ is a most serious and disabling condition, causing severe impairment of quality of life.

Hypocalcaemia can be associated with life-threatening conditions, if untreated, such as QT prolongation and cardiac arrhythmia. Patients with renal impairment who are treated with denosumab are at increased risk of hypocalcaemia.

For severe infection, patients may be hospitalised for treatment. Generally, patients recover when their infection is treated.

For severe hypersensitivity reactions, patients may be hospitalised for treatment. Generally, patients recover when their hypersensitivity is treated.

Musculoskeletal pain may lead to severe, generalised or incapacitating pain and discontinuation of treatment.

Benefit-risk balance

Showing efficacy in fracture risk reduction is regarded as the most relevant endpoint in trials of osteoporosis treatments. For denosumab, efficacy in clinical fracture risk reduction was shown in studies in PMO women but not in men with HALT. Changes in BMD correlate to the decrease in fracture risk. BMD measurement is therefore considered a valid surrogate endpoint in bridging studies. If the conditions of the bridging approach are fulfilled, efficacy based on BMD increase can be concluded according the Osteoporosis guideline (CPMP/EWP/552/95 Rev.2).

The Osteoporosis guideline (CPMP/EWP/552/95 Rev.2) defines minimal requirements for granting an indication for the treatment of osteoporosis in men at increased risk of fracture. As far as duration of the study and justification of the dose are concerned, the present application fulfils these requirements. Inclusion criteria chosen for men in the pivotal study should "generate a fracture risk of a similar magnitude compared with the postmenopausal women that were recruited in the studies used to obtain the indication "Treatment of postmenopausal osteoporosis in women at increased risk of fracture"." The guideline does not provide exact guidance on how the bridging from a male osteoporosis study to earlier PMO studies with the same drug should be undertaken.

The mean baseline BMD was higher and 10-year fracture risk was clearly lower in this male osteoporosis study compared to PMO women, questioning the fulfilment of the requirement of the applicable osteoporosis guideline in this respect.

Additional analyses comparing the treatment effect in a risk matched female and male population were required and confirmed that the effect on BMD was consistent.

The guideline further postulates that the magnitude of the BMD changes versus placebo should be similar to that observed in PMO women. BMD information at the 12-month time point was available only for a minority of subjects in the pivotal PMO study and HALT male studies. The comparison of male osteoporosis BMD results are therefore made with the small DXA substudies of the pivotal PMO study. The MAH has justified that the subjects in these DXA substudies were comparable with the total PMO population in terms of baseline BMD, age, previous fractures, and fracture risk.

Finally, the guideline states that the observed BMD changes should be proportional to the decreased incidence of fractures in treated women. This requirement has been fulfilled.

There is no reason to doubt the efficacy of treatment with denosumab in the studied male osteoporosis population in increasing BMD T-score, although no clinical benefit in terms of reduced fracture risk was observed in this small study and factors independent of bone density contribute to susceptibility to fracture in men to a greater extent than in women.

There was a numerical increase of total number of serious adverse events with active treatment in this study and denosumab is associated with previously identified risks such as ONJ and atypical femoral fractures that may occur at increasing frequencies in longer-term treatment duration. These issues need to be followed in the future PSURs.

The bridging approach to the PMO studies has been clarified by the MAH and the approach can generally be agreed.

4. Recommendations

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 changes:

Variation requested		**Type**
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	II

Extension of Indication to add the new therapeutic indication: treatment of osteoporosis in men at increased risk of fracture. As a consequence sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the statement in section 5.1 of the SmPC related to the paediatric investigation plan has been updated.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.