



European Medicines Agency  
*Evaluation of Medicines for Human Use*

London, 18 March 2010  
Doc.Ref.: EMA/21672/2010

**CHMP ASSESSMENT REPORT**

**FOR**

**Prolia**

International Nonproprietary Name: **denosumab**

**Procedure No. EMEA/H/C/001120**

Assessment Report as adopted by the CHMP with  
all information of a commercially confidential nature deleted.

## TABLE OF CONTENTS

<b>1.</b>	<b>BACKGROUND INFORMATION ON THE PROCEDURE.....</b>	<b>3</b>
1.1	Submission of the dossier .....	3
1.2	Steps taken for the assessment of the product.....	3
<b>2</b>	<b>SCIENTIFIC DISCUSSION.....</b>	<b>5</b>
3.1	Introduction.....	5
3.2	Quality aspects.....	6
3.3	Non-clinical aspects .....	11
3.4	Clinical aspects .....	18
3.5	Pharmacovigilance.....	42
3.6	Overall conclusions, risk/benefit assessment and recommendation .....	50

# 1. BACKGROUND INFORMATION ON THE PROCEDURE

## 1.1 Submission of the dossier

The applicant Amgen Europe B.V. submitted on 09 January 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Prolia, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication:

The treatment of osteoporosis in postmenopausal women at increased risk of fractures. Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures.

The treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures

### Information on Paediatric requirements

Pursuant to Article 7, the application included an EMA Decision P/89/2008 for the denosumab on the granting of a product-specific waiver in indication of bone loss associated with sex hormone ablative therapy.

Pursuant to Article 7, the application included an EMA Decision P/47/2008 for the following condition:

- *Treatment of menopausal and other perimenopausal disorders.*

on the granting of a class waiver.

### Scientific Advice

The applicant did not seek scientific advice at the CHMP for these conditions.

### Licensing status:

The product was not licensed in any country at the time of submission of the application. A new application was filed in the following countries: USA, Canada.

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

Rapporteur: **Tomas Salmonson** Co-Rapporteur: **Christian K. Schneider**

## 1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 09 January 2009.
- The procedure started on 28 January 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 April 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 April 2009.

- During the meeting on 29 May 2009 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 29 May 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 August 2009.
- The Integrated Inspection Report of the GCP routine inspection carried out at the following site(s): Argentina on 16-19 June 09, Brazil on 22-24 June 2009 and at CRO site on 26-28 May 09 was issued on 17 September 09.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 October 2009.
- During a meeting of a Biologics Working Party on 12-14 October 2009 experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 22 October 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 09 November 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 01 December 2009.
- During the meeting on 14-17 December 2009 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Prolia on 17 December 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 15 December 2009.
- The applicant provided information of a case of osteonecrosis of the jaw (ONJ) from an open label extension trial in postmenopausal osteoporosis on 11 February 2010, and subsequently a report on this case was provided on 12 February. The Rapporteur circulated Preliminary Assessment Report on 16 February 2010 to all CHMP members. During the CHMP meeting on 17 February 2010 it was decided to continue assessment and discuss final Assessment Report during CHMP meeting in March 2010.
- The applicant provided a data summary from study 20050103 on 17 February 2010 pertaining new safety information for denosumab and further also data from studies 20050136 and 20050244.
- On 24 February 2010 EMA informed European Commission about new safety information and subsequently the preparation of the Commission decision was suspended.
- Preliminary Assessment Report was circulated to all CHMP members on 5 March 2010. This Assessment Report was discussed during PhVWP on 16 March 2010.
- During the meeting of 15 – 18 March 2010 the CHMP concluded that overall balance of benefit-risk remains positive. In the light of the information submitted and the proposed revisions of the Summary of Product Characteristics, Package Leaflet and Risk Management Plan the CHMP adopted a revised opinion for granting a Marketing Authorisation for Prolia on 18 March 2010. The applicant provided the letter of undertaking on follow-up measures to be fulfilled post-authorisation on 17 March 2010.

## 2 SCIENTIFIC DISCUSSION

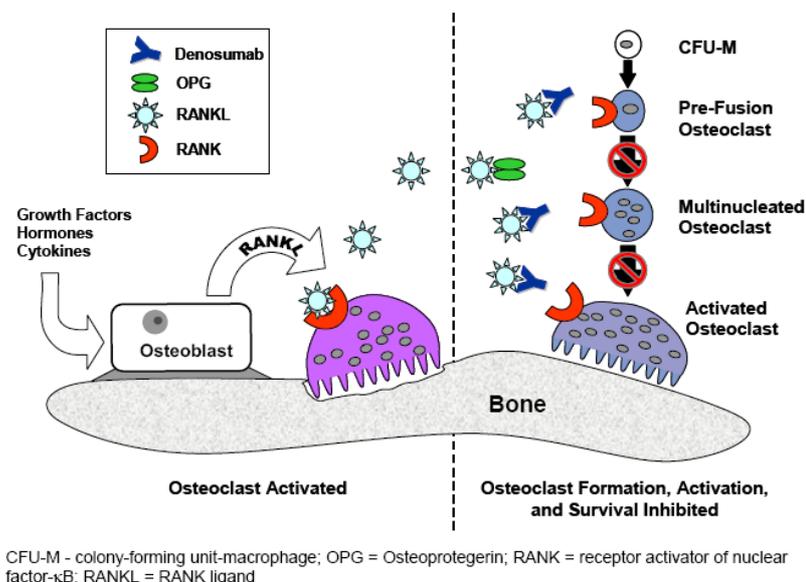
### 2.2 Introduction

Osteoporosis is a systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fractures. Age and menopause are the two main determinants of osteoporosis. There are also other risk factors for osteoporotic fractures such as race, being underweight, hormone ablation therapy, dietary calcium deficiency, sedentary lifestyle, alcohol use, family history, and cigarette smoking. Compression fractures of the vertebrae and traumatic fractures of the wrist and femoral neck are the most common osteoporotic fractures, which cause a substantial clinical and economic burden for society.

The aim of the pharmacological intervention is to decrease the incidence of fractures. Intake of adequate amounts of calcium and vitamin D and continuing exercise are basic preventive measures for persons of all ages. Earlier approved classes of drugs for this indication are antiresorptive agents (bisphosphonates, hormone replacement therapy (HRT) and selective estrogen-receptor modulators); the parathyroid hormone analogue teriparatide that has an anabolic effect on bone tissue, and strontium ranelate that increases bone formation and decreases bone resorption.

Denosumab represents a new therapeutic principle for the treatment of osteoporosis. Denosumab is a fully human monoclonal antibody of IgG<sub>2</sub> subtype, inhibiting RANK ligand (RANKL), which is an essential factor for the formation, activation and survival of osteoclasts (see Figure 1). Inhibition of RANKL is a possible intervention point to interfere with conditions with increased bone resorption. RANKL production is increased when estrogen is decreased, as it is after menopause and in conditions of hormone ablation, leading to an increased bone resorption.

Mechanism of action for denosumab.



This application concerns the centralised procedure (Regulation (EC) No 726/2004, article 3(1) indent 1 of regulation (EC) No.726/2004) as biotech medicinal product.

It is submitted in accordance with Article 8(3) in Directive 2001/83/EC for a new active substance.

Conditional approval, an approval under exceptional circumstances or an accelerated review were not requested.

The claimed indication was:

“The treatment of osteoporosis in postmenopausal women at increased risk of fractures. Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures.

The treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.”

The approved indications are:

“Treatment of osteoporosis in postmenopausal women at increased risk of fractures. 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. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.”

## **2.3 Quality aspects**

### **Introduction**

Denosumab is a full-length human monoclonal produced in Chinese hamster ovary (CHO) cells. Denosumab targets the RANK ligand which stimulates osteoclast differentiation.

The Prolia drug product is supplied as a sterile, preservative-free solution, intended for delivery by subcutaneous injection.

There are two presentations, a vial and a pre-filled syringe strength, both at a strength of 60 mg. The same acetate-sorbitol formulation is used, except for the addition of Polysorbate 20 to the pre-filled syringes.

### **Active Substance**

#### *Description of the drug substance*

Denosumab is a full-length human monoclonal antibody of the IgG2 subclass, consisting of 2 heavy chains, and 2 light chains of the kappa subclass. Denosumab contains 36 total cysteine residues, which are involved in both intrachain and interchain disulfide bonds.

Each heavy chain contains an N-linked glycan at the consensus glycosylation site at asparagine 298. Each light chain contains 215 amino acids, with 2 intramolecular disulfides. Each heavy chain contains 448 amino acids, with 4 intramolecular disulfides.

#### *Manufacture*

The manufacture of the drug substance takes place mainly at two sites: Amgen Inc. (ACO) located in Boulder, Colorado and Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma or BIP in Biberach an der Riss, Germany).

Denosumab is manufactured by a batch-wise cell culture process in the production bioreactor followed by a harvest process using conventional unit operations (centrifugation and membrane filtration) and a purification process employing several chromatography steps (protein A, cation exchange and hydrophobic interaction), a viral inactivation step and a viral removal step. Finally, formulation is made by means of ultrafiltration/ diafiltration.

#### *Cell line development*

Denosumab is a full-length human monoclonal antibody and produced in Chinese hamster ovary (CHO) cells.

#### *Development genetics*

Lymph node cells from immunized animals were fused to create hybridomas. The hybridoma cell line was identified and subcloned. The cDNA encoding the light chain and the variable portion of the heavy chain was generated and used to construct, intermediate vectors, which were transfected into CHO cells. After subsequent rounds of subcloning, a clone was chosen as the manufacturing cell line and a Master Cell bank (MCB) was established.

The generation of the cell substrate has been sufficiently described.

#### *Cell bank system*

A tiered cell bank system of Master Cell Bank (MCB) and Working Cell Bank (WCB) was developed and maintained in accordance to GMP and ICH Q5D guidelines.

The Working Cell Bank (WCB) was prepared from a single vial of MCB according to an established manufacturing procedure and is used for manufacture in both manufacturing sites.

Procedures followed in the preparation of MCB and WCB have been appropriately described. Validation was accomplished through an evaluation of performance parameters for the operations in the cell culture and harvest process. The cell banks are well tested with regards to safety and identity.

#### *Cell culture, harvest and recovery*

The CHO cell culture expansion process includes vial thaw, primary, secondary, and maintenance shake flasks, and consecutive cell expansion steps. The cell culture process in the production bioreactor proceeds as a batch culture, one cell-culture batch constitutes the basis for one drug substance batch. There are no components of animal origin in the cell culture medium.

Cell culture conditions and in-process controls including viable cell density, culture viability and microscopic examination are tested during the culture expansion and at the end of the production. Each harvest is sampled for bioburden, mycoplasma testing, adventitious virus and titre of denosumab.

#### *Purification process*

The purification process of the cell harvest consists of the following chromatographic, and viral inactivation and filtration steps: Protein A chromatography, viral inactivation, Cation exchange chromatography, Viral filtration, Hydrophobic interaction chromatography and Ultrafiltration/Diafiltration.

There are no formal control steps for intermediates in the drug substance manufacturing process, since the current validated product pool hold times are within the acceptable hold times established through process characterization. Clarifications on the different designs of hold time studies between the two sites (ACO versus BI Pharma) have been provided and the description of the manufacturing process is thereby acceptable.

There are minor differences (equipment and medium component related) between the ACO and BIP versions of the processes. The applicant has committed to amend the ACO process in line with the BIP process specifications as regards certain differences, as further addressed in relation to the Comparability assessment.

To evaluate the robustness of the process and to develop a comprehensive understanding of the process to support process validation and in-process controls, the applicant has developed a design space, classified as “Characterization Range”, “Acceptable Range” and “Operational Range”, along with a control strategy, including a risk analysis of the process (Failure Modes and Effects Analysis; FMEA), by large in line with ICH Topic Q8, step 4 Annex to Pharmaceutical Development (EMEA/CHMP/ICH/518819/2007). Amgen is not requesting registration based on a design space concept, but the “design space” was identified for the purpose of process characterisation. The process

conditions will remain within the “Operational range”, and any departure from this range will trigger a variation.

Reprocessing is allowed at some unit operations during the drug substance manufacturing process. Reprocessing is not allowed in response to a failing adventitious virus or bioburden result.

#### *Manufacturing process development and validation.*

The drug substance manufactured to support the initial phase 1 and phase 2 clinical trials was produced at the clinical manufacturing site. A process suitable for commercial production of denosumab and used in all pivotal clinical trials (Phase 3) was subsequently developed.

Extensive comparability exercises comparing the different materials showed minor quantitative differences in the glycosylation, size and charge profiles with no impact on the *in-vitro* potency of the drug substance and the comparative non-clinical PK/PD study in cynomolgus monkeys.

During scale-up of the process and transfer, minor changes to the process related to up-scaling and facility/equipment related have been made. As regards the process as performed at the two authorised manufacturing sites, comparability was demonstrated by comparison of IPC data, batch data on drug substance, additional characterisation data and data of forced degradation.

According to most of the analytical results, the materials derived from the two sites were comparable. However, a difference in charge profile was found in the extended biochemical characterisation in the comparability analysis. The root cause was found to relate to a component of the culture medium. The variant forms are clinically qualified, because the clinical experience of the C-terminal variants, spans the range of the observed variability. Nevertheless, the applicant has committed to further harmonize the process, as performed at the two sites.

The manufacturing process has been validated using data from consecutive commercial manufacturing scale lots at the two authorised manufacturing sites. The process validation studies include validation of the cell culture operations, purification operations, and drug substance fill.

The results of the process validations performed at the two authorised manufacturing sites, provide evidence that the cell culture, recovery and harvest, and purification processes consistently produce Prolia drug substance that meets pre defined specifications. Some minor issues remaining as concerns process validation are agreed to be solved by follow-up measures post-approval.

#### *Characterisation*

The biochemical characterisation, conducted using commercial scale material, has been performed using state-of-the art methods.

The primary, secondary and tertiary structures of denosumab were analysed by various techniques and conformed to that expected from the IgG2 antibody construct.

The primary peptide structure of denosumab was characterized through the application of orthogonal methods including Edman N-terminal sequence analysis, peptide mapping studies and mass spectrometry.

The secondary and tertiary structures were analysed by far and near UV circular dichroism spectroscopy respectively.

Characterisation of glycosylation indicated that denosumab is N-glycosylated at a single site in each heavy chain Asn299. The N-linked structures consist of biantennal, core-fucosylated species with galactose and sialic acid heterogeneity.

The structures of minor product-related variants were also determined to an acceptable extent.

Data demonstrate that process-related impurities are adequately controlled and cleared to acceptable levels by the commercial manufacturing process. The applicant has demonstrated here (and also by batch analysis data) that process related impurities can constantly be reduced below the detection levels.

Biological characterisation and immunological characterisation, including antigen specificity, has been made using adequate methods. The mechanism of action of denosumab is to bind RANKL outside the cell, and prevent it from associating with the RANK receptor.

Different potency assays have been used in the biological characterization of denosumab. The potency assay has been shown to be stability indicating.

In conclusion, the characterisation is considered acceptable and in line with the guideline on monoclonal antibodies, EMEA/CHMP/BWP/157653/2007.

#### *Control of drug substance*

The methods used for routine control are deduced from the characterisation studies, and the specification limits are set in line with batch data, including batches used in clinical trials.

The drug substance specifications include tests for appearance, identity, purity, adventitious agents, potency, and quantity.

The applicant justified not to include specifications for some impurities based on 1) the process characterisation and validation data, showing consistent reduction of these impurities to levels below or comparable with the drug substance material used in clinical trials, and 2) the action or alert in-process controls in place for these impurities.

#### *Stability*

The design of the stability program, including the testing intervals and storage temperature conditions are in accordance with current ICH guidelines. The tests chosen are a subset of tests from the release specifications selected for stability indicating properties.

### **Drug Product**

#### *Composition, pharmaceutical development*

The Prolia drug product is supplied as a sterile, preservative-free solution, intended for delivery by subcutaneous injection. There are two presentations, a vial and a pre-filled syringe strength, both at a strength of 60 mg. The same acetate-sorbitol formulation is used, except for the addition of polysorbate 20 to the pre-filled syringes.

The qualitative composition of the drug product is: denosumab, sorbitol, acetate, polysorbate 20 (pre-filled syringe only), sodium hydroxide and water for injection.

In order to develop the proposed commercial formulations, screening studies were conducted to evaluate drug product attributes at accelerated temperatures as a function of pH, protein concentration, buffer type, buffer concentration, excipient type (polar or non polar) and excipient concentration.

The applicant developed a polysorbate-containing PFS formulation that has demonstrated comparable long-term stability data at the recommended storage temperature of 2°C to 8°C and the absence of particle formation.

In the vial formulation translucent particles have been found in aged containers in the inventory of the clinical material. Isolated denosumab-derived particles and microbubbles were identified. Since the visible particles have been observed in a majority of the denosumab vial lots inspected, there is a high probability that denosumab-treated subjects in clinical studies have been exposed to visible particles. In over 8,000 subjects treated with denosumab, no neutralizing antibodies to denosumab have been

detected and less than 1% of the treated subjects developed non-neutralizing binding antibodies which were mostly transient.

During the procedure, additional information regarding particle formation in vials and possible formulation optimization in vials were requested. Proteinaceous particles are unwanted in a drug product solution and should be eliminated as far as possible.

As a consequence, the applicant implemented more defined criteria in the inspection and testing procedure for evaluation of particle content. By the responses provided, and considering that the route of administration in this case is subcutaneous, the issue on the control of particles is considered satisfactorily solved. In addition, the applicant has also committed to further characterize the effect of formulation parameters, on the propensity for low-level particle formation in the 60 mg/mL vial formulation and to undertake further studies on alternative formulations.

The pre-filled syringe is presented either with or without an automatic needle guard (ANG). Most of the clinical trials were performed using the vial presentation. The applicant provided in-use studies on the handling of the pre-filled syringe with the ANG device.

#### *Manufacture*

The manufacturing process is a standard aseptic process. Formulation buffer is prepared by pooling the drug substance, adding polysorbate 20 solution (only for PFS) and diluting with formulation buffer to a target drug concentration prior to transferring into a surge vessel which is attached to the syringe filler or the vial filler.

Drug product lots that do not meet the established release specification cannot be reprocessed.

Comparability studies to address a change of manufacturing site and the difference in composition between the vial and the pre-filled syringe were performed. Analytical comparability between the two presentations, lot release, additional product characterization, forced degradation, and accelerated stability studies were performed. In the extended characterisation, the two presentations have been thoroughly compared side-by side using a wide range of biochemical and biophysical methods along with a comparison of the potency. The comparability program is considered sufficient, and, based on the results, comparability is considered acceptably demonstrated from a pharmaceutical point of view. Furthermore, a bioequivalence study and an immunogenicity study have been made in support of comparability claim.

The comparability of the materials filled at the two sites is also considered satisfactorily shown. The manufacturing process is acceptably validated.

#### *Control of drug product*

The specifications are primarily based on the batch and stability data derived from the batches derived from the drug substance process. This is considered acceptable for the time being, taking into account that the applicant has committed to reconsider and propose to narrow limits, as appropriate, when more batch data has been gathered.

#### *Stability*

Stability studies were performed per the ICH Guidelines Stability Testing of Biotechnological/Biological Products (Q5C) and Stability Testing of New Drug Substances and Products (Q1A). Stability studies at elevated temperatures have also been conducted in order to assess the effect of these conditions and to compare relative degradation rates. Furthermore, stability to light exposure has been studied. The stability protocol includes stability indicating specifications, as based on the biochemical characterisation.

Stability data for the two presentations have been combined. This is considered acceptable, based on the comparability data presented including the similar stability profiles.

Based on the presented data the claimed 30 months shelf life when stored at 2-8°C is acceptable.

### *Safety as regards adventitious agents*

The applicant has provided a complete assessment of the TSE risk for raw and starting materials of animal origin, including associated Certificates of Suitability. The approach taken by the applicant is therefore considered acceptable. The mycoplasma testing is also deemed adequate.

The applicant has demonstrated that the scale-down models used in the execution of the virus validation studies are applicable to commercial purification process operations. All chromatography steps were evaluated in the viral spiking studies. The virus validation studies are deemed well performed with adequate design of interference and cytotoxicity studies. The *in vitro* adventitious agent testing is found adequate.

The overall viral clearance capacity was found to be high for the enveloped viruses and medium high for non-enveloped viruses.

### **Discussion on chemical, pharmaceutical and biological aspects**

Overall, information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics.

At the time of the opinion, there were some minor unresolved quality issues having no impact on the risk-benefit balance of the product. The applicant gave a Letter of Undertaking and committed to resolve them after the opinion within an agreed timeframe.

## **2.4 Non-clinical aspects**

### **Introduction**

Denosumab is the first proposed antiresorptive therapy for osteoporosis targeting the ligand for RANK. RANKL is together with its receptor RANK and osteoprotegerin is the key mediator in the pathway involved in regulating bone resorption. Denosumab's binding to RANKL prevents the RANKL-RANK interaction, inhibiting osteoclast formation, function and survival. Denosumab is a fully human IgG2 mAb and does not recognize rodent RANKL. Several studies have been conducted with a transgenic huRANKL knock-in mouse model expressing chimeric RANKL that can be recognized and neutralized by denosumab. Since denosumab recognizes and neutralizes RANKL in non human primates, the cynomolgus monkey was identified as a relevant species and the main studies have been conducted in ovariectomized animals.

### **Pharmacology**

- Primary pharmacodynamics

#### *In vitro primary pharmacodynamic studies*

*In vitro* studies demonstrated that denosumab binds with high affinity to huRANKL (K<sub>d</sub> 3x10<sup>-12</sup>M which is comparable to huOPG-Fc) but not to muRANKL. These data support the use of huOPG-Fc as surrogate molecule in mechanistic studies. Denosumab did not bind to the other TNF family members, TNF-α, TNF-β, TRAIL and CD40L, indicating specificity to target. Osteoclast formation was suppressed by denosumab in cell culture systems with huRANKL (IC<sub>50</sub> of 10<sup>-14</sup>M), while no effects were detected on osteoblast proliferation.

#### *In vivo primary pharmacodynamic studies*

*The huRANKL knock-in mice* appeared to have a moderately high bone mass phenotype compared to wild type mice. This bone phenotype is not anticipated to have any implications for the overall evaluation of denosumab's mechanism of action. Denosumab caused reduction in bone resorption and increased volumetric bone mineral density in the knock-in mice.

A fracture healing study in male huRANKL KI mice (R2006458), suggested that treatment with denosumab delayed the removal of cartilage and remodelling of the fracture callus compared to control. Despite this finding, denosumab did not seem to negatively affect the overall biomechanical strength. An increase in torsional stiffness compared to control and an increase in max torque compared to contralateral bones were observed 42 days after fracture. These findings are mentioned in section 5.3 in the SmPC.

The disease model in ovariectomized cynomolgus monkeys is considered a relevant model for the indication of postmenopausal osteoporosis.

### Summary of primary pharmacodynamic studies performed with denosumab in cynomolgus monkeys.

Type of Study	Test System (method, cell line, species/strain)	Noteworthy Findings	Report No
<b>Effects of denosumab on bone parameters in adult ovariectomized cynomolgus monkeys (16 month study)</b>			
Effects on hormone levels (estradiol, PTH, 1,25-dihydroxy-vitamin and 25-hydroxyvitamin D)	Female OVX cynomolgus monkeys n=20/group, SC injections, 0, 25 and 50 mg/kg + sham operated vehicle controls, once/month for 16 months. Injections started one month after OVX or sham surgery. Samples taken post dose 3, 6, 9, 12 and 16.	1. There were no effects of treatment with denosumab on <u>estradiol</u> levels. 2. Significant increases in <u>PTH</u> were observed for both denosumab-treated groups following dose 3, 6 and 16 when compared to OVX and/or Sham vehicle controls. 3. For <u>1,25-dihydroxyvitamin D</u> levels a linear dose effect was noted for adjusted values post dose 3 and 6 with values for both denosumab-treated groups significantly increased compared to OVX and sham vehicle controls. 4. There were no effects of treatment with denosumab on <u>25-hydroxyvitamin D</u> levels	103981
Effects on OC, sALP, CTx, NTx and TRACP-5b	As above	Treatment with denosumab at 25 or 50 mg/kg/dose resulted in significant suppression of all biochemical markers of bone turnover compared to OVX and sham vehicle controls on each post dose occasion.	103981
Effects on bone densitometry measured by DXA and pQCT	As above. Scans taken post dose 3, 6, 12 and 16.	<u>DXA</u> : Both doses of denosumab completely prevented the OVX-induced effects at all sites evaluated compared to OVX and sham vehicle controls, positive gains in BMD were also observed.	103981
Effects on histomorphometry (cancellous bone and cortical bone)	As above	Both doses of denosumab fully prevented OVX-related changes while reducing most values significantly below those of sham controls. Cortical bone turnover was also increased in OVX-vehicle. Both doses of denosumab fully prevented the OVX-related changes while reducing labelled perimeter and BFR significantly below sham control levels.	103981
Effects on biomechanical testing	As above	Denosumab significantly increased bone strength parameters compared to OVX and Sham controls. Disproportionate increases in bone strength relative to bone mass were observed at the lumbar spine following treatment with denosumab at 25 and 50 mg/kg/dose and at the femoral neck at the 50 mg/kg/dose group.	103981

**Effects on bone parameters in adult ovariectomized cynomolgus monkeys, transition from 6-months treatment with alendronate, a nitrogen-containing biphosphonate, to denosumab (12 month study)**

Summary of study design of report no 106564

Group Number /Identification	Phase I Dose 1 to 6*	Phase II Dose 7 to 12*	Number of Females
1/Vehicle <sup>#</sup>	Vehicle (SC) + PBS <sup>&amp;</sup> (IV)	Vehicle (SC) + PBS (IV)	10
2/Vehicle + denosumab <sup>#</sup>	Vehicle (SC) + PBS (IV)	Denosumab (SC) + PBS (IV)	10
3/ALN <sup>&amp;</sup>	ALN (IV)	ALN (IV)	10
4/ALN + denosumab	ALN (IV)	Denosumab (SC) + PBS (IV)	11
5/denosumab	Denosumab (SC) + PBS (IV)	Denosumab (SC) + PBS (IV)	11

\* Relative to denosumab dosing occasions.

<sup>#</sup> Denosumab (25 mg/kg) or vehicle used as denosumab placebo were injected SC once every 28 days.

<sup>&</sup> Alendronate (ALN) at 50 µg/kg or Dulbecco's PBS saline were injected IV once every 14 days.

Effects on serum calcium and phosphorous levels	Female OVX cynomolgus monkeys, study design described above.	Denosumab caused a significant but transient hypocalcemia with corresponding change in phosphorus compared to vehicle controls for up to 14 days. The maximum relative reduction in serum calcium compared to vehicle control was 15.2 %.	106564
Effects on PTH	Female OVX cynomolgus monkeys, study design described above.	Denosumab significantly increased PTH during 6 months of treatment. PTH levels declined to control or baseline levels during the next 6 months. Prior treatment with ALN caused transient increase of PTH up to 72 hours post dose.	106564
Effects on TRACP-5b, sALP, OC and CTx	Female OVX cynomolgus monkeys, study design described above.	TRACP-5b, sALP, OC and CTx were significantly reduced by both denosumab and ALN throughout the 12-month treatment period. All markers were similarly suppressed during the latter 6 months of treatment with denosumab. CTx and OC were significantly decreased in the denosumab-denosumab group compared to the ALN-ALN group.	106564
Effects on bone densitometry using DXA and pQCT	Female OVX cynomolgus monkeys, study design described above.	As a result of treatment with denosumab and ALN significant gains in bone mass were observed most notably at trabecular bone sites. Pretreatment with ALN did not modify the response to denosumab. Denosumab and ALN caused significant gains in bone mass observed in both trabecular and cortical bone compartments.	106564
Effects on biomechanical testing	Female OVX cynomolgus monkeys, study design described above. Bone strength measured at the 12 month time point.	Denosumab significantly increased bone strength parameters at the lumbar spine compared to vehicle treated controls. There were no differences between the ALN-denosumab group and denosumab-denosumab group. There were no statistically significant differences between groups at the femoral neck or femur.	106564
Effects on histomorpho-metry. Biopsies of right 7 <sup>th</sup> rib and right ilium were taken post dose 6. After complete study also right proximal and central tibia, second lumbar vertebra (L2), left ilium and left 7 <sup>th</sup> rib were analysed	Female OVX cynomolgus monkeys, study design described above.	Endocortical and intracortical bone formation rates at the rib and tibial diaphysis were significantly decreased by 12 months of denosumab or ALN treatment, compared to vehicle controls which was associated with significantly lower levels of cortical porosity in month 6 and 12 rib biopsies. In cancellous bone, both denosumab and ALN significantly lowered mineralizing surface, mineral apposition rate, bone formation rate, and activation frequency relative to vehicle controls. Denosumab treatment significantly reduced osteoclast surfaces at all cancellous sites at month 12.	106564

No studies were conducted in a disease model for hormone ablation therapy in males. According to the guideline on the evaluation of medicinal products in the treatment of primary osteoporosis, CPMP/EWP/552/95 Rev.2, gender-specific toxicity and efficacy should be extensively investigated in a relevant animal model. Bone efficacy endpoints were addressed in a toxicology study in male and

female cynomolgus monkeys (102090) but few animals made statistics difficult. However, clinical studies in males have addressed the incidence of new vertebral fractures and these data supersede the lack of a non-clinical disease model in males.

A trend towards gender-specificity of the pharmacological effect was indicated in cynomolgus monkeys. Effects on biochemical markers were dose-dependent and shown in both genders, while significant and consistent increases in bone mineral content and density, cortical area and thickness as well as bone strength were mainly described in males. The pharmacodynamic effects on bone mass and strength is influenced by skeletal growth rate, which can differ between genders before skeletal maturity. The Applicant further explains these differences to be due to the inclusion of a female that developed antidenosumab antibodies, to differences in baseline bone mass and to a greater rate of bone growth in adolescent males. An inhibitory influence of estradiol on RANKL expression and on downstream effects has been published and in such circumstances denosumab would lack a target which could partially account for the differences. Furthermore, the results in ovariectomized female Cynomolgus monkeys differ from the minimal effects of denosumab on bone mineralization, density and strength observed in gonad-intact females. In this context a potential effect of estrogen supplementation in postmenopausal women on the efficacy of denosumab could be an issue to consider.

- Secondary pharmacodynamics

*A study on bone growth and tooth eruption in neonatal pre-weaning rats* treated with OPG-Fc (1 and 10 mg/kg/week) for 6 weeks caused a dose-dependent reduction in long bone growth, suggested to be related to osteoclast inhibition. High-dose OPG-Fc significantly inhibited incisor growth and prevented the eruption of all 3<sup>rd</sup> molars and 84% of 2<sup>nd</sup> molars.

*Studies on immunomodulatory effects* have been incorporated in some pharmacology and toxicology studies in cynomolgus monkeys. These studies did not reveal any major differences compared to controls. The applicant also refers to published literature and abstracts from Amgen on the role of RANKL on immune functions using OPG-TG mice and rats and OPG-Fc treated WT mice. The relevance of using these models instead of denosumab in studies on immunomodulatory effects is uncertain and considering the mechanism of action of denosumab, potential effects on immunomodulation and immunosuppression cannot be ruled out.

- Safety pharmacology programme

The safety pharmacology package included two studies (see table below); one of these was incorporated in a toxicology study in accordance with ICH S6 and ICH S7A. According to the guideline, clinical observation of animals is generally not adequate to assess respiratory function. However, since no indication of denosumab to affect respiratory function were noted, the current study is considered sufficient.

Summary of safety pharmacology studies performed with denosumab.

Type of Study	Test System (method, cell line, species/strain)	Noteworthy Findings	Report No
Effects of denosumab on blood pressure, heart rate, ECG activity, respiration rate and cageside observations	Male cynomolgus monkey (n=3/group, single SC injection, 0, 0.3, 3, and 30 mg/kg	One animal (3 mg/kg) had a run of four ventricular premature complexes (VPCs) approximately 45 minutes following administration of the test article. This episode was not considered to be related to treatment with denosumab. No treatment related changes in respiration rate were observed. No treatment related cageside observations were observed	101606
Effects of denosumab on blood pressure and ECG	Male and female cynomolgus monkey (n=3/group, 3 months recovery n=2/group,	There was no ECG evidence of cardiotoxicity after 53 weeks of treatment with denosumab. Isolated cases of slight bradycardia, fused P-T wave or slight tachycardia were observed in	102090 (tox study)

SC injection, 0, 1, 10 and 50 mg/kg once/month for 6 or 12 months)	single animals. These findings were not considered to be related to the administration of the test material. Two male animals died in the high dose group. According to the Applicant these deaths were not related to treatment.
--------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

- Pharmacodynamic drug interactions

No specific preclinical studies have been conducted addressing drug interactions. In the switch study performed in OVX cynomolgus monkeys with 6 months pretreatment of alendronate before 6 months treatment of denosumab (report 106564) no adverse effects on the pharmacodynamic activity of either alendronate or denosumab were noted. The absence of pharmacodynamic drug interaction studies is considered acceptable.

### Pharmacokinetics

Levels of free denosumab in serum from mouse, rat and monkey were measured by an ELISA method. Denosumab does not bind to RANKL in mouse and rat and this could be related to linear pharmacokinetics evident after intravenous doses of 0.1 to 10 mg/kg. Subcutaneous doses were associated with a good bioavailability in all species. Further, clearance was low in rodents and volume of distribution similar to plasma volume. In contrast, clearance was 6- to 15- fold higher in knock-in mice that express a chimeric form of RANKL and in knock-out mice that lack expression of the Fc neonatal receptor. The terminal half-lives were 19 days in mouse and 11 days in rat.

In the cynomolgus monkey pharmacokinetics were linear over both intravenous and subcutaneous dose range of 1 to 3 mg/kg, but were non-linear at doses below 1 mg/kg. Values for volume of distribution indicated lack of extravascular distribution. The non-linearity in monkeys may reflect that binding of denosumab to RANKL leads to accelerated, but saturable, elimination and that elimination also involves the neonatal receptor Fc (FcRn) and the reticuloendothelial system. A 50% effective concentration of 464 ng/mL and an Emax of 77.6% were calculated using pharmacokinetic/pharmacodynamic modelling and bone resorption marker N-telopeptide of type I collagen in serum data.

Denosumab labelled with <sup>125</sup>I was widely distributed in monkey after subcutaneous doses with most of the circulating radioactivity being intact antibody as indicated by acid-precipitation. No particular sequestration to bone was reported. Levels of radioactivity declined to non-quantifiable levels by 672 hours at a dose of 0.1 mg/kg, but levels were measurable at the injection site, eye (cornea), large intestine (males) contents, lymph nodes, spleen, stomach contents (males) and thyroid. The tissue distribution or radioactivity at later time points was consistent with distribution of free iodine radiolabel (example thyroid). No obvious or remarkable differences in pattern of distribution between genders were evident, but the highest dose used was 1 mg/kg and animals developed antibodies to denosumab. There were indications that denosumab has limited potential to cross the blood/brain barrier, the blood/testis barrier as well as the placental barrier, although this data is confounded by the presence of radiolabel in blood vessels and an unknown contribution of free radiolabel. In this context the distribution of RANKL could be of interest and RANKL protein and mRNA expression has been reported in bone, brain, heart, kidney, liver, lung, intestine, skeletal muscle, mammary tissue, placenta, spleen, thymus and testis. However, data on the specific distribution of various forms of RANKL does not appear to be available.

Denosumab is a monoclonal antibody and current knowledge concerning the clearance of antibodies indicates that metabolism may be mediated through internalization followed by intracellular degradation to small peptides and amino acids. Antibodies may be protected from lysosomal degradation through binding to the Fc region of the neonatal receptor FcRn and data from studies in FcRn knock-out mice were consistent with that FcRn protects denosumab from elimination and so may influence tissue distribution.

Radioactivity was primarily excreted in urine with only 1 to 3% recovered in faeces.

Plasma levels and systemic exposure to denosumab manufactured by two methods differed by 23 to 16%. Overall the product used in pivotal toxicity studies is considered representative for the clinical formulation of denosumab.

After repeated subcutaneous doses of 0.1 to 50 mg/kg in monkey approximately linear pharmacokinetics were reported. Anti denosumab antibodies were recorded in the majority of non-clinical studies, however exposures achieved in toxicology studies still corresponded to high multiples in comparison with expected clinical levels.

## **Toxicology**

- Single dose toxicity

A specific single dose toxicity study was not conducted and this is also consistent with ICH guidance. A cardiovascular safety pharmacology study evaluated single subcutaneous doses of up to 30 mg/kg in the cynomolgus monkey. No evidence of toxicity was reported.

- Repeat dose toxicity (with toxicokinetics)

In the 1 month repeat dose toxicity study (101447) in young adult Cynomolgus monkeys, as the only potentially drug-related change of statistically significant elevated thyroid weights were noted in females of the high dose group that were not confirmed by histopathological findings. Despite the high immunogenicity observed in all dose groups, a dose dependent change in some PD parameters was observed. In 6/12-Month Repeated-dose Study in Monkeys (102090) denosumab was administered at doses of 0, 1, 10, and 50 mg/kg. Overall, no effects on organ weights or macroscopic or microscopic evidence of target organ toxicity were noted. Denosumab also had no untoward effects on sperm motility or morphology. The previously reported effects on thyroid weight (study 101447) were not confirmed. Consistent with the 1-month study, denosumab was highly immunogenic in monkeys.

- Genotoxicity

No studies were conducted. Denosumab is a recombinant protein and contains no inorganic or synthetic organic linkages or other non-protein portions. Regulatory guidance is consistent with studies on genotoxicity not being necessary for this type of product.

- Carcinogenicity

No carcinogenicity studies were conducted in accordance with available regulatory guidance. Ovariectomized monkey treated for up to 16 months with denosumab showed no evidence of pre neoplastic lesions. However, potential to interfere with the immune system cannot be discounted. The multiple signalling pathways involved in OPG effects, and by analogy possibly also relevant in the case of denosumab, indicate a potential for dysregulation of functions that could be critical in e.g. cancer pathogenesis.

- Reproduction Toxicity

The potential for reproduction toxicity of denosumab was evaluated in monkey. Female fertility and early embryonic development did not appear to be influenced by weekly doses of denosumab up to 12.5 mg/kg. Evaluation of sperm motility and flow cytometric data, and testicular tissue in the 12 month monkey toxicity study did not indicate adverse effects of denosumab on male fertility. Denosumab and anti-denosumab antibodies crossed the placenta as indicated by analysis of fetal serum samples at caesarean section. In an embryotoxicity study similar incidences of external, visceral and skeletal finding in both control and treated groups were reported. While constitutive deficiency of RANK/RANKL may not be directly comparable to situations of exogenously induced inhibition, data that RANK/RANKL are essential for the development of the lactating mammary gland during pregnancy could be of interest for assessment of use of denosumab during pregnancy and lactation. The proposed text in the relevant sections of the SmPC has overall sufficiently considered these possibilities.

- Toxicokinetic data

Toxicokinetic data indicated no significant differences in exposure in male and female monkeys. Toxicokinetic data is presented in relation to relevant studies.

- Local tolerance

No specific studies were conducted. Evaluation in repeated dose toxicity studies did not indicate any relevant irritation at the site of application. Incidences of haemorrhages at the injection site were noted in the denosumab treated monkey, but not in control monkeys in the 12 months study. Clinical data are expected to be sufficient to assess any possible local reactions.

- Other toxicity studies

No specific studies were conducted.

### **Ecotoxicity/environmental risk assessment**

Denosumab is a sequence of amino acids and a protein and in accordance with the CHMP guideline on the environmental risk assessment (EMA/CHMP/SWP/4447/00) is exempt from testing because of the chemical structure.

### **Discussion on the non-clinical aspects**

Overall the preclinical studies characterized the pharmacological, pharmacodynamic and toxicological properties of denosumab and demonstrated its activity in vitro and in vivo. The following discussion highlights issues identified during evaluation process.

The binding affinity of denosumab for Cynomolgus monkey RANKL was not tested. This absence is acceptably justified by the fact that the RANKL domain to which denosumab binds is entirely conserved between cynomolgus monkeys and humans. The choice of Cynomolgus monkey as relevant animal model is justified considering the highly selective binding and neutralizing effect of denosumab on human and non-human primate RANKL. Supportive data were derived from studies in rodents. The applicant has satisfactorily discussed the choice of recombinant OPG and knock-in mice versus a surrogate mAb in the rodent osteoporosis model. No disease model for hormone ablation therapy in males has been used. However, clinical studies in males are available which supersede the lack of non-clinical data. Gender difference observed in gonad-intact animals with female animals not responding in a comparable way as males to the treatment was adequately discussed by applicant. However, provided information should not be translated into the adult population. In general, high immunogenicity was observed in all studies and the results need to be interpreted with caution. The pharmacological effect of transitioning from alendronate to denosumab was investigated in the appropriate animal model of ovariectomized Cynomolgus monkeys. The potential risk of denosumab to interfere with fracture healing was sufficiently assessed in huRANKL knock-in mice in comparison to alendronate.

For PK evaluation serum denosumab concentration was measured by ELISA assay which detects only free denosumab in serum. Therefore, the PK profile has to be interpreted with caution. A difference was found in the single dose PK (linear) of rodents, where denosumab does not bind RANKL, and the PK (non linear) of Cynomolgus monkeys. By the means of supportive studies in huRANKL knock-in mice and in FcRn knock-out mice this was attributed to the role of RANKL binding and FcRn in denosumab disposition. In Cynomolgus monkey a non-linear PK was demonstrated following IV and SC administration. SC bioavailability increased from 28% up to 100% with increasing dose, but dropped at the highest dose steps tested from 100% (at 1 mg/kg) to 59% (at 3 mg/kg). This drop was

explained by the applicant as an artefact caused by the criteria set to define the best fit compartmental model. In general, the high percentage of animals developing anti-drug-antibodies impacted the PK analysis. Especially at the high dose range, the PK data need to be interpreted with caution. The formation of these antibodies appeared to markedly increase the rate of elimination of denosumab. Thus, the extent of the disproportional dose-exposure relationship is likely underestimated, given the prevalence of antibody formation at the higher doses. However, the apparent increased rate of elimination at lower denosumab concentrations was also observed at the lowest 2 doses (for which no animals developed antibodies) and in antibody-negative animals at the higher doses. Thus, the conclusion of non-linear PK with dose or concentration in monkey is not confounded by anti-drug antibody formation.

Studies on immunomodulatory effects were incorporated in some pharmacology and toxicology studies in cynomolgus monkeys. These studies did not reveal any major differences compared to controls. However, considering the mechanism of action of denosumab, potential effects on immunomodulation cannot be ruled out. No specific studies on potential for immunotoxicity have been conducted and it is referred to literature data that RANKL has no significant role in the functional responses of an adult animal with an intact immune system while RANKL has a role in the developing immune system

OPG and RANKL are discussed to play a role in arteriosclerotic plaque formation suggesting a potentially increased risk of denosumab treatment in postmenopausal women. The preclinical study results in OVX Cynomolgus monkeys have not addressed this issue. However it is acknowledged, that important results addressing this issue are obtained from PMO clinical study. The absence of genotoxicity and carcinogenicity studies was sufficiently justified. However, the multiple signalling pathways involved in OPG effects and recent literature indicating a role of OPG and RANKL in angiogenesis and endothelial cell function suggest a potential for dysregulation of functions critical in e.g. tumour development.

Considering the potential for reproduction toxicity the collective findings indicate that denosumab is neither a maternal nor an overt developmental hazard. However, even though no safety signals were seen in the animal studies with denosumab, it has been reported in the literature that RANK/RANKL knock-out mice had an absence of lactation due to inhibition of mammary gland maturation. In conclusion non-clinical data supported the clinical development of denosumab in the current indication

## **2.5 Clinical aspects**

### **Introduction**

The Figure below shows the clinical studies submitted for this application. Study 20010223 was the main dose-response study, study 20030216 was the pivotal study for the PMO indication, study 20040135 was the pivotal study for the hormone ablation therapy (HALT) indication in females while 20040138 was the pivotal study for the HALT indication in males.

An overview of the therapeutic confirmatory trials can be found in the Clinical Efficacy section.

The claimed indication for Prolia was:

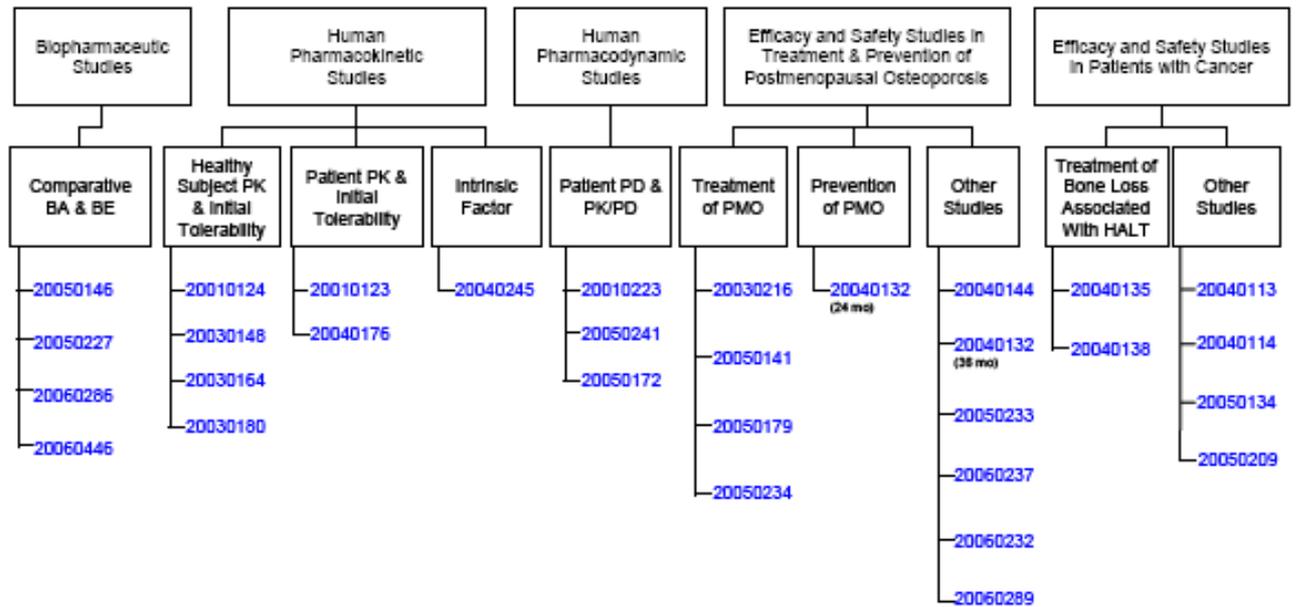
“The treatment of osteoporosis in postmenopausal women at increased risk of fractures. Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures.

The treatment of bone loss associated with hormone ablation in men with prostate cancer and in women with breast cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.”

The approved indication and posology are the following:

“Treatment of osteoporosis in postmenopausal women at increased risk of fractures. 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. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.”

Organisation scheme for denosumab clinical studies.



BA = bioavailability; BE = bioequivalence; HALT = hormone ablation therapy; PD = pharmacodynamics; PK = pharmacokinetics; PMO = postmenopausal osteoporosis  
 Note: Prevention of PMO is not a proposed indication for the EU; thus, Study 20040132 is included as a supportive efficacy and safety study only for the EU.

## GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

On request from the CHMP, a GCP inspection was undertaken of the clinical study 20030216 - A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis (FREEDOM: Fracture REDuction Evaluation of Denosumab in Osteoporosis every 6 Months). The inspection was carried out on study sites 413 (139 included subjects) and 430 (160 included subjects) plus at the CRO performing the assessments of X-rays and DXA-scans. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure. In conclusion, the major findings in the inspection report from inspection (INS/GCP/2009/03) were the following:

- Investigators were not informed about the cases where trial subjects had positive antibody tests or unexpectedly low BMD results
- Drug accountability for calcium and vitamin D supplementation was not performed
- Inconsistencies were detected between Bone biopsy sub-study’s Manual and protocol; the manual did not reflect the protocol
- Fracture status could be changed from “incident” to “prevalent” without adjudication of the X-ray investigation. Fracture status was changed by a late reader for 288 trial subjects; fracture status at screening was changed for more than 75 % of these subjects

Some of the critical deviations related to the CRO procedures had already been detected during a previous inspection and insufficient corrective/preventive actions had been implemented. It is

therefore recommended that a follow-up inspection should be performed. The re-inspection will not be a part of the Prolia application.

## **Pharmacokinetics**

Twelve studies were primarily designed as clinical pharmacology studies or bioequivalence studies and 11 studies were primarily designed to address other objectives but provide supportive pharmacokinetic and pharmacodynamic data. The bioanalytical methods used in bioequivalence studies and the clinical pharmacology studies seem adequately validated.

- Absorption

Based on a Population PK analysis the absolute bioavailability was estimated to be 61%, which is supported by data on relative exposures from Study 20010124. Formal bioavailability, plasma protein binding, and other human biomaterials studies have not been conducted. Comparison of the PK, as well as PD profiles of denosumab demonstrated bioequivalence between denosumab from different production sites and in different drug product presentations.

- Distribution

Volume of distribution was determined in the dose-escalation study 20010124. Mean volume of distribution at steady-state increased slightly across the IV dose range from approximately 29 to 55 mL/kg and were similar to that for plasma (43 mL/kg). In the Population PK Analysis after IV administration, the volume of distribution was also similar to plasma volume (approximately 3760 mL 66 kg individual), with a lack of extensive extravascular distribution. This data is consistent with results for other monoclonal antibodies.

- Elimination

It is generally accepted that monoclonal antibodies are eliminated by catabolism or receptor-mediated processes and not by hepatic metabolic clearance or renal excretion. Denosumab is likely eliminated through a non-specific, linear pathway via the reticuloendothelial system and a target-mediated, nonlinear pathway. This assumption is supported by PK data provided.

- Dose proportionality and time dependencies

Denosumab displays nonlinear PK across the 0.01- to 3.0 mg/kg IV and SC dose range investigated which is most pronounced at lower doses. Data are consistent with 2 mechanisms of elimination, a saturable one predominating at low serum concentrations and a nonsaturable mechanism that predominates elimination at higher serum concentrations.

At the 1.0 mg/kg SC dose median time to  $C_{max}$  ranged from 7 to 42 days and the mean half-life was about 30 days. No accumulation in serum denosumab concentrations is observed with repeated doses of 60 mg Q6M and pharmacokinetics do not appear to change with time for up to 4 years of exposure.

- Special populations

### *Impaired renal function*

In Study 20040245 the PK profile was not notably affected by varying degrees of renal function. Thus no dose adjustments are required with different degrees of renal impairment. Transient decreases in median serum calcium concentration were observed following administration, most notably in patients with severe kidney disease.

### *Impaired hepatic function*

As denosumab is a monoclonal antibody and not eliminated via hepatic metabolic mechanisms, hepatic impairment studies have not been conducted.

### *Gender*

Despite a higher average body weight in the men (mean 85.2 vs. 69.8 kg), no notable differences in exposure were observed following 60 mg denosumab SC between men and women.

#### *Ethnicity*

Although data are very limited in non-Caucasians, there did not appear to be notable differences in exposure in Caucasians compared with non-Caucasians. Results are consistent with those from phase 3 studies 20030216 and 20040138 where denosumab increased BMD across all racial groups examined. However PK data in non-Caucasians are sparse and the grouping in Caucasians and non-Caucasians is very vague considering ethnicities subsumed. Comparison between Japanese and non-Japanese subjects support the finding of no influence of ethnicity on PK and thus no further evaluations are required.

#### *Weight*

Exposure based on AUC and  $C_{max}$ , tended to be lower for heavier subjects following 60 mg SC dose. The trend of lower exposure with higher body weight did not result in a reduction in PD effect. Results are consistent with that from phase 3 studies.

#### *Elderly*

No relationship has been detected between denosumab concentration and age, except a trend to lower exposure in postmenopausal women 65 to 80 years of age compared to <65 years. This had no influence on PD parameters, consistent with findings in the pivotal phase 3 studies.

#### *Children*

The applicant has obtained necessary waivers for paediatric development pertaining to the indications contained within this MAA in all age subsets of the paediatric population.

- Pharmacokinetic interaction studies

No formal drug interaction studies were performed because denosumab is a monoclonal antibody and is not eliminated via hepatic metabolic mechanisms and interaction potential is considered to be low. However, the impact of previous bisphosphonate treatment on the pharmacokinetics of denosumab was assessed in the study 20050241 in which pharmacokinetics of denosumab was not altered in subjects who transitioned from alendronate to denosumab.

### **Pharmacodynamics**

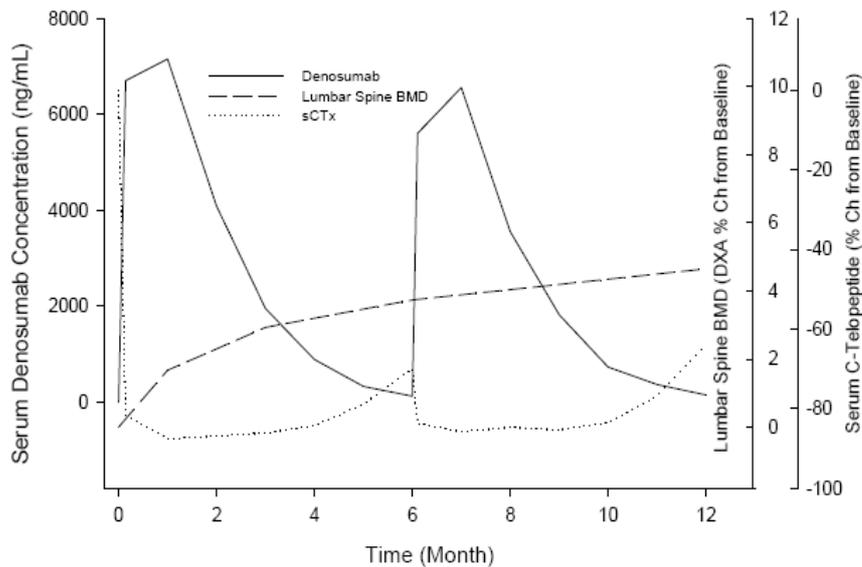
- Mechanism of action

Denosumab is a fully human IgG2 mAb is RANK Ligand (RANKL). RANKL is together with its receptor RANK and osteoprotegerin the key mediator in the pathway involved in regulating bone resorption. Denosumab's binding to RANKL prevents the RANKL-RANK interaction, inhibiting osteoclast formation, function and survival.

- Primary and Secondary pharmacology

While a high prevalence of binding and/or neutralizing antibodies was seen at all doses in cynomolgus monkeys treated with denosumab, no corresponding production of antibodies was seen in humans. The proposed dose regime, 60 mg every 6 month, has support from the presented pharmacodynamic data in several studies (see figure below).

Results in study 20010223, following two 60 mg Q6M doses: mean serum denosumab concentrations and mean % change from baseline for serum CTX1 and lumbar spine BMD.



Instead of formal PKPD analysis a kinetic-pharmacodynamic (K-PD) model was developed describing the serum CTX1 and BMD time profiles utilizing dose information and assumptions of 1<sup>st</sup> order kinetics of denosumab in the biophase as drug input. This approach seems questionable for a drug with highly non-linear pharmacokinetics. The model cannot aid in judging whether difference in PK is of relevance and thus is considered to be of limited value.

Study 20010223 was a phase II study with the primary objective to determine the effect of denosumab treatment compared with placebo over 12 months on BMD of the lumbar spine in postmenopausal women with low BMD and with the secondary objectives to choose a dose regimen of denosumab for future studies and to evaluate the effect of denosumab on BMD, plus safety and tolerability profiles over 12 months.

Study 20050172 was a phase II randomised double-blind placebo-controlled dose response study of denosumab in Japanese postmenopausal osteoporotic women, conducted at 21 sites in Japan. The primary study objective was to assess the effect of denosumab on the lumbar spine BMD at month 12, plus the safety profile. Doses of 14, 60 or 100 mg were administered SC once every 6 months. The dose of 60 mg denosumab administered Q6M appeared to be optimal.

In the dose response Studies 20010223 and 20050172, significant effects on BMD were seen after 48 months over the Q3M (6 mg, 14 mg, 30 mg) and Q6M (14 mg, 60 mg, 100 mg, 210 mg) doses investigated. At earlier time points the effect seen with the 14 mg Q6M dose was less pronounced. After discontinuation, BMD levels returned to baseline values without a rebound effect. Significant suppression of markers of bone turnover was apparent. During approximately the last 2 months of the Q6M dosing interval, levels of denosumab appear to be too low to sustain the effect on serum CTX1, although the applicant argues that a significant suppression of  $\geq 55\%$  remains. Data from the off-treatment period indicate that the effects of denosumab on BMD are mitigated at discontinuation. The applicant could, in the response to the D120 LoQ, reasonably justify that only the 60 mg Q6M dose was chosen for the pivotal trials.

Study 20010124 was a phase I multicenter randomised placebo-controlled double-blind single dose escalation study in healthy postmenopausal Japanese women. Doses of 0.03 - 3.0 mg/kg, administered SC, maintained decreases in bone turnover markers for at least 6 months. Safety parameters (primary endpoint) were satisfactory.

Study 20030164 was a phase I study conducted to evaluate the PK, PD, safety and tolerability of denosumab administration in healthy Japanese postmenopausal women. These women were administered doses between 0.01 and 3.0 mg/kg SC or IV; one dosing group got a repeat dose 3 months later. Bone turnover markers were evaluated for efficacy and a number of safety parameters were recorded.

Study 20050241 was a study to evaluate the safety of transitioning postmenopausal women with low BMD currently receiving alendronate to a single dose of denosumab (15 – 60 mg SC). Twenty patients were included in this 128 day US 2-center phase I study.

Study 20040113 was a phase II tricontinental study in women with *breast cancer* (n = 255) with *metastases* who had not previously been treated with bisphosphonates. This was a denosumab dose finding study, evaluating the effect of denosumab on the percentage change from baseline in urinary NTX at week 13. Denosumab was administered SC doses of 30, 120, or 180 mg Q4W or 60 or 180 mg Q12W.

## Clinical efficacy

- Dose response studies

The dosage of 60 mg per dose was selected based on results from study 20010223. Doses of 30 mg Q3M and 60 mg Q6M were similar in pharmacodynamic activity and the dose interval of 6 months was selected for phase 3 studies as being the most convenient effective dose interval. The pharmacokinetics and pharmacodynamics of this dosing schedule was further studied in three pivotal studies (20030216, 2004135, 20040138). The dose and dose intervals selected had adequate support in pharmacokinetic and pharmacodynamic studies.

- Main studies

**Study 20030216** was the pivotal phase 3 study in PMO population titled ‘A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis: FREEDOM (Fracture REDuction Evaluation of Denosumab in Osteoporosis every 6 Months)’.

## METHODS

### *Study Participants*

Postmenopausal women with osteoporosis, as defined by a BMD T-score at the total hip or lumbar spine < -2.5 were included in the study. Subjects with BMD T-scores < -4.0 at the total hip or lumbar spine were not eligible as it was considered unethical to leave placebo-treated subjects untreated for 3 years. Study participants were to be in good health and not to be on any other medication affecting bone metabolism. This study was conducted in Europe, North and South America, Australia and New Zealand.

### *Treatments*

Subjects received either denosumab 60 mg or placebo every 6 months (Q6M) subcutaneously (SC) for 3 years (last dose at month 30; follow-up to month 36). All subjects received daily calcium ( $\geq 1$  g) and vitamin D ( $\geq 400$  IU) supplementation.

### *Outcomes/endpoints*

The primary efficacy endpoint was the incidence of new vertebral fractures after 3 years of treatment. Secondary objectives were the time to first nonvertebral fracture and time to first hip fracture.

### *Sample size*

The sample size was planned to provide adequate statistical power to detect, at a minimum, a 45% reduction in the incidence of new vertebral fracture, a 40% decrease in the risk of nonvertebral and hip fracture with assumptions of a vertebral, nonvertebral and hip fracture rate in the placebo arm of 4%, 3.3% and 1.0% per year respectively and a loss-to-follow-up vertebral radiograph rate of 5% per year.

### *Randomisation*

Subjects were randomised (1:1) in a double-blinded fashion to receive either denosumab or placebo. Randomisation was stratified by age at entry: 60 to 64 years, 65 to 69 years, 70 to 74 years, and  $\geq 75$  years.

### Blinding (masking)

Denosumab and placebo vials had the same appearance and subjects, investigators, and site staffs were blinded to identity. Unblinding was limited to cases where knowledge was essential for further management. Unblinding for medical emergencies occurred for 7 subjects, 2 on denosumab and 5 on placebo.

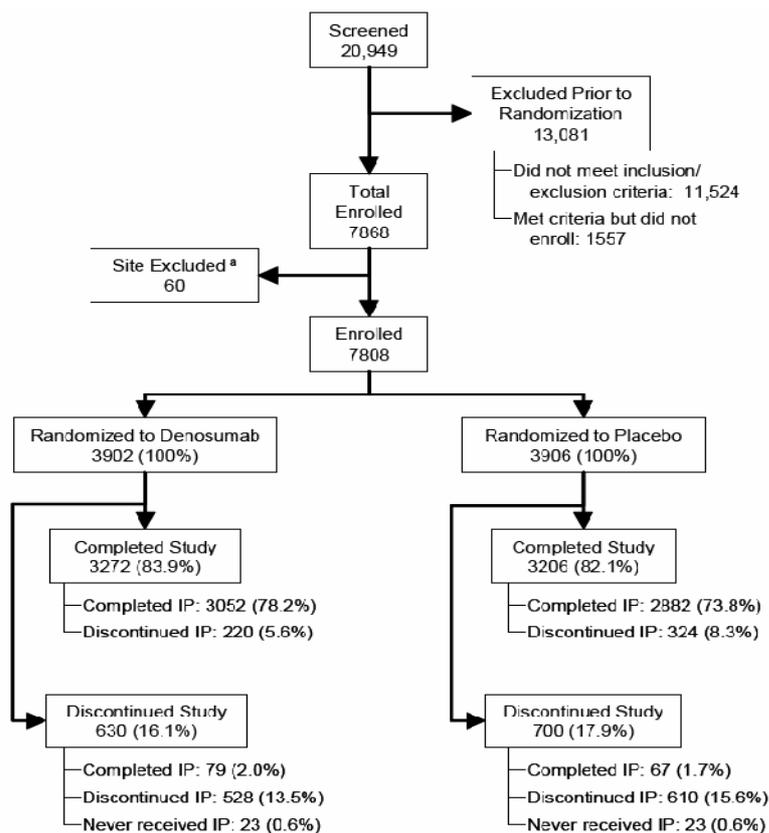
### Statistical methods

For the primary efficacy endpoint and the two secondary efficacy endpoints, a fixed sequence testing procedure was used. The significance of the treatment comparisons between denosumab and placebo were assessed using the score test from a logistic regression model. In addition to the estimate of the odds ratio from the logistic regression model, point estimates of absolute risk reduction and risk ratio as well as the corresponding 95% confidence intervals were calculated using Mantel-Haenszel methodology. The significance of the treatment effect between denosumab and placebo on time-to-event endpoints was assessed using the score test from a stratified Cox proportional hazards.

## RESULTS

### Participant flow

Subject disposition and exposure to investigational product in study 20030216



IP = investigational product:

Subjects completed IP if they received all 6 planned doses.

Subjects could continue on study after withdrawal from IP.

<sup>a</sup> Data obtained at site 803 were excluded from all efficacy and safety analyses; key safety data were summarized (Section 8.2).

### Recruitment

The study was conducted from 03 August 2004 to 17 June 2008.

### Conduct of the study

Important eligibility protocol deviations were reported for 9.2% in the denosumab and 9.0% in the placebo group. Most subjects did not meet inclusion criterion “screening BMD T-score < -2.5”. These deviations from the eligibility criteria would not be expected to impact the study results. On-study important protocol deviations were reported for 9.4% in the denosumab and 13.7% in the placebo group. The greater incidence of on-study important protocol deviations in the placebo group was due to an imbalance in the concomitant administration of bisphosphonates. These deviations were judged unlikely to have affected the interpretation of the study results. Site 803 was closed in May 2007 after an inspection by the Lithuanian health authority, due to violation of GCP. All subjects from this site underwent full early study termination procedures and the decision was made to exclude from all analyses the 60 subjects from site 803 because of the seriousness of the GCP violations. Severe findings were made at a later GCP inspection carried out at the CRO performing the assessments of X-rays and DXA-scans and this inspection, and at two study sites.

### Baseline data

Baseline mean age for study participants was 72.3 years, baseline mean lumbar spine BMD was -2.8 and years since menopause was 24.2. Baseline mean 10-year probabilities of major osteoporotic fractures and of hip fractures were 18.66±10.65 % in the placebo group and 18.54±10.61 % in the denosumab group while the corresponding risk of hip fractures was for the high risk group (defined as meeting ≥ 2 of the following criteria: age > 70 years, baseline BMD T-score ≤ -3, prevalent vertebral fracture at baseline) , 44.9 % in the placebo group and 45.1 % in the denosumab group. 53.5 % of all study subjects had at least one fracture in their medical history at baseline.

### Numbers analysed

Numbers analysed per treatment group are summarized in table below.

#### Analysis Sets for Key Endpoints (Randomised Subjects)

Endpoint	Placebo (N = 3906)	Denosumab 60 mg Q6M (N = 3902)	All (N = 7808)
Analysis subset	n (%)	n (%)	n (%)
New vertebral fractures through month 36			
Primary efficacy subset	3691 (94.5)	3702 (94.9)	7393 (94.7)
Per protocol subset	2960 (75.8)	3034 (77.8)	5994 (76.8)
Additional exploratory per protocol subset	3328 (85.2)	3334 (85.4)	6662 (85.3)
N = Number of subjects randomised			
Percentages based on number of subjects randomised			
* Numbers (n) in safety subset based on the actual treatment received			

Over 3 years, 17.0% withdrew from study (16.1% denosumab, 17.9% placebo). The reasons for withdrawal are summarized in table below.

#### Reasons for Study Discontinuation (Randomised Subjects)

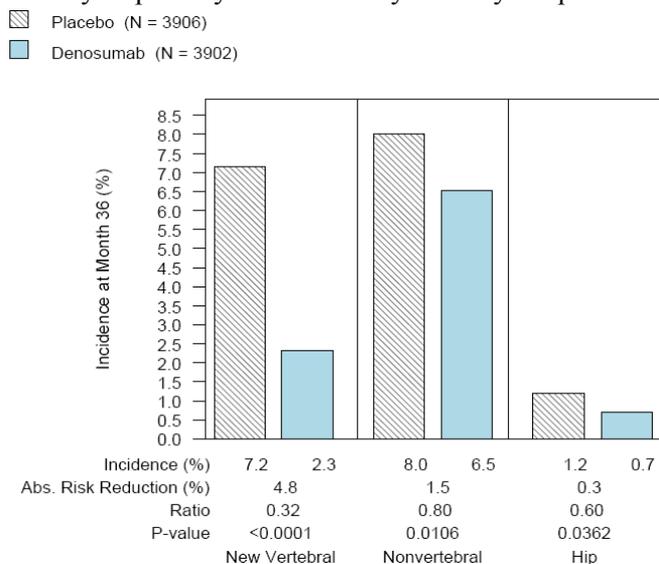
	Placebo n (%)	Denosumab 60 mg n (%)	All n (%)
Randomised	3906	3902	7808
Completed study	3206 (82.1)	3272 (83.9)	6478 (83.0)
Discontinued study	700 (17.9)	630 (16.1)	1330 (17.0)
Consent withdrawn	403 (10.3)	344 (8.8)	747 (9.6)
AE	81 (2.1)	93 (2.4)	174 (2.2)
Death	78 (2.0)	62 (1.6)	140 (1.8)
Lost to follow-up	57 (1.5)	57 (1.5)	114 (1.5)
Other	40 (1.2)	42 (1.1)	82 (1.1)
Noncompliance	17 (0.4)	13 (0.3)	30 (0.4)
Protocol deviation	12 (0.3)	10 (0.3)	22 (0.3)
Ineligibility determined	12 (0.3)	9 (0.2)	21 (0.3)
Percentages based on number of subjects randomised			

### Outcomes and estimation

Denosumab 60 mg SC Q6M for 3 years significantly reduced risk of new vertebral, nonvertebral, and hip fractures in women with osteoporosis compared to placebo. RR reductions at month 36 for new

vertebral, nonvertebral, and hip fractures were 68%, 20%, and 40%, respectively. The main results are summarized in figure and table below.

Summary of primary and secondary efficacy endpoints in study 20030216.



Summary of additional fracture endpoints in study 20030216.

Fracture Category	Ratio Point Estimate <sup>a</sup>	95% CI	p-value
New and worsening vertebral <sup>b</sup>	0.33	(0.26, 0.42)	< 0.0001
Multiple new vertebral <sup>b</sup>	0.39	(0.24, 0.63)	< 0.0001
Major osteoporotic <sup>c</sup>	0.65	(0.55, 0.78)	< 0.0001
Major nonvertebral <sup>c</sup>	0.80	(0.66, 0.97)	0.0224
Clinical <sup>c</sup>	0.70	(0.59, 0.81)	< 0.0001
Clinical vertebral <sup>c</sup>	0.31	(0.20, 0.47)	< 0.0001
Any osteoporotic <sup>b</sup>	0.60	(0.53, 0.69)	< 0.0001

#### Ancillary analyses

7834 subjects were tested for anti-denosumab antibodies and 43 subjects in the safety analysis set tested positive for nonneutralizing, binding antibodies. Four subjects in the placebo group (0.1%) and 5 in the denosumab group tested positive for pre-existing antidenosumab nonneutralizing, binding antibodies. Ten subjects in the placebo group (0.3%) and 24 in the denosumab group (0.6%) tested positive for development of antidenosumab nonneutralizing, binding antibodies in postbaseline samples. Nine of these subjects in the placebo group and all 24 in the denosumab group were transiently positive since the last time point tested was negative. The few patients who tested positive for antidenosumab antibodies did not seem to have lower BMD gains than other patients. Antibodies will be monitored in extension studies.

Increases from baseline to month 36 in lumbar spine BMD in body weight were similar among denosumab-treated subjects within those subgroups. The difference between the denosumab and placebo groups decreased with increasing body weight and BMI subgroups.

**Study 20040135** was the pivotal phase 3 study in the HALT population, titled ‘A Randomised, Double-blind, Placebo-controlled Study to Evaluate AMG 162 in the Treatment of Bone Loss in Subjects Undergoing Aromatase Inhibitor Therapy for Nonmetastatic Breast Cancer’.

#### METHODS

##### Study Participants

Women  $\geq 18$  years with histologically or cytologically confirmed early-stage, estrogen-receptor-positive adenocarcinoma of the breast with completed treatment pathway and currently on or initiating aromatase inhibitor therapy for the duration of the study. Subjects had to

have lumbar spine, total hip, or femoral neck BMD T-score of -1.0 to -2.5 and none of these anatomic sites could have been in the BMD range corresponding to a T-score of < -2.5. The study was conducted at 53 sites in the United States and Canada.

#### *Treatments*

Subjects received either denosumab 60 mg or placebo every 6 months (Q6M) subcutaneously (SC) for a total of 4 doses during 24 month treatment period. All subjects received daily calcium ( $\geq 1$  g) and vitamin D ( $\geq 400$  IU) supplementation.

#### *Outcomes/endpoints*

The primary objective was to determine whether denosumab compared with placebo preserved lumbar spine BMD during aromatase inhibitor therapy in subjects with nonmetastatic breast cancer after 12 months. The secondary objectives were to assess the effect on BMD of the total hip and femoral neck and the safety and PK of denosumab.

#### *Sample size*

A sample size of 104 subjects enrolled in each group was considered to provide a 95% power to detect a 2% difference between denosumab and placebo in the percentage of change of BMD for lumbar spine at 12 months with expected loss to follow-up rate of 20% per year.

#### *Randomisation*

Subjects were classified by duration of aromatase inhibitor therapy at study entry of  $\leq 6$  months or  $> 6$  months and equally allocated 1:1 to treatment groups using a stratified randomisation schedule.

#### *Blinding (masking)*

Denosumab and placebo vials had the same appearance and subjects, investigators, and site staffs were blinded to identity. Unblinding was limited to cases where knowledge was essential for further management. No treatment assignments were unblinded during the first 24 months of the study.

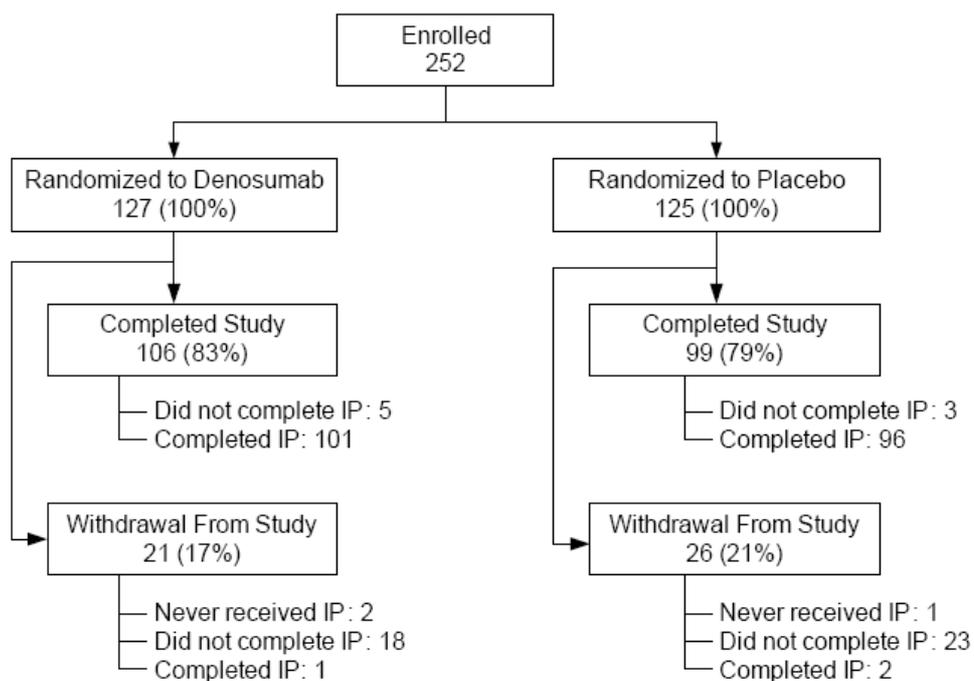
#### *Statistical methods*

Analysis of the primary and secondary BMD endpoints employed an ANCOVA model using the LOCF imputation. Primary conclusions on the efficacy of denosumab were made using the difference of the point estimates for the least-squares mean and the 2-sided 95% CI for treatment difference at month 12. Sensitivity analyses were also conducted.

## RESULTS

### *Participant flow*

Subject disposition and exposure to investigational product in study 20040135



### Recruitment

The study was conducted from 04 October 2004 to 11 May 2007.

### Conduct of the study

The original study protocol was approved on 04 May 2004 and subsequently amended 3 times. Important eligibility criteria deviations were reported for 8% overall (9% denosumab, 8% placebo). On-study important protocol deviations were reported for 19% of subjects overall (17% denosumab, 21% placebo). Protocol deviations are not considered to have influenced the validity of the results.

### Baseline data

Mean (SD) age was 59.5 (9.3) years comparable in both groups. Baseline disease characteristics were generally balanced between treatment groups. Of subjects with known ECOG values, all had either score 0 (90% denosumab, 84% placebo) or 1 (10% denosumab, 11% placebo); 6 subjects (5%) on placebo had unknown ECOG scores. Baseline BMD T-scores were similar between treatment groups.

### Numbers analysed

252 subjects were enrolled, 127 randomised to denosumab and 125 to placebo. Of the 252 subjects, 249 (125 denosumab, 124 placebo) received at least 1 dose. 83% in the denosumab and 79% in the placebo group completed the 24-month treatment period. 93 subjects (47 denosumab, 46 placebo) were in the  $\leq 6$  months of aromatase inhibitor stratum, and 159 (63%) (80 denosumab, 79 placebo) in the  $> 6$  months of aromatase inhibitor therapy stratum.

### Outcomes and estimation

All primary and secondary efficacy endpoints were met with statistical significance. Treatment with denosumab statistically significantly increased BMD, as assessed by DXA, at the lumbar spine, total hip, and femoral neck at months 6 and 12 ( $p < 0.0001$ ). The main results are summarized in table below

Primary and secondary efficacy endpoints: ANCOVA model, study 20040135 (primary efficacy subset, LOCF). Figures in the two left columns indicate numbers analysed.

	Placebo N	Denosumab 60 mg Q6M N	Estimate	95% CI	p-value	Adjusted p- value <sup>c</sup>
Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 6 <sup>a</sup>						
Difference from Placebo	122	123	4.3	(3.6, 5.0)	<0.0001	<0.0001
Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 12 <sup>a, b</sup>						
Difference from Placebo	122	123	5.5	(4.8, 6.3)	<0.0001	-
Total Hip Bone Mineral Density Percent Change From Baseline at Month 6 <sup>a</sup>						
Difference from Placebo	122	123	2.7	(2.1, 3.3)	<0.0001	<0.0001
Total Hip Bone Mineral Density Percent Change From Baseline at Month 12 <sup>a</sup>						
Difference from Placebo	122	123	3.7	(3.1, 4.4)	<0.0001	<0.0001
Femoral Neck Bone Mineral Density Percent Change From Baseline at Month 6 <sup>a</sup>						
Difference from Placebo	122	123	2.1	(1.3, 2.9)	<0.0001	<0.0001
Femoral Neck Bone Mineral Density Percent Change From Baseline at Month 12 <sup>a</sup>						
Difference from Placebo	122	123	2.5	(1.6, 3.3)	<0.0001	<0.0001

N = Number of subjects who had a baseline value and at least 1 post baseline value before or at the time point of interest

<sup>a</sup> Based on ANCOVA model adjusting for treatment, stratification variable, baseline BMD value, machine type, and baseline BMD value-by-machine type interaction.

<sup>b</sup> For the primary endpoint, the p-value is not adjusted.

<sup>c</sup> P-values for all secondary endpoints are adjusted with Hochberg's procedure for multiple comparisons.

### Ancillary analyses

The mean serum denosumab concentration observed was with a lack of change in PK with time and a lack of accumulation with repeated dosing. Treatment with denosumab resulted in rapid and sustained decreases in concentrations of sCTx1 relative to placebo at each postbaseline assessment ( $p < 0.0001$ ). Denosumab reduced serum concentrations of P1NP relative to placebo at each postbaseline assessment, with the greatest median reduction obtained at month 6 and sustained through month 24 ( $p < 0.0001$ ). Kaplan-Meier estimates of the risk of nonvertebral fracture were 3.3% for denosumab and 3.5% for placebo at month 12 and 7.2% for both treatment groups at month 24. No vertebral fractures were reported during the 24-month treatment period. There was only 1 death per group, thus an analysis of overall survival at month 24 was not conducted.

**Study 20040138** was the pivotal phase 3 study in the HALT population, titled 'A Randomised, Double-blind, Placebo-controlled Study to Evaluate AMG 162 in the Treatment of Bone Loss in Subjects Undergoing Androgen-deprivation Therapy for Nonmetastatic Prostate Cancer'.

## METHODS

### Study Participants

Men  $\geq 70$  years of age with histologically confirmed prostate cancer, or men  $< 70$  years of age with histologically confirmed prostate cancer and a history of osteoporotic fracture or BMD T-score at the lumbar spine, total hip, or femoral neck  $< -1.0$ , but not  $< -4.0$ . Subjects had to have undergone bilateral orchiectomy or initiated ADT with GnRH agonists and are expected to continue with ADT for at least 12 months. The study was conducted at 156 sites in the United States, Canada, Mexico, and Europe.

### Treatments

Subjects received either denosumab 60 mg or placebo every 6 months (Q6M) subcutaneously (SC) for 3 years (last dose at month 30; follow-up to month 36). All subjects received daily calcium ( $\geq 1$  g) and vitamin D ( $\geq 400$  IU) supplementation. The 60-month study includes a 24-month safety follow-up period.

### Outcomes/endpoints

The primary endpoint was percentage change in lumbar spine BMD from baseline to month 24. Secondary efficacy endpoints were percentage change in femoral neck and total hip BMD from baseline to month 24, percentage change in lumbar spine, femoral neck, and total hip BMD from baseline to month 36, subject incidence of any fracture and subject incidence of new vertebral fracture over the 36-month treatment period, time to first clinical fracture over the 36-month treatment period, and subject incidence of any fracture over the 24-month treatment period.

#### *Sample size*

The sample size of 1226 subjects was planned to provide adequate statistical power to detect a 2% difference between the denosumab and placebo groups in the percentage change from baseline in lumbar spine BMD after 24 months of treatment, a reduction in the risk of developing any fractures by 45% over 36 months, and a reduction in the risk of developing new vertebral fractures by 45% over 36 months.

#### *Randomisation*

Subjects were randomised 1:1 to receive placebo or denosumab. Randomisation was stratified by age group (< 70 years vs ≥ 70 years) and duration of ADT with a GnRH agonists or orchiectomy at study entry (≤ 6 months vs > 6 months).

#### *Blinding (masking)*

Denosumab and placebo vials had the same appearance and subjects, investigators, and site staffs were blinded to identity. Unblinding was limited to cases where knowledge was essential for further management. Treatment assignment was unblinded for 1 subject receiving denosumab.

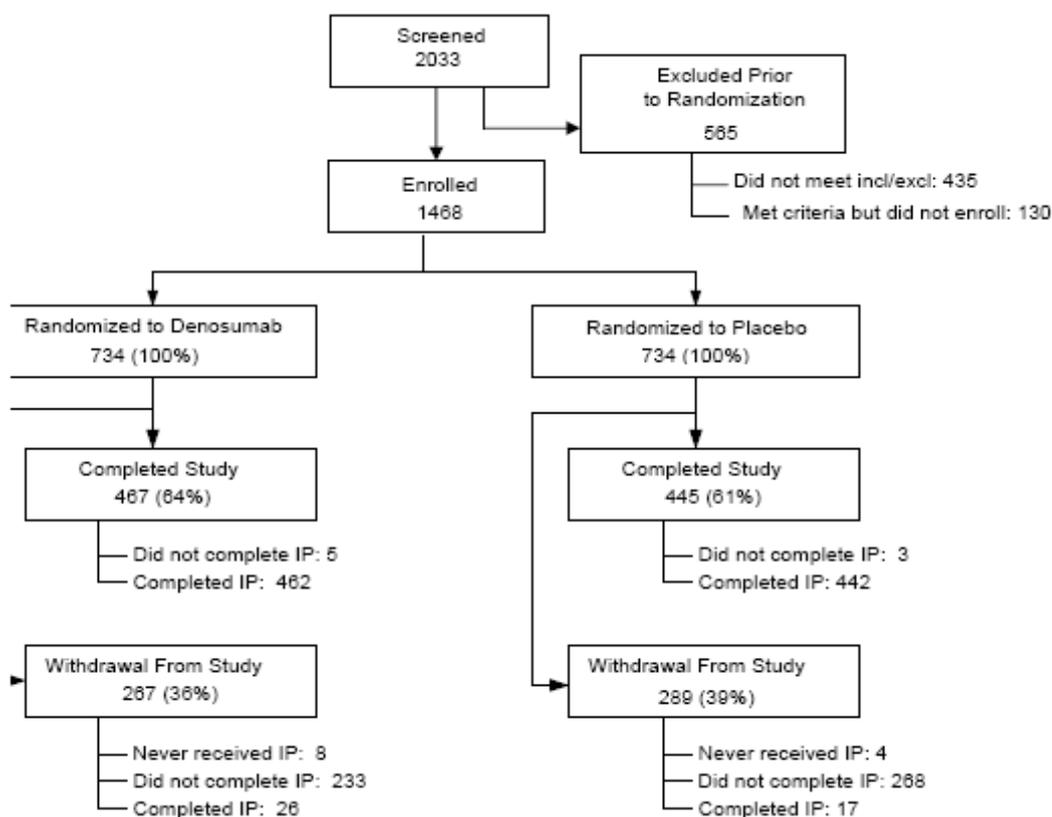
#### *Statistical methods*

Analysis of the continuous primary and secondary BMD endpoints employed an ANCOVA model using LOCF imputation with treatment group, baseline BMD value, machine type, the interaction of baseline BMD value and machine type, age group (< 70 versus ≥ 70 years), and duration of ADT (≤ 6 versus > 6 months) as covariates. Efficacy conclusions based on the primary endpoint were made using the least-squares mean estimate for the treatment difference (denosumab – placebo) and its 2-sided 95% CI at month 24.

## RESULTS

### *Participant flow*

Subject disposition and exposure to investigational product; all randomised subjects in study 20040138.



### Recruitment

The study was conducted from 02 August 2004 until 16 May 2008. Upon completion of the 36-month treatment period, subjects were continued on study for 24 months during which no investigational product was administered, or were offered enrolment in a 2-year extension study (20080537). These both are ongoing and not part of the dossier.

### Conduct of the study

The original protocol was approved on 04 May 2004 and subsequently amended 5 times. Important eligibility criteria deviations were reported for 4% of subjects, inclusion criteria for 1% of subjects and exclusion criteria deviations for 3% of subjects. On-study important protocol deviations were reported for 18% of subjects overall (19% denosumab, 17% placebo). Protocol deviations are not considered to have influenced the validity of the results.

### Baseline data

Most subjects (83%) were white. The mean (SD) age was 75.4 (7.1) years, and 93% were  $\geq 65$  years of age. Mean (SD) weight and BMI were 83.58 (13.46) kg and 28.2 (4.0) kg/m<sup>2</sup>, respectively. The majority (63%) (460 denosumab, 460 placebo) were in the stratum of subjects  $\geq 70$  years of age who had received  $> 6$  months ADT. A medical history of at least 1 fracture was noted for 34% in the denosumab and 37% of subjects in the placebo group.

### Numbers analysed

A total of 1468 subjects were enrolled, 734 randomised to denosumab and 734 to placebo. 1456 (726 denosumab, 730 placebo) received at least 1 dose. 64% in the denosumab and 61% in the placebo group completed the 36-month treatment period. 309 subjects (161 denosumab, 148 placebo) participated in the substudy evaluating BMD of the distal 1/3 radius and total body.

### Outcomes and estimation

The primary efficacy endpoint and the secondary BMD endpoints were met with statistical significance. Treatment with denosumab increased significantly BMD relative to placebo both for the

primary and the secondary efficacy endpoints; the effect on lumbar spine BMD is considered clinically relevant (6.7% difference). Main results are summarized in table below.

Summary of Treatment Group Comparisons for Primary and Secondary Efficacy Endpoints

	Denosumab		Estimate	95% CI	p-value	Adjusted p-value <sup>g</sup>
	Placebo (N=734) n	60 mg Q6M (N=734) n				
<b>BMD Endpoints</b>						
Lumbar spine BMD Percent change from baseline at Month 24 <sup>a</sup>	716	714	6.7	(6.2, 7.1)	<.0001	<.0001
Femoral neck BMD Percent change from baseline at Month 24 <sup>a</sup>	706	701	3.9	(3.5, 4.4)	<.0001	<.0001
Total hip BMD Percent change from baseline at Month 24 <sup>a</sup>	706	701	4.8	(4.4, 5.1)	<.0001	<.0001
Lumbar spine BMD Percent change from baseline at Month 36 <sup>a</sup>	716	714	7.9	(7.4, 8.4)	<.0001	<.0001
Femoral neck BMD Percent change from baseline at Month 36 <sup>a</sup>	706	701	4.9	(4.4, 5.4)	<.0001	<.0001
Total hip BMD Percent change from baseline at Month 36 <sup>a</sup>	706	701	5.7	(5.4, 6.1)	<.0001	<.0001
<b>Fracture Endpoints</b>						
Subject incidence of any fracture through Month 36 <sup>b</sup>	734	734	0.70	(0.46, 1.08)	0.1048	0.1048
Subject incidence of new vertebral fracture through Month 36 <sup>b,e</sup>	673	679	0.37	(0.18, 0.78)	0.0063	0.0125
Time to first clinical fracture through Month 36 <sup>c</sup>	734	734	0.94	(0.57, 1.55)	0.7961	0.7961
Subject incidence of any fracture through Month 24 <sup>b</sup>	734	734	0.70	(0.44, 1.11)	0.1282	0.7961

<sup>a</sup> Difference from placebo ANCOVA model adjusting for age group, ADT duration at study entry, baseline value, machine type, and baseline value-by machine type interaction; <sup>b</sup> Odds ratio relative to placebo logistic regression model adjusting for age group and ADT duration at entry; <sup>c</sup> Hazard ratio relative to placebo Cox proportional hazards model stratified by age group and ADT duration at entry; <sup>d</sup> P-values for all endpoints adjusted for multiplicity (sequential testing); <sup>e</sup> Only subjects with nonmissing baseline and  $\geq 1$  postbaseline assessment included

*Ancillary analyses*

The mean serum denosumab concentration observed was with a lack of change in PK with time. Treatment with denosumab resulted in rapid and sustained decreases in concentrations of serum Type 1 CTX and TRAP 5b relative to placebo at each postbaseline assessment ( $p < 0.0001$ ). At the end of the SC dosing interval at month 6, attenuation of month 1 suppression was noted. Suppression of P1NP with denosumab temporally followed suppression of serum Type 1 CTX. Total testosterone and PSA and incidences of PSA rise were similar between treatment groups. Overall, there did not appear to be any clinically meaningful differences in HRQoL or pain throughout the duration of the study in either treatment group. In addition, no clinically significant differences in HRQoL or pain were noted between treatment groups. There was no difference in overall survival between denosumab and placebo.

- Analysis performed across trials (pooled analyses and meta-analysis)

BMD data were only data compared between pivotal studies for the two different indications and found to be of similar magnitude (see table below).

Comparison of change in BMD from baseline to month 24 compared to placebo between PMO and HALT studies (ANCOVA, LOCF).

	Study 20030216 <sup>a</sup>	Study 20040135 <sup>b</sup>	Study 20040138 <sup>c</sup>
Percent Change (least squares mean [95% CI])			
Lumbar Spine	7.5 (6.6, 8.3)	7.6 (6.6, 8.6)	6.7 (6.2, 7.1)
Total Hip	4.8 (4.2, 5.4)	4.7 (4.0, 5.5)	4.8 (4.4, 5.1)
Femoral Neck	4.5 (3.7, 5.2)	3.6 (2.7, 4.6)	3.9 (3.5, 4.4)
Actual Change (g/cm <sup>2</sup> ) (least squares mean [95% CI])			
Lumbar Spine	0.057 (0.050, 0.063)	0.076 (0.066, 0.087)	0.073 (0.068, 0.078)
Total Hip	0.034 (0.030, 0.039)	0.041 (0.035, 0.048)	0.044 (0.041, 0.047)
Femoral Neck	0.027 (0.022, 0.031)	0.030 (0.022, 0.037)	0.032 (0.028, 0.036)

- Clinical studies in special populations

**Study 20040245** was carried out in male or female volunteers to evaluate the effects of denosumab in subjects with impaired renal function: subjects in group 1 (n = 12) had normal renal function, group 2 (n = 10) had creatinine clearance (CrCl) 50 – 80 ml/min, group 3 (n = 10) had CrCl 30 – 49 ml/min, group 4 (n = 7) had CrCl < 30 ml/min and group 5 (n = 7) were on hemodialysis. The pharmacokinetic profile of denosumab was not notably affected by varying degrees of renal impairment. Parametric and nonparametric analyses did not indicate a significant relationship between renal function and PK parameters of denosumab. These data indicate that denosumab does not need dose adjustment in patients with renal impairment.

- Supportive studies

*Supportive studies for the PMO indication* are studies 20040132, 20050233, 20060289, 20010223, 20050179, 20050141 and 20050324. The latter three were alendronate-controlled studies.

**Study 20040132** was a North American 36 month multicenter study with the primary objective to determine if denosumab treatment could *prevent* lumbar spine BMD loss, measured as % change from baseline in lumbar spine BMD, at 24 months of treatment in women with PMO and basal lumbar spine BMD T-score between -1.0 and -2.5. The study included 332 women and showed significantly greater BMD increases at all anatomic sites for the denosumab-treated subjects during the 24-month treatment period. Subjects were randomised 1:1 to receive either denosumab or placebo; randomisation was stratified by time since onset of menopause ( $\leq 5$  years or  $> 5$  years). During the on-treatment period (baseline to month 24), subjects received blinded investigational product Q6M SC (last dose at month 18). During the off-treatment period (months 25 to 48), administration of investigational product was discontinued. Within 12 months of discontinuation of denosumab treatment, BMD returned to approximately baseline levels. Bone turnover markers did no longer remain reduced 3 months after discontinuation of treatment.

**Study 20050233** is an ongoing 1-year continuation study for those patients in study 20010223 who completed 4 years of denosumab treatment; 113 subjects in this study completed 5 years of denosumab therapy. The placebo cohort received placebo SC for 4 years, and then active treatment.

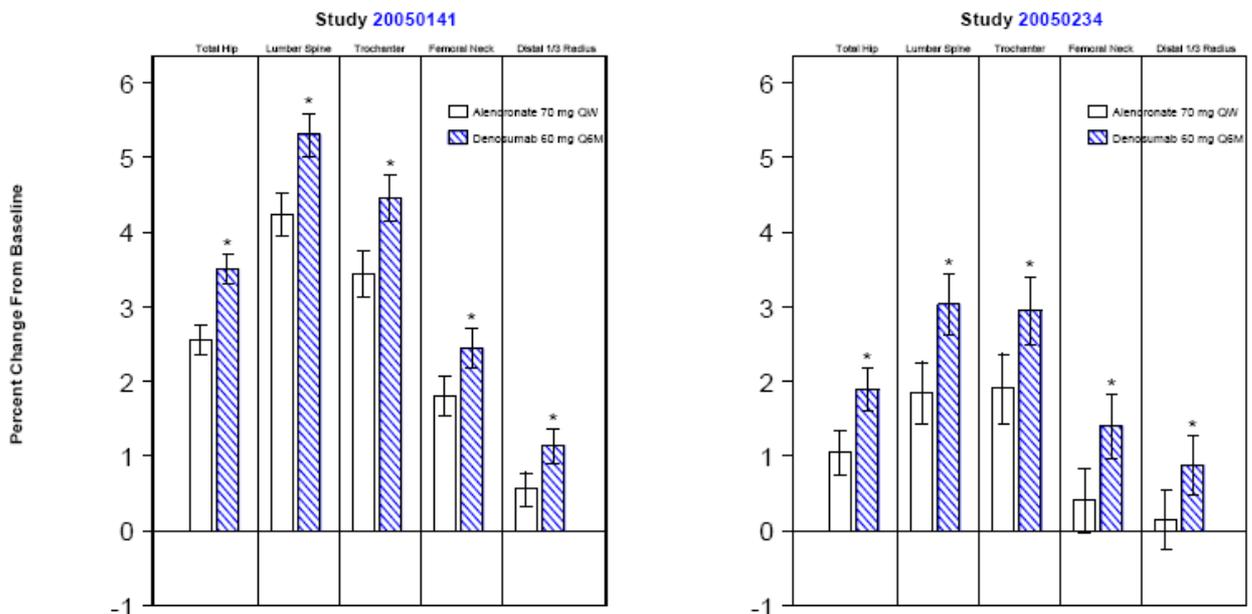
**Study 20060289** is a 7 -year open-label extension of study 20030216, to provide 10 years of total exposure to denosumab in women who were receiving denosumab in that study. This study is presently ongoing.

**Study 20050179** included 247 subjects in a phase II randomised placebo-controlled trial to estimate the treatment effects of denosumab and alendronate sodium, compared to placebo, in PMO subjects with low mineral density. Effects were evaluated at distal radius, using in vivo high-resolution peripheral quantitative computed tomography at 12 months. Increases in BMD occurred within both the cortical and the trabecular bone compartments and the skeletal changes observed were greater with denosumab than with alendronate. Formal statistics were not calculated in this study.

**Study 20050141** included 1189 postmenopausal women with lumbar spine BMD  $\leq -2.0$ . Study subjects were randomised 1:1 to receive denosumab plus placebo or alendronate plus placebo. At month 12, noninferiority was met for the primary endpoint: the mean percent change in total hip BMD was 3.5% in the denosumab and 2.6% in the alendronate group (1-sided  $p < 0.0001$ ). The prespecified secondary endpoints were inferentially evaluated. Results of superiority testing were statistically significantly in favour of denosumab for the total hip, hip trochanter, and distal 1/3 radius at month 12 (1-sided  $p \leq 0.0001$  after multiplicity adjustment).

**Study 2005234** was a phase III multicenter study to evaluate the effect of denosumab 60 mg SC every 6 month on total hip BMD (primary endpoint) at 12 months in postmenopausal women with low BMD previously treated with alendronate 70 mg weekly or equivalent, compared to patients continuing alendronate therapy. Five hundred and four subjects, with a mean age of  $67.6 \pm$  years, were included. Subjects were stratified according to previous alendronate exposure. Greater increases in BMD were seen at the total hip, lumbar spine, femoral neck, hip trochanter and distal radius in denosumab treated patients compared with those continuing on alendronate therapy. Bone turnover markers were significantly more reduced in the denosumab group than in the alendronate group. Bone histology was evaluated in 39 of the study subjects and revealed no abnormal findings.

**Fig 7.** Studies 20050141 and 2005234: BMD by DXA; % change from Baseline to month12 at all anatomic sites (Primary efficacy subset).

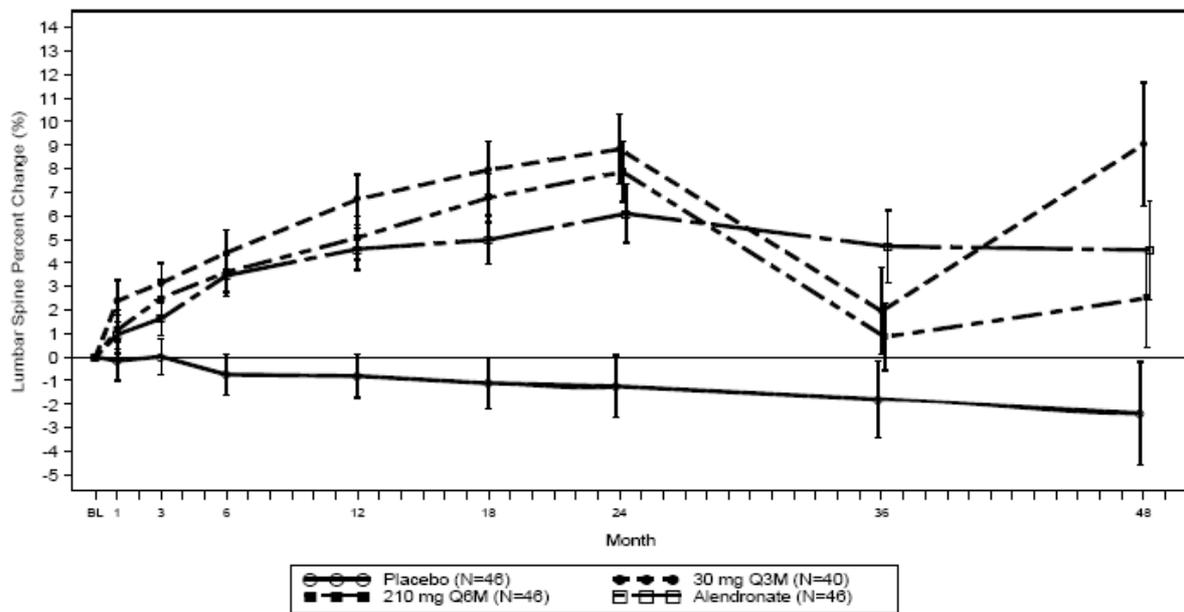


Number of subjects with values at baseline and at  $\geq 1$  postbaseline visit: Study 20050141 (bisphosphonate-naive subjects) - alendronate 572 and denosumab 579; Study 2005234 (subjects transitioning from alendronate therapy) - alendronate 241 and denosumab 248. Least squares means with 95% CIs based on an ANCOVA model (for Study 20050141) adjusting for treatment, machine type, baseline value, and baseline value-by machine type interaction; a repeated measures model (for Study 2005234) adjusting for treatment, length of prior alendronate stratification variable, visit, baseline value, machine type, treatment by visit interaction, and baseline value by machine type interaction. \* Indicates significance at 5% nominal level

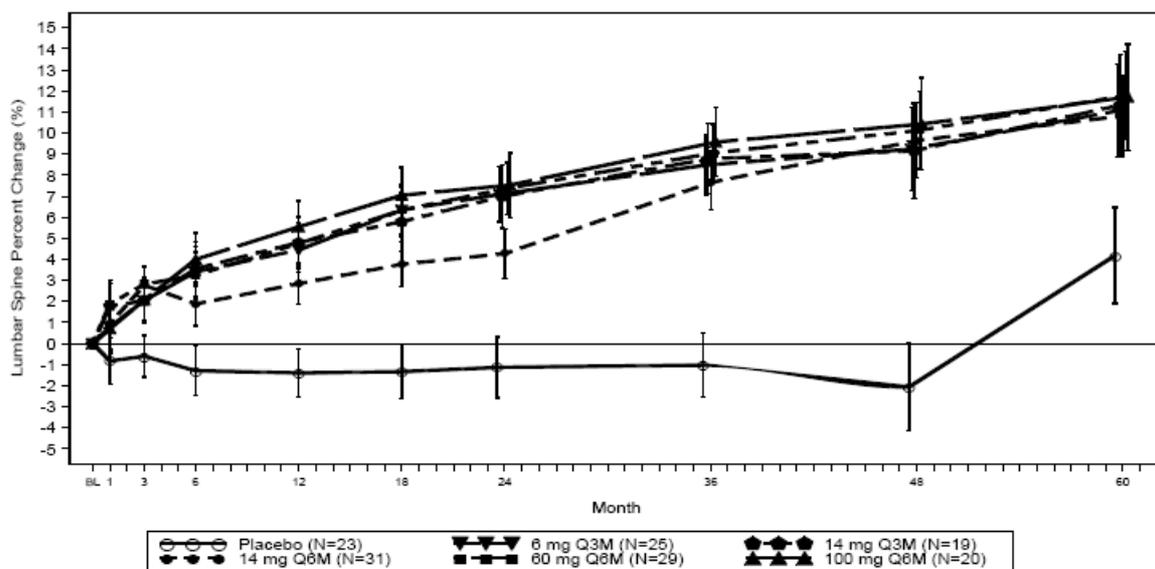
*Supportive studies for the PMO indication: Discontinuation of denosumab*

In the US osteoporosis prevention study 20040132 (in which subjects received denosumab or placebo for 2 years and then were observed for another 2 years without treatment), off-treatment exploratory objectives were to evaluate changes in BMD and bone turnover markers during the off-treatment period, and the safety profile of denosumab during the off-treatment period. Within 12 months of discontinuation of denosumab treatment, BMD returned to approximately baseline levels. Bone turnover markers did no longer remain reduced 3 months after discontinuation of treatment. Discontinuation of denosumab was also investigated in the phase II PK study 20010223 in PMO patients (in this study, some cohorts were retreated with denosumab after a period of placebo treatment, see fig 4) and also in study 20040144 (phase II study in patients with rheumatoid arthritis in which patients were treated for 12 months and then observed, without treatment, for another 12 months). While bisphosphonates bind to the skeleton and are active for several years after discontinuation, denosumab treatment effects disappear within month after drug discontinuation.

Study 20010223: percent change in BMD of lumbar spine from baseline, off-treatment and retreatment denosumab cohorts; cf also fig 4.



Studies 20010223 and 20050233: Lumbar spine BMD percent change from 20010223 baseline (LSM + 95% CI), continuous denosumab cohorts.



Treatment groups are the original assignments in the 20010223 study; All subjects in 20050233 were to receive denosumab 60mg Q6M. Population includes all subjects enrolled in 20050233 with at least one 20010223 baseline and at least one postbaseline measurement. Note: Least squares means and 95% confidence intervals are from a linear model with percent change from 20010223 baseline value as the dependent variable and treatment, geographic location and baseline value as independent variables.

Study 20010223 had a 24 month off-treatment period and study 20040144 had a 12 month treatment period, followed by a 12 month off treatment observation period. In these studies, BMD returned to approximately baseline levels 12 months after the end of the treatment period, and remained at baseline during the subsequent year off treatment (study 20010223 only: see figs 4 and 9). No further decline in BMD was observed. Increases in bone turnover markers above baseline were observed 12 months after the end of the treatment period. Subsequently, bone turnover marker values returned to baseline levels and remained at near baseline levels through 24 months after the discontinuation of treatment.

*Other supportive studies*, for denosumab in general, are the following:

**Study 20040114:** In this study, 111 subjects of both sexes and with solid carcinomas or multiple myeloma with bone metastases and earlier treated with bisphosphonates were enrolled in an open-

label active-controlled study, comparing IV bisphosphonate (pamidronate or zoledronic acid) therapy with denosumab therapy. The primary endpoint was the proportion of subjects with urinary NTX/Cr < 50 nM/mM at week 13. A significantly greater proportion of subjects administered denosumab than with bisphosphonates responded to study treatment.

**Study 20040144** was a 24-month phase II study recruiting 227 patients, with the primary objective to evaluate the efficacy and safety denosumab in decreasing the progression of periarticular bone erosions in subjects with *rheumatoid arthritis* on methotrexate treatment. Study results indicated a positive effect on joint erosions.

**Study 20050134** is an ongoing open phase II multicenter proof-of concept study with denosumab treatment in subjects with relapsed or plateau-phase multiple myeloma.

**Study 20050209** is an ongoing phase III multicenter randomised double-blind placebo-controlled study to determine the treatment effect of denosumab in subjects with nonmetastatic breast cancer treated with an aromatase inhibitor. The primary endpoint is time to first clinical fracture. 2800 subjects are planned to be included in this event-driven Austrian study.

**Study 20060237** is an ongoing phase III study with the primary objective to compare the immunogenicity profiles of denosumab using a pre-filled syringe and denosumab using a vial. The study is including only postmenopausal females with low BMD who have successfully completed study 20050141. No subjects have so far developed denosumab antibodies.

**Study 20060232** is a phase III randomised cross-over open-label North American study, with the primary objective to evaluate the treatment adherence, preference and satisfaction of subjects who receive 60 mg SC injections of denosumab every 6 months, compared to oral 70 mg alendronate weekly. Study patients are postmenopausal women with low BMD (T-scores -2.0 – 4.0). This study is planned to enrol 250 patients and is still ongoing.

- Discussion on clinical efficacy

For the PMO indication efficacy as reduction of the incidence of new vertebral fractures was clearly demonstrated in a placebo controlled study of 3 years duration, as required in the PMO osteoporosis guideline (CPMP/EWP/552/rev 2). A reduction of the incidence of hip fractures and non-vertebral fractures was also demonstrated in the PMO study. Efficacy for denosumab was also demonstrated in another PMO study with regard to change in BMD with alendronate as the active control. BMD at different locations increased more with denosumab than with alendronate during a 12 month treatment period in controlled studies. A continuous gain in lumbar spine BMD was seen during 60 months of denosumab treatment in a long term study. Thus, the pivotal study for this indication was adequately sized, designed and performed and the efficacy results were equal to or better than what has earlier been demonstrated for other drugs approved for the treatment of osteoporosis in postmenopausal women at increased risk of fracture.

In addition, a number of supportive studies provide additional support for the efficacy of denosumab in this indication.

No CHMP guideline exists on the evaluation of medicinal products in the treatment of bone loss associated with hormone ablation and no medicinal product has hitherto been approved for this indication.

The pivotal study 20040138 for denosumab in male HALT indication was properly designed and conducted. Denosumab significantly increased the percentage change in lumbar spine BMD from baseline to month 24 in all subgroups for BMI, age and duration of ADT. The incidence of new vertebral fractures was significantly reduced, at 3 years by 62%, in the denosumab group and BMD relative to placebo at lumbar spine, total hip and femoral neck at month 24 and month 36 was significantly increased (adjusted  $p < 0.0001$ ). Higher withdrawal rate was observed in this study in comparison to study 20030216. The major difference was related to the higher rate of consent withdrawn at the prolongation of the study. Thus, efficacy was clearly shown as vertebral fracture incidence reduction as well as for lumbar spine BMD gain in the pivotal study.

The pivotal study 20040135 for denosumab in female HALT indication was not powered to demonstrate a difference in fracture incidence between groups. In this study, a significant gain in lumbar spine was demonstrated in the denosumab-treated group. Notably few non-Caucasians were included in this study. The applicant's conclusion that efficacy results by ethnic subgroups from the entire denosumab program can be extrapolated to the Study 20040135 patient population is endorsed. Information on the exact duration of aromatase inhibitor therapy in female HALT study was not initially provided. Additionally provided information suggested that median treatment time with aromatase inhibitors before onset of denosumab therapy was evenly distributed between treatment groups and was about 10 months with significant standard deviation of about 11 months. This could suggest that denosumab can be initiated at the start of aromatase inhibitor therapy. The risk of fracture in the populations studied in the female HALT study was not clearly demonstrated to be increased at baseline. The Applicant provided justification based on published information concluding that women on aromatase inhibitor therapy have an increased risk of fractures.

The CHMP Osteoporosis guideline states that in male osteoporosis studies, where a significant effect is demonstrated for gain in lumbar spine also in studies of the same size as this study, such data can bridge to a convincing fracture reduction effect demonstrated in a corresponding population in the opposite sex provided that the male population is also at an increased risk of fractures. In the case of aromatase inhibitor treated women with nonmetastatic breast cancer, these women should by definition be postmenopausal and are therefore considered to be included in the general PMO indication rather than being included in a separate indication.

The incidence of antidenosumab antibodies in all studies was low. Such antibodies could however, if present, possibly affect the efficacy of the drug. However additionally provided data did not give evidence of lower efficacy of denosumab in those patients who developed antibodies to denosumab. In conclusion efficacy of denosumab has been adequately discussed in the clinical part of dossier.

## **Clinical safety**

- Patient exposure

Altogether, more than 13.000 patients have been exposed to denosumab in 31 clinical studies. Of these, approximately 11.000 were postmenopausal women with osteoporosis or low bone mass, 252 were women with breast cancer receiving aromatase inhibitor therapy and 1468 were men receiving androgen deprivation therapy for prostate cancer. The absolute majority of patients, with the exception of patients in dose finding studies, received the dose of 60 mg subcutaneously every 6 months. Long time safety data are available for 5 years or more for 113 patients, 4 years or more for 168 patients, 3 years or more for 4016 patients and 2 years or more for 4625 patients. Studies 20030216, 20040132, 20040135, and 20040138, with 9800 evaluable subjects altogether, provide the primary data sets for discussions of safety for the PMO indication.

- Adverse events

In study 20030216 healing complications for nonvertebral fractures were infrequent in both treatment groups (2 subjects = 0.1% denosumab, 3 subjects = 0.1% placebo). The majority of all fractures in all clinical studies healed without complications in the denosumab as well as in the placebo treatment group. No cases of osteonecrosis of the jaw were seen in the clinical studies. There was no overfrequency of cardiovascular events or abnormal ECGs in denosumab treated patients. The evaluation of the type and amount of immunoglobulins (Igs A, G and M) in studies 20010124 and 20030148 did not show any effect of denosumab on Ig production. In the US prevention PMO study 20040132 (332 patients included), more subjects receiving denosumab developed an infection that required hospitalisation compared with subjects receiving placebo (4.9% vs 0.6%). In the dose finding study 20010223 (406 patients dosed with study drug), infection resulting in hospitalisation was reported in 3.2% of subjects receiving denosumab compared with 0% of subjects receiving placebo or alendronate. The types of SAEs of infections reported among the denosumab-treated subjects were characterized by common infections (e. g. pneumonia, urinary tract infection, cellulitis, appendicitis, and diverticulitis) and the events were not distinguishable as opportunistic infections. The serious infection events tended to occur 6 to 12 months after the initial administration of denosumab. This observed imbalance in hospitalizations in these two studies (20040132 and 20010223) was not seen in

any other denosumab studies. When the 4 pivotal studies were pooled in the Combined safety analysis set, the small differences noted in individual studies in certain SAEs were not evident. The incidences of AEs of acute renal events was 1.3% in both denosumab and placebo treatment groups in the Combined safety analysis set (including data from all clinical denosumab studies). Patients with severe renal impairment or end-stage renal disease should be adequately supplemented with calcium and vitamin D, and be adequately supervised for serum calcium levels, when administered denosumab.

- Serious adverse event/deaths/other significant events

Fatalities in the denosumab and placebo occurred with the same frequencies in the PMO as well as in the HALT studies. In the PMO study 20040132, significantly more patients in the denosumab group than in the placebo group reported SAEs, particularly osteoarthritis and pneumonia. In the other PMO studies, and in the combined PMO safety dataset, there were no significant differences in SAEs between treatment groups. In the Primary HALT Safety Analysis Set, combining data from the two HALT studies, the overall incidence of SAEs was 31.6% in the denosumab group and 27.6% in the placebo group. No pattern was observed with respect to the types of SAEs that were reported with greater incidence in each treatment group. The only SAE that occurred with  $\geq 1\%$  difference in incidence was bone metastases, which occurred in 3 subjects (0.3%) in the denosumab group and 11 subjects (1.3%) in the placebo group.

No single type of malignancy was reported at an increased frequency in clinical studies with denosumab. In the male HALT study 20040138, in contrast to in other clinical studies, there was a higher all over frequency of neoplasm AEs in the denosumab group (16.3%), compared to placebo (11.9%). In this study, new primary malignancies were reported with similar frequency. The higher incidence of neoplasm AEs in the denosumab group in study 20040138 was mainly explained by a higher incidence of non-specific benign conditions, in particular basal cell cancers, in this treatment group.

Denosumab treated patients in the male HALT study 20040138 had a significantly higher incidence of *cataract* than patients in the control group (4.7% in the denosumab group and 1.2% in the placebo group). On-study AEs of cataracts in the denosumab group were more prevalent in the first year of study than in subsequent years, with 18 of 34 subjects (52.9%) with cataracts reporting events in year 1 compared with 17.6% of cataract subjects reporting events in year 3. The subject incidence of cataracts reported in the third study year for the denosumab group (1.0%) approximated that reported for the placebo group (0.7%). Cataract development and progression will prospectively be studied in a prospective, randomized, placebo-controlled study in men with nonmetastatic prostate cancer receiving denosumab for bone loss due to androgen-deprivation therapy.

- Laboratory findings

*Hypocalcaemia* was mild and transient in clinical denosumab studies when denosumab was administered together with vitamin D and calcium. In phase 1 studies in healthy volunteers who were not supplemented with calcium or vitamin D, the changes in serum calcium were generally characterized by transient decreases of approximately 3 - 8% observed within the first 2 weeks after denosumab administration. In the clinical studies, where patients were prescribed calcium and vitamin D, 5 subjects (3 denosumab-treated, 2 placebo-treated) in the denosumab PMO studies received IV calcium while on study. Four subjects treated with denosumab received IV calcium for hypocalcaemia in studies of subjects with advanced cancer (1 in study 20040176 and 3 in study 20050134), in which much higher doses of denosumab are used than in the PMO and HALT studies. *Thyroid function tests, vitamin D- or PTH* values were not prospectively recorded in the pivotal studies. In study 20010223, compensatory increases in median changes from baseline for *iPTH* occurred (46% to 82%) during the first month following dosing. The magnitude of these increases diminished steadily to near-baseline levels at month 12, when they ranged from 11% below baseline to 22% above baseline for the denosumab cohorts. In the HALT safety population in clinical studies, there was an almost 3-fold greater frequency of hypothyroidism in the denosumab compared to the placebo group.

The applicant provided additional study data on AEs of hypothyroidism and on thyroid function tests in clinical studies. It is concluded that it is unlikely that denosumab should be the cause of hypothyroidism. Consequently, hypothyroidism at present does not warrant inclusion in the RMP.

- Bone biopsy studies

A total of 237 bone biopsies were evaluable for histology, after 12 months of treatment in studies 20010223 and 20050234, and after 24 and/or 36 months of treatment in study 20030216. Bone biopsies were obtained from substudy participants in clinical studies 20010223 (37 evaluable samples), 20030216 (115 evaluable samples), and 20050234 (36 evaluable samples) to evaluate histologic and histomorphometric changes resulting from denosumab administration. In these substudies, the bone tissue looked normal: normal lamellar bone, normal mineralization, and normal osteoid without evidence of pathologic findings such as woven bone or marrow fibrosis. In study 20030216, 5 subjects in the denosumab-treated group at month 24 did not have osteoid that could be visualized. Histomorphometric evaluation demonstrated lower osteoclast cell counts compared with placebo or alendronate, as indicated by decreased surface- and length-based osteoclast numbers. Indicators associated with bone formation also showed decreases with denosumab compared with placebo or alendronate, with lower osteoblast-osteoid interface, osteoid surface, and osteoid width. MicroCT analysis: Bone biopsies obtained in the substudy of study 20030216 were further evaluated by microCT analysis at month 24, 68 biopsies (31 denosumab, 37 placebo); month 36, 45 biopsies (21 on denosumab, 24 on placebo). After 24 or 36 months of treatment, several trabecular-related structural parameters, including trabecular number, trabecular separation, bone volume, and structural model index, showed a trend of improvement compared with placebo. A significant decrease in cortical porosity and an increase in cortical bone mineral density was observed in the denosumab group at 24 months.

- Safety in special populations

Study 20040245 evaluated denosumab in 42 subjects with impaired renal function. Clinically significant hypocalcemia was observed in 3 (1 with mild and 2 with severe renal impairment) of the first 19 subjects enrolled. Two of the 3 events were reported as SAEs; both subjects received IV calcium. None of the 3 subjects with clinically significant hypocalcemia were receiving both calcium and vitamin D supplementation, and 2 of them had severe renal impairment and secondary hyperparathyroidism. Subsequent to these AEs, the study protocol was amended to minimize the potential for development of hypocalcemia. Two subjects with end stage renal disease who were enrolled under the amended protocol had transient, asymptomatic decreases in albumin-adjusted serum calcium concentration. No other notable safety findings were observed to be associated with denosumab administration relevant to renal impairment in the study population.

Calcium evaluations by baseline creatinine clearance were performed in the Primary PMO safety analysis set as well as in the Primary PMO safety analysis set. Serum calcium assessments and AEs representing potential clinical manifestations of hypocalcemia were evaluated by baseline creatinine clearance to provide an indication of whether denosumab administration is associated with greater decreases in serum calcium in subjects with impaired renal function. No clinically important differences between groups were seen.

Subgroup analyses for sex, race, age and BMI did not show differences in safety profiles between groups. Some differences in frequency of AES were noted between different geographic regions but these differences were the same in the placebo group as in the denosumab group.

Patients with hepatic impairment were not studied. Denosumab was not administered to children or during pregnancy.

- Safety related to drug-drug interactions and other interactions

No drug/drug interaction studies have been conducted with denosumab. The interaction potential is considered low and the lack of formal interaction studies is acceptable.

- Discontinuation due to adverse events

The number of patients discontinuing investigational product was not higher in the denosumab group than in the placebo group in any of the pivotal studies for PMO or HALT (see tables below).

AEs leading to investigational product discontinuation of  $\geq 4$  subjects (0.1%) in either treatment group by Preferred Term in descending order of frequency, Primary PMO safety analysis set.

Preferred Term	Study 20040132		Study 20030216		Overall	
	Placebo (N=165) n (%)	Denosumab 60 mg Q6M (N=164) n (%)	Placebo (N=3876) n (%)	Denosumab 60 mg Q6M (N=3886) n (%)	Placebo (N=4041) n (%)	Denosumab 60 mg Q6M (N=4050) n (%)
Number of subjects reporting adverse events leading to investigational product discontinuation	6 (3.6)	5 (3.0)	202 (5.2)	192 (4.9)	208 (5.1)	197 (4.9)
Breast cancer	0 (0.0)	0 (0.0)	10 (0.3)	20 (0.5)	10 (0.2)	20 (0.5)
Back pain	0 (0.0)	0 (0.0)	10 (0.3)	6 (0.2)	10 (0.2)	6 (0.1)
Constipation	0 (0.0)	0 (0.0)	6 (0.2)	6 (0.2)	6 (0.1)	6 (0.1)
Headache	0 (0.0)	0 (0.0)	4 (0.1)	6 (0.2)	4 (0.1)	6 (0.1)
Nausea	0 (0.0)	1 (0.6)	1 (<0.1)	5 (0.1)	1 (<0.1)	6 (0.1)
Colon cancer	0 (0.0)	0 (0.0)	4 (0.1)	5 (0.1)	4 (0.1)	5 (0.1)
Diarrhoea	0 (0.0)	0 (0.0)	4 (0.1)	5 (0.1)	4 (0.1)	5 (0.1)
Cerebrovascular accident	0 (0.0)	0 (0.0)	3 (0.1)	5 (0.1)	3 (0.1)	5 (0.1)
Fatigue	0 (0.0)	0 (0.0)	2 (0.1)	5 (0.1)	2 (<0.1)	5 (0.1)
Gastric cancer	0 (0.0)	0 (0.0)	1 (<0.1)	5 (0.1)	1 (<0.1)	5 (0.1)
Asthenia	0 (0.0)	0 (0.0)	3 (0.1)	4 (0.1)	3 (0.1)	4 (0.1)
Muscle spasms	1 (0.6)	0 (0.0)	2 (0.1)	4 (0.1)	3 (0.1)	4 (0.1)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	1 (<0.1)	4 (0.1)	1 (<0.1)	4 (0.1)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)	4 (0.1)
Polymyalgia rheumatica	0 (0.0)	0 (0.0)	4 (0.1)	3 (0.1)	4 (0.1)	3 (0.1)
Lumbar vertebral fracture	0 (0.0)	0 (0.0)	12 (0.3)	2 (0.1)	12 (0.3)	2 (<0.1)
Femur fracture	0 (0.0)	0 (0.0)	5 (0.1)	2 (0.1)	5 (0.1)	2 (<0.1)
Thoracic vertebral fracture	0 (0.0)	0 (0.0)	8 (0.2)	1 (<0.1)	8 (0.2)	1 (<0.1)
Rheumatoid arthritis	0 (0.0)	0 (0.0)	4 (0.1)	1 (<0.1)	4 (0.1)	1 (<0.1)
Resorption bone increased	0 (0.0)	0 (0.0)	5 (0.1)	0 (0.0)	5 (0.1)	0 (0.0)

Page 2 of 2

N = Number of subjects who received  $\geq 1$  dose of investigational product

n = Number of subjects reporting  $\geq 1$  event

Includes only treatment-emergent adverse events.

Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 11.0.

AEs leading to investigational product discontinuation of  $\geq 2$  subjects (0.2%) in either treatment group by Preferred Term in descending order of frequency, Primary HALT safety analysis set.

Preferred Term	Study 20040135		Study 20040138		Overall	
	Placebo (N=120) n (%)	Denosumab 60 mg Q6M (N=129) n (%)	Placebo (N=725) n (%)	Denosumab 60 mg Q6M (N=731) n (%)	Placebo (N=845) n (%)	Denosumab 60 mg Q6M (N=860) n (%)
Number of subjects reporting adverse events leading to investigational product discontinuation	5 (4.2)	2 (1.6)	47 (6.5)	49 (6.7)	52 (6.2)	51 (5.9)
Metastases to bone	1 (0.8)	2 (1.6)	9 (1.2)	8 (1.1)	10 (1.2)	10 (1.2)
Metastases to liver	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.3)	0 (0.0)	3 (0.3)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	3 (0.3)
Cardiac arrest	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.3)	1 (0.1)	2 (0.2)
Fatigue	1 (0.8)	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.1)	2 (0.2)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.3)	1 (0.1)	2 (0.2)
Malignant neoplasm progression	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Metastases to spine	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)
Depression	0 (0.0)	0 (0.0)	2 (0.3)	1 (0.1)	2 (0.2)	1 (0.1)
Nausea	1 (0.8)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)
Asthenia	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)	0 (0.0)
Resorption bone increased	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.2)	0 (0.0)
Rib fracture	1 (0.8)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)

Page 2 of 2

N = Number of subjects who received  $\geq 1$  dose of investigational product

n = Number of subjects reporting  $\geq 1$  event

Includes only treatment-emergent adverse events.

Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA version 11.0.

- Post marketing experience

Denosumab has not been marketed in any part of world.

- Discussion on clinical safety

A sufficient number of patients have been exposed to the drug in clinical studies but data from long time exposure are still limited. Some extension or follow-up phases as well as some clinical trials are currently ongoing.

Overall analysis of death and non-fatal SAEs did not indicate significant differences between denosumab and placebo.

RANKL inhibition by denosumab theoretically can be linked to an increased incidence of infectious complications and malignancies during denosumab treatment. Although an increased incidence of cellulitis was seen with denosumab treatment in the PMO pivotal study and an increased incidence of diverticulitis in the male HALT study, there was no overrepresentation of infectious complications in the overall safety data analysis set. Opportunistic infections were not overrepresented among patients treated with denosumab. No single type of malignancy was reported at an increased frequency in clinical studies with denosumab. However, there was a higher overall frequency of neoplasm AEs in the denosumab group than in the placebo group in the male HALT study. The higher incidence of neoplasm AEs in the denosumab group in study 20040138 was mainly explained by a higher incidence of non-specific benign conditions, in particular basal cell cancers, in this treatment group.

Delayed fracture healing and osteonecrosis of the jaw were other areas that have been prospectively monitored in clinical studies with denosumab, so far with no confirmed cases identified. Hitherto, denosumab has not shown any tendency to cause an increased incidence of cardiovascular or renal events. Denosumab can cause hypocalcaemia, especially in patients with renal impairment. This has however not been a significant problem in clinical studies, with concomitant oral administration of vitamin D and calcium. The incidence of cataract was increased in the male HALT study. Cataract development and progression will prospectively be studied in a prospective, randomized, placebo-controlled study in men. Data on thyroid function were not prospectively recorded in the pivotal studies. In the HALT safety population, there was an almost 3-fold greater frequency of hypothyroidism in the denosumab compared to the placebo group. The applicant provided additional study data on AEs of hypothyroidism and on thyroid function tests in clinical studies. It is concluded that it is unlikely that denosumab should be the cause of hypothyroidism.

In conclusion, the Applicant has appropriately addressed safety issues of denosumab in clinical part of dossier.

#### Additional safety information

The MAH reported to the Rapporteur on 11 February 2010 a case of osteonecrosis of the jaw (ONJ) from an open label extension trial in postmenopausal osteoporosis, and then provided a further report to the Rapporteur on this case on 12 February. The patient was an 83 year old female included in the PMO study 20030216 in January 2008 and then in the extension trial 20060289. Her medical history included breast cancer, cardiovascular disease, dementia, and repeated dental procedures. Mandibular osteomyelitis was first reported in August 2009 and adjudicated ONJ was reported in February 2010 and the case was discussed by the CHMP in February 2010.

Because of the nature of the lesions reported and the course of the complication, plus the relation in time to the denosumab treatment, this reported case of ONJ was regarded as possibly related to denosumab treatment. This first reported case of ONJ was considered to confirm the risk for ONJ and warrant an update of the SPC and PL and also an update of the RMP before placing the product on the market.

On 17 February, Amgen submitted to the EMA a data summary from study 20050103, "A Randomized, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer". Integrated efficacy and safety data from the three denosumab pivotal studies in advanced cancer (Studies 20050136, 20050244 and 20050103) were later provided and also subject listings and narratives for cases of ONJ, cerebrovascular accidents and new primary malignancies.

A first preliminary analysis of the combined data set from these three oncology studies arouse a suspicion of an overrepresentation of osteonecrosis, ONJ and hypocalcaemia in the denosumab

treatment group compared to the zoledronic acid treatment group. The findings in these oncology studies are however difficult to extrapolate to Prolia since the dose of denosumab in these studies was 13 times the dose of Prolia and the study populations different to patient populations in Prolia studies.

The data were assessed by the Rapporteurs and discussed by the PhVWP and CHMP in March 2010. The benefit risk balance for Prolia was concluded to remain positive. Safety and efficacy data for denosumab in the treatment of advanced cancer will be thoroughly assessed in a coming submission of complete study data in a marketing authorisation application for denosumab in this indication.

Furthermore it was concluded that amendments to the Product Information and to the Risk Management Plan for Prolia should be undertaken. The updated Prolia RMP should include a discussion of the possible risk of increase of ONJ in patient previously treated with bisphosphonates before start of denosumab treatment as well as information on ONJ cases reported in the oncology clinical trials. Cases of ONJ identified in the postmarketing epidemiological studies in the US and Scandinavian countries should be identified continuously and reported expeditiously to the authorities. Active surveillance by setting up Sentinel sites combined with follow-up questionnaire should also be considered and the sentinels site feasibility should be added in the PV plan for ONJ. Furthermore, osteonecrosis outside the jaw should be added as a potential risk in the safety specification and Pharmacovigilance activities should be specified. A detailed updated RMP according to this should be provided by the applicant by 15.05.2010.

## **2.6 Pharmacovigilance**

### **Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### **Risk Management Plan**

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety issue	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
<b>Identified Risks</b>		
Hypocalcemia	<p>Routine PV activities, including:</p> <ul style="list-style-type: none"> <li>Cumulative reporting in periodic reports and assessment of events from ongoing clinical trials and spontaneous reports</li> </ul> <p>Proactive surveillance:</p> <ul style="list-style-type: none"> <li>Targeted follow-up of postmarketing reports using a focused questionnaire</li> </ul> <p>Identification of rates of serious hypocalcemia in postmarketing safety observational study, including events in patients with low calcium and/or low vitamin D prior to the start of therapy</p> <ul style="list-style-type: none"> <li>Cumulative analysis of reports of hypocalcemia in PSURs</li> </ul>	<p>4.2 Posology and Method of Administration Patients must be adequately supplemented with calcium and vitamin D.</p> <p>4.3 Contraindications Hypocalcemia</p> <p>4.4 Special Warnings and Precautions for Use Adequate intake of calcium and vitamin D is important in all patients. Hypocalcemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients with severe renal impairment (creatinine clearance &lt; 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcemia. Clinical monitoring of calcium levels is recommended in patients predisposed to hypocalcemia.</p> <p>4.8 Undesirable Effects Tabulated Summary of Adverse Reactions: Hypocalcemia is listed under metabolism and nutrition disorders as very rare. Description of Selected Adverse Reactions, Hypocalcemia: In 2 phase 3 placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4050) of patients had declines of serum calcium levels (less than 1.88 mmol/L) following denosumab administration. Declines of serum calcium levels (less than 1.88 mmol/L) were not reported in the 2 phase 3 placebo-controlled clinical trials in patients receiving hormone ablation. Other Special Populations: In clinical studies, patients with severe renal impairment (creatinine clearance &lt; 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcemia in the absence of calcium supplementation. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis.</p> <p>5.3 Preclinical Safety Data Calcium levels were transiently decreased and parathyroid levels transiently increased in ovariectomized monkeys treated with denosumab.</p>
Skin Infections Leading to Hospitalization	<p>Routine PV activities, including:</p> <ul style="list-style-type: none"> <li>Assessment of events reported from ongoing clinical trials and spontaneous reports</li> </ul> <p>Proactive surveillance:</p> <ul style="list-style-type: none"> <li>Targeted follow-up of postmarketing reports using a focused questionnaire (Annex 12) to identify risk factors, identify bacterial</li> </ul>	<p>4.4 Special Warnings and Precautions for Use Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalization. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.</p> <p>4.8 Undesirable Effects Tabulated Summary of Adverse Reactions: Cellulitis is listed under infections and infestations as uncommon.</p>

	<p>pathogens, and to determine clinical outcome</p> <ul style="list-style-type: none"> <li>• Identification of event rates in postmarketing safety observational study to further elucidate risks, seriousness, nature, outcome, and incidence</li> </ul> <p>Cumulative analysis in PSURs</p>	<p>Description of Selected Adverse Reactions, Skin Infections: In phase 3 placebo-controlled clinical trials, the overall incidence of skin infections was similar in the placebo and the denosumab groups in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4041] vs. denosumab [1.5%, 59 out of 4050]) and in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] vs. denosumab [1.4%, 12 out of 860]). Skin infections leading to hospitalization were reported in 0.1% (3 out of 4041) of postmenopausal women with osteoporosis receiving placebo vs 0.4% (16 out of 4050) of women receiving denosumab. 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 denosumab (0.6%, 5 out of 860) groups in the breast and prostate cancer studies.</p>
--	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

ONJ	<p>Routine PV activities, including:</p> <ul style="list-style-type: none"> <li>Assessment of events reported from ongoing clinical trials and spontaneous reports</li> </ul> <p>Proactive surveillance:</p> <ul style="list-style-type: none"> <li>Targeted follow-up of postmarketing reports using a focused questionnaire</li> <li>Ongoing adjudication in clinical trials</li> <li>Identification of events in postmarketing safety observational study to further elucidate risk and incidence</li> </ul> <p>Cumulative analysis in PSURs including annual reports of the postmarketing safety observational study</p>	<p><u>4.4 Special Warnings and Precautions for Use</u></p> <p>Osteonecrosis of the jaw (ONJ) has been reported in patients treated with denosumab or bisphosphonates, another class of anti-resorptive agents. Most cases have been in cancer patients; however some have occurred in patients with osteoporosis.</p> <p>ONJ has been reported rarely in clinical studies in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis.</p> <p>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, comorbid disorders (eg, pre-existing dental disease, anaemia, coagulopathy, infection) and previous treatment with bisphosphonates.</p> <p>A dental examination with appropriate preventive dentistry should be considered prior to treatment with denosumab in patients with concomitant risk factors. While on treatment, these patients should avoid invasive dental procedures if possible.</p> <p>Good oral hygiene practices should be maintained during treatment with denosumab. For patients who develop ONJ while on denosumab therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with denosumab, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation.</p> <p><u>4.8 Undesirable Effects</u></p> <p><i>Description of Selected Adverse Reactions, Osteonecrosis of the Jaw:</i></p> <p>In the osteoporosis clinical trial program (8710 patients treated <math>\geq</math> 1 year), ONJ was reported rarely with denosumab.</p>
<b>Potential Risks</b>		
Fracture Healing Complications	<p>Routine PV activities, including:</p> <ul style="list-style-type: none"> <li>Assessment of events reported from ongoing clinical trials and spontaneous reports</li> </ul> <p>Proactive surveillance:</p> <ul style="list-style-type: none"> <li>Targeted follow-up of postmarketing reports using a focused questionnaire (Annex 12)</li> <li>In ongoing Study 20050209, information on fracture healing is captured for all fracture adverse</li> </ul>	<p><u>5.3 Preclinical Safety Data</u></p> <p>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.</p>

	<p>events using a specific CRF</p> <ul style="list-style-type: none"> <li>• Identification of event rates in postmarketing safety observational study</li> <li>• Cumulative analysis in PSURs</li> </ul>	
Infection	<p>Routine PV activities, including:</p> <ul style="list-style-type: none"> <li>• Assessment of serious adverse events of infection from ongoing clinical trials and spontaneous reports</li> <li>• Proactive surveillance:</li> <li>• Targeted follow-up postmarketing reports using a focused questionnaire (Annex 12) to identify risk factors and causative pathogen and to determine clinical outcome</li> <li>• Identification of rates of serious adverse events of infection in postmarketing safety observational study to further elucidate risk and incidence</li> </ul> <p>Cumulative analysis of serious adverse events of infection in PSURs</p>	<p>4.8 Undesirable Effects</p> <p>Tabulated Summary of Adverse Reactions: Listed under infections and infestations are diverticulitis (uncommon), upper respiratory tract infection (common), urinary tract infection (common), and ear infection (uncommon). Description of Selected Adverse Reactions, Diverticulitis: In a single phase 3 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 or in women undergoing aromatase inhibitor therapy for nonmetastatic breast cancer.</p>
Hypersensitivity Reactions	<p>Routine PV activities, including:</p> <ul style="list-style-type: none"> <li>• Assessment of events reported from ongoing clinical trials and spontaneous reports</li> </ul> <p>Proactive surveillance:</p> <ul style="list-style-type: none"> <li>• Targeted follow-up of postmarketing reports using a focused questionnaire (Annex 12)</li> </ul> <p>Cumulative analysis in PSURs</p>	<p>4.3 Contraindications</p> <p>Hypersensitivity to the active substance or to any of the excipients</p>
Cataracts in Men With Prostate Cancer Receiving ADT	<p>Routine PV activities, including:</p> <ul style="list-style-type: none"> <li>• Assessment of events reported from ongoing clinical trials and spontaneous reports</li> </ul> <p>Proactive surveillance:</p> <p>A prospective, randomized, placebo-controlled study is being conducted to further evaluate the incidence of cataracts in men receiving denosumab concurrently with ADT for prostate cancer</p>	<p>4.8 Undesirable Effects</p> <p>Tabulated Summary of Adverse Reactions: Cataracts are listed under eye disorders as common. Description of Selected Adverse Reactions, Cataracts: In a single phase 3 placebo-controlled clinical trial in patients with prostate cancer receiving 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.</p>
Cardiovascular Risk	<p>Routine PV activities, including:</p> <p>Assessment of events reported from ongoing clinical trials and spontaneous reports</p>	<p>No risk minimization activities given the lack of evidence for cardiovascular risk</p> <p>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</p>

		<p>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. Cardiovascular adverse events will continue to be assessed in clinical trials.</p> <p>If a safety risk for cardiovascular events is identified in the postmarketing setting, appropriate risk minimization activities will be implemented.</p>
Malignancy	<p>Routine PV activities, including:</p> <ul style="list-style-type: none"> <li>Assessment of events reported from ongoing clinical trials and spontaneous reports</li> </ul> <p>Proactive surveillance:</p> <ul style="list-style-type: none"> <li>Identification of rates of new primary malignancy in postmarketing safety observational study</li> <li>Cumulative analysis in PSURs</li> <li>In ongoing Studies 20050209, 20050103, 20050136, 20050147, 20050244, and 20060359, information on new primary malignancies is being captured.</li> </ul> <p>Information on progression of malignancy will be obtained from ongoing studies in advanced cancer (Studies 20050136, 20050244, 20050103, 20050147, and 20060359)</p>	<p>No risk minimization activities proposed given the lack of evidence for malignancy associated with denosumab.</p> <p>Nonclinical studies have examined a wide range of human tumor types and indicate no carcinogenic risk associated with RANKL inhibition. Results from the large pivotal studies demonstrate no increased risk of malignancy in denosumab-treated subjects, and the incidence of malignancies was balanced between the denosumab and comparator treatment groups. There was no evidence of progression of malignancy associated with denosumab administration in subjects with nonmetastatic prostate cancer and breast cancer.</p> <p>Malignancy will continue to be followed in ongoing studies and results will be reported.</p> <p>If a safety risk for malignancy is identified in the postmarketing setting from clinical trials or spontaneous reports, appropriate risk minimization activities will be implemented.</p>
Immunogenicity	<p>Proactive surveillance:</p> <ul style="list-style-type: none"> <li>Testing for antidenosumab antibodies in all ongoing clinical trials</li> <li>Evaluation of relationship between development of antidenosumab antibodies and changes in adverse event profiles, changes in pharmacodynamic profiles, or delayed or missed doses in clinical trials</li> <li>Evaluation of relationship between development of antidenosumab antibodies and hypersensitivity reaction adverse events in clinical trials</li> </ul> <p>During the postmarketing period, testing for antidenosumab antibodies will be available for any patient on denosumab at the request of the treating physician</p>	<p>5.1 Pharmacodynamic Properties</p> <p>Immunogenicity: In clinical studies, neutralizing antibodies have not been observed for denosumab. Using a sensitive immunoassay, &lt; 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.</p>
Atypical Fracture	<ul style="list-style-type: none"> <li>Routine PV activities, including assessment of events reported</li> </ul>	<p>No risk minimization activities proposed.</p> <p>No atypical fractures have been observed with</p>

	<p>from ongoing clinical trials and spontaneous reports.</p> <ul style="list-style-type: none"> <li>• Proactive surveillance:</li> <li>• Targeted follow-up of postmarketing reports using a focused questionnaire (Annex 12)</li> <li>• Identification of rates of atypical fracture from postmarketing safety observational studies</li> <li>• Data on atypical fracture from clinical studies in subjects receiving long-term treatment with denosumab will be summarized in CSRs and PSURs (Studies 20050233, 20080537, 20050209, and 20060289).</li> </ul>	<p>denosumab treatment up to 6 years' duration in the clinical program, and no causal relationship has been established between suppression of bone remodeling and occurrence of atypical fractures. If a safety risk for atypical fracture is identified in the postmarketing setting, appropriate risk minimization activities will be implemented.</p>
--	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Osteonecrosis outside the jaw (avascular necrosis)	Routine PV activities, including assessment of events reported from ongoing clinical trials and spontaneous reports, including cumulative analysis in PSURs.	No risk minimization activities proposed. There is no known biological mechanism by which denosumab would impair blood supply, the known mechanism for osteonecrosis outside the jaw (avascular necrosis). Event rates are low and the affected subjects had risk factors for the development of osteonecrosis.
<b>Important Missing or Limited Information</b>		
Pregnant Women	<p>Routine PV activities, including:</p> <ul style="list-style-type: none"> <li>• Pregnancy registry based on Amgen Pregnant Surveillance System established on the basis of Spontaneous Reporting Safety System. All patients who report having a pregnancy during denosumab treatment will be followed to observe birth outcomes</li> </ul> <p>Proactive surveillance: A prospective, observational, matched-cohort study will be conducted in pregnant women in the US who are exposed to denosumab during pregnancy and of their live born children up to one year of age; includes matched denosumab-unexposed group</p>	<ul style="list-style-type: none"> <li>• 4.6 Fertility, Pregnancy and Lactation</li> <li>• Pregnancy: There are no adequate data from the use of denosumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In genetically engineered mice in which RANK ligand (RANKL) has been turned off by gene removal (a “knockout mouse”), studies suggest absence of RANK ligand (the target of denosumab) could interfere with the development of lymph nodes in the fetus and could lead to postnatal impairment of dentition and bone growth. Denosumab is not recommended for use in pregnant women.</li> <li>• 5.3 Preclinical Safety Data</li> <li>• At exposures up to 100-fold higher than the human exposure, denosumab showed no evidence of impaired female fertility and harm to the fetus in cynomolgus monkeys in development toxicity studies. In preclinical studies conducted in knockout mice lacking RANK or RANKL, impairment of lymph node formation was observed in the fetus. Knockout mice 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. The reversibility of the effects of OPG-Fc has not been examined.</li> </ul>
Lactating Women	Routine. No additional PV activities.	<p>4.6 Pregnancy and Lactation</p> <p>Lactation: It is unknown whether denosumab is excreted in human milk. Knockout mouse studies suggest absence of RANK ligand during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation postpartum. A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of denosumab therapy to the woman.</p> <p>5.3 Preclinical Safety Data</p>

		An absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) was also observed in knockout mice lacking RANK or RANKL.
Children, Including Off-label Pediatric Use	<p>Routine PV activities, including cumulative reports in PSURs</p> <p>Proactive surveillance:</p> <ul style="list-style-type: none"> <li>Monitoring for off-label use in children through postmarketing surveillance and from drug utilization patterns obtained from the postmarketing safety observational study</li> <li>Study 20090695 will collect data on pediatric off-label use</li> </ul> <p>Clinical trial activities as described in the PIP</p>	<p>4.2 Posology and Method of Administration</p> <p>Pediatric Population: Denosumab is not recommended in pediatric patients (age &lt; 18) as the safety and efficacy of denosumab in these patients have not been established.</p> <p>5.2 Pharmacokinetic Properties</p> <p>Special Populations: The pharmacokinetic profile in pediatric populations has not been assessed.</p> <p>5.3 Preclinical Safety Data</p> <p>Knockout mice 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. The reversibility of the effects of OPG-Fc has not been examined. 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.</p>
Potential Adult Off-label Use	<ul style="list-style-type: none"> <li>Routine PV activities, including cumulative reports in PSURs</li> </ul> <p>Proactive surveillance:</p> <ul style="list-style-type: none"> <li>Monitoring for off-label use in the postmarketing safety observational study</li> </ul> <p>Study 20090695 will collect data on off-label use</p>	<p>4.1 Therapeutic indications:</p> <p>Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Denosumab significantly reduces the risk of vertebral, nonvertebral and hip fractures.</p> <p>Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures.</p>
Use in Patients with Hepatic Impairment	Routine PV activities, including evaluation in the PSUR of hepatic adverse events under the hepatobiliary system organ class	<p>4.2 Posology and Method of Administration</p> <p>Patients with Hepatic Impairment: The safety and efficacy of denosumab have not been studied in patients with hepatic impairment.</p> <p>5.2 Pharmacokinetic Properties</p> <p>Special Populations: 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.</p>

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

### 3.1 Overall conclusions, risk/benefit assessment and recommendation

## Quality

Based on the submitted data, the marketing authorisation application for Prolia is recommended for approval based on quality grounds.

## Non-clinical pharmacology and toxicology

*In vitro* studies showed that denosumab binds to huRANKL with high affinity and specificity. No binding to TNF- $\alpha$ , TNF- $\beta$ , TRAIL or CD40L was observed. In vivo, denosumab significantly reduced biochemical bone turnover markers in ovariectomized cynomolgus monkeys which was associated with increased trabecular and cortical bone volume and density and increased biomechanical parameters of bone strength. Hence, denosumab has demonstrated efficacy in a relevant model for PMO. No disease model for hormone ablation therapy in males has been used. However, clinical studies in males are available which supersede the lack of non-clinical data. Safety pharmacology studies revealed no major cause for concern. Considering the mechanism of action of denosumab, potential effects on immunomodulation and immunosuppression cannot be ruled out.

Repeated dose toxicity studies in monkey did not indicate any specific target organ toxicity of denosumab. Reproduction toxicity studies in monkey did not show any teratogenic potential, but data from RANKL knock out mouse show that the RANK/RANKL system is essential for the development of lactating mammary gland. However, available studies do not permit to rule out a potential for adverse interactions with the immune system. Because of the immunogenicity of denosumab, leading to development of anti-drug antibodies in most animals in the preclinical studies, the preclinical toxicity profile may not have been fully identified.

## Efficacy

The efficacy of denosumab in postmenopausal osteoporosis was demonstrated in the pivotal **study 20030216** in postmenopausal women at high risk of fracture. A significant risk reduction was demonstrated for the incidence of new vertebral fractures. RR reductions at month 36 was 68%. A reduction of the incidence of hip fractures and non-vertebral fractures as well as a significant gain in lumbar spine BMD were also shown in this study. Risk reduction for hip fracture during the study period (40 %) in this study was similar to what has previously been demonstrated for zoledronic acid. The study was designed and conducted in accordance with the CHMP Osteoporosis guideline (CPMP/EWP/552/rev 2). Subgroup analyses did not reveal insignificant treatment effect in any of the subgroups analysed.

The primary efficacy results in the pivotal PMO study 20030216 were questioned as an inspection at the CRO responsible for assessment of X-rays evaluation status revealed that change of fracture status from 'incident' to 'prevalent' could be done without adjudication which could possibly have influenced the study result. After alternative analyses on basis of different readings of these fracture data it was concluded that the changes made did not significantly influence the primary efficacy parameter outcome.

Efficacy for denosumab was also demonstrated in a PMO study with regard to BMD with alendronate as the active control: BMD at different locations increased significantly more with denosumab than with alendronate during a 12 month treatment period. A continuous gain in lumbar spine BMD was seen during 60 months of denosumab treatment in a long time study. After discontinuation of denosumab, BMD and bone turnover markers returned to baseline within 1-2 years after denosumab discontinuation, in contrast to alendronate treated group.

The incidence of antidenosumab antibody formation was low; no neutralising antibodies were detected and efficacy was demonstrated after retreatment with denosumab in one study cohort.

No CHMP guideline exists on the evaluation of medicinal products in the *treatment of bone loss associated with hormone ablation in women with breast cancer* and no medicinal product has hitherto been approved for this indication.

The pivotal study for denosumab in this category of patients, **study 20040135** was not powered to demonstrate a difference in fracture incidence between groups. These women had a moderately decreased lumbar spine BMD at baseline (-1.1), low numbers of prevalent vertebral fractures at baseline (8 and 4 % in treatment groups). Lumbar spine BMD increase from baseline to month 12 (primary endpoint) was significantly increased in the denosumab group, as compared to placebo ( $p < 0.0001$ ). Secondary endpoints (BMD at other locations) also increased significantly more in the denosumab group. The study was adequately designed and conducted and drop out rates were reasonable. In this small study, a significant gain in lumbar spine was demonstrated in the denosumab-treated group, of the same magnitude that had been demonstrated in larger denosumab studies in other indications and therefore it was considered reasonable by the CHMP to extrapolate to fracture results from these studies. The female HALT population would be considered by definition as postmenopausal. Treatment with an aromatase inhibitor is a clear risk factor in this group of patients and the applicant has demonstrated an effect of denosumab also in this sub-population. Hence, the indication valid for postmenopausal osteoporosis (“Postmenopausal women at increased risk of fractures”) is also valid for women treated with aromatase inhibitors for non-metastatic breast cancer. A separate indication for the female HALT population was thus considered not to be necessary by the CHMP.

No CHMP guideline exists on the evaluation of medicinal products in the *treatment of bone loss associated with hormone ablation in men with prostate cancer* and no medicinal product has hitherto been approved for this indication.

The pivotal **study 20040138** for denosumab in the treatment of bone loss associated with hormone ablation in men with prostate cancer Prevalent vertebral fractures were present at baseline in 21 % of denosumab subjects and 24 % of placebo subjects (as compared to 45 % of patients at baseline in the pivotal PMO study). Calculated FRAX data were not presented and baseline lumbar spine BMD was -0.3 and -0.4 in treatment groups.

Denosumab significantly increased the percentage change in lumbar spine BMD from baseline to month 24 (primary endpoint) in all subgroups for BMI, age and duration of ADT. The incidence of new vertebral fractures (secondary endpoint) was significantly reduced, at 3 years by 62 %, in the denosumab group and BMD relative to placebo at lumbar spine, total hip and femoral neck at month 24 and month 36 (secondary endpoints) was significantly increased (adjusted  $p < 0.0001$ ).

Thus, efficacy was clearly shown as vertebral fracture incidence reduction as well as lumbar spine BMD gain in the pivotal study.

## Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Denosumab is a first in class drug, with a new mechanism of action that could theoretically interfere with the immune system and the indications applied for are very wide. Although more than 13.000 patients have been exposed to at least one dose of denosumab, there is still limited experience of long term treatment with the drug, with less than 200 patient that have been on denosumab for more than 4 years.

An overrepresentation of infectious adverse events leading to hospitalisation was seen in two studies in postmenopausal osteoporosis; this was due to all kinds of common infections but without any reports of opportunistic infections. In the pivotal PMO study, a small overrepresentation of cellulitis and erysipelas was found in the denosumab treatment group, compared to placebo; and in the male HALT study, the denosumab group had a small overrepresentation of diverticulitis. This was not seen in other studies or in pooled safety data from several studies.

There was an increased incidence of neoplasm adverse events in the pivotal study for males with prostate cancer on hormone ablation therapy. The higher incidence of neoplasm AEs in the denosumab group seems to be mainly explained by a higher incidence of non-specific benign conditions, in particular basal cell cancers, in this treatment group. The remaining concerns regarding

immunomodulatory effects of denosumab in terms of malignancies and infections have been adequately addressed in the Risk Management Plan.

Hypocalcaemia is a defined risk, especially in patients with impaired renal function, but was mostly mild and transient in clinical studies where patients were on calcium and vitamin D co-medication.

For unclear reasons, cataract was overrepresented in denosumab treated patients in the male HALT study, but the prevalence in this treatment group did not exceed that in the general age-matched population. Cataract development and progression will prospectively be studied in a planned clinical study in this category of patients.

The effects on parathyroid function and thyroid function have not been fully evaluated. In contrast to bisphosphonates, denosumab did not cause an higher frequency of gastrointestinal adverse effects in clinical studies, and no higher frequency of cardiovascular events.

To address remaining concerns the applicant will perform a study for patients with PMO to further follow up of the following risks: hypocalcaemia leading to hospitalisation, ONJ, infections leading to hospitalisation, hypersensitivity leading to hospitalisation, fracture healing complications and malignancies. A prospective randomised study to further evaluate the incidence of cataracts in men receiving denosumab with ADT for prostate cancer is also planned.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A full User Test (UT) has been performed. In the first UT report all per protocol questions met the criteria and at least 99.4 % were able to find the information, and of these, at least 99.15 % were able to understand it. Regarding the choice of Test Questions and Model Answers, the questionnaire shows an imbalance between general and specific issues, e.g. just 2 questions are linked to side effects and seems in principle easy designed with appropriate sparsely answers; 3 yes/no answers and 4 contain “contact/tell your doctor-like” answers. Furthermore, a general open question reflecting the subjects’ impression of layout and design of the PL was only asked the subjects in the pilot phase. The Applicant was asked to submit the ratings and an analysis of the quantitative evaluation of responses, since it was missing in the first UT report. Their response did not reveal any new presentation/summary or analysis other than a repetition of the timescales used in the test with a maximum of 4 min 30 s per question. Although a pie chart was submitted, including the overall results of the 24 participants, this does not add any information to the issue. The timescales definitions should be expressed more precisely in future tests (here; very easily: within 30 s, easily: within 30 s to 1min 30 s, little difficulty: within 1 min 30 s to 3 min etc.) in order to e.g. avoid question marks/overlapping how to grade if exactly 1 min 30 s. The Applicant was asked to provide an analysis and a new summary of the “Assessment of Responses” for test rounds 1 and 2 since it was missing in the first UT report. The response contained new information as requested.

*In conclusion*, the user test is judged acceptable but the Applicant is asked to perform a new more complete user test (including a more complete set of summaries/ranges/analyses/diagrams/definitions etc. and at least one open general question asking all subjects about the PL layout and design), of 10 subjects, in case a variation procedure becomes necessary affecting the key safety messages of the package information leaflet.

### **Risk-benefit assessment**

Benefits with denosumab are:

- For the indications applied for, administration is simple as the drug is administered as a subcutaneous injection of a fix dose once every 6 months, and many patients can probably be trained to administer

the injections themselves. The treatment effect of denosumab is reversible and study data indicate that bone formation returns to base levels within one year after the cessation of denosumab therapy.

- For treatment of osteoporosis in postmenopausal women at increased risk of fractures, the pivotal study for this indication was adequately sized, designed and performed and the efficacy results were similar to or better than what has earlier been demonstrated for other drugs approved for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. The risks for interference with the immune system seem to be moderate according to data from large clinical studies. Treatment of bone loss associated with hormone ablation in women with breast cancer at increased risk of fractures is not considered to be a separate indication as these patients are considered to be postmenopausal and at increased risk of fracture and thus to be included in the PMO indication.

- For treatment of bone loss associated with hormone ablation in men with prostate cancer, efficacy was clearly shown as fracture incidence reduction and this effect is clinically relevant. This positive effect must be weighed against the risks of interference with the immune system. The men in the pivotal study for this indication exhibited an overfrequency of adverse events of neoplasms, mainly attributed to benign neoplasms, especially basal cell cancer. In addition, a high risk group for fractures needs to be better defined within this indication.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

### **Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered By consensus that the risk-benefit balance of Prolia in the following indication:

“Treatment of osteoporosis in postmenopausal women at increased risk of fractures. 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. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.”

was favourable and therefore recommended the granting of the marketing authorisation.