EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ASSESSMENT REPORT
FOR
XGEVA

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/002173

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

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Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 4 June 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for XGEVA, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 November 2008.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / Known active substance.

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: "Prevention of skeletal related events in adults with advanced malignancies involving bone".

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/14/2010 for the following conditions:

- Bone loss associated with sex hormone ablative therapy
- Bone metastases
- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Giant cell tumour of bone

on the agreement of a paediatric investigation plan (PIP)

The PIP is not yet completed.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Information relating to (Extended) Data / Market Exclusivity

As part of this Marketing Authorisation Application, the applicant requested the extension by 1 year of the 10-year period of marketing protection for denosumab, according to Articles 10(1) of Directive 2001/83/EC, as amended, and Article 14(11) of Regulation (EC) No 726/2004. The grounds for this request are that the applicant considers the prevention of skeletal related events in adults with advanced cancer involving bones to represent a new therapeutic indication for denosumab, compared to the authorised indications for Prolia (EU/1/10/618/001-004), and a significant clinical benefit in comparison with existing therapies for this indication. Both Prolia and the present MAA for XGEVA fall under the concept of a "global marketing authorisation" within the meaning of Article 6(1) of Directive 2001/83/EC, as amended.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 14 December 2005. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

XGEVA has been given a Marketing Authorisation in the USA on 18 November 2010 and in Canada on 10 May 2011.

A new application was filed in the following countries: Switzerland, Japan, Mexico, Russia and Australia.

1.2. Steps taken for the assessment of the product

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

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

- The application was received by the EMA on 4 June 2010.
- The procedure started on 23 June 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 September 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 September 2010.
- During the meeting on 21 October 2010, 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 25 October 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 January 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 February 2011.
- During the CHMP meeting on 17 March 2011, 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 20 April 2011.
- The Rapporteurs circulated the preliminary Joint Assessment Report on the applicant's responses to the list of outstanding issues on 30 April 2011.
- Following the CHMP request, a Scientific Advisory Group (SAG) meeting took place on 3 May 2011 to provide advice on the list of questions adopted by the CHMP at its March 2011 meeting.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues on 13 May 2011.
- During the meeting on 19 May 2011, 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 XGEVA on 19 May 2011. Furthermore, the CHMP reviewed the clinical data submitted by the applicant, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considered the therapeutic indication to be new for denosumab and that it brings significant clinical benefit in comparison with existing therapies for this indication. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 May 2011.

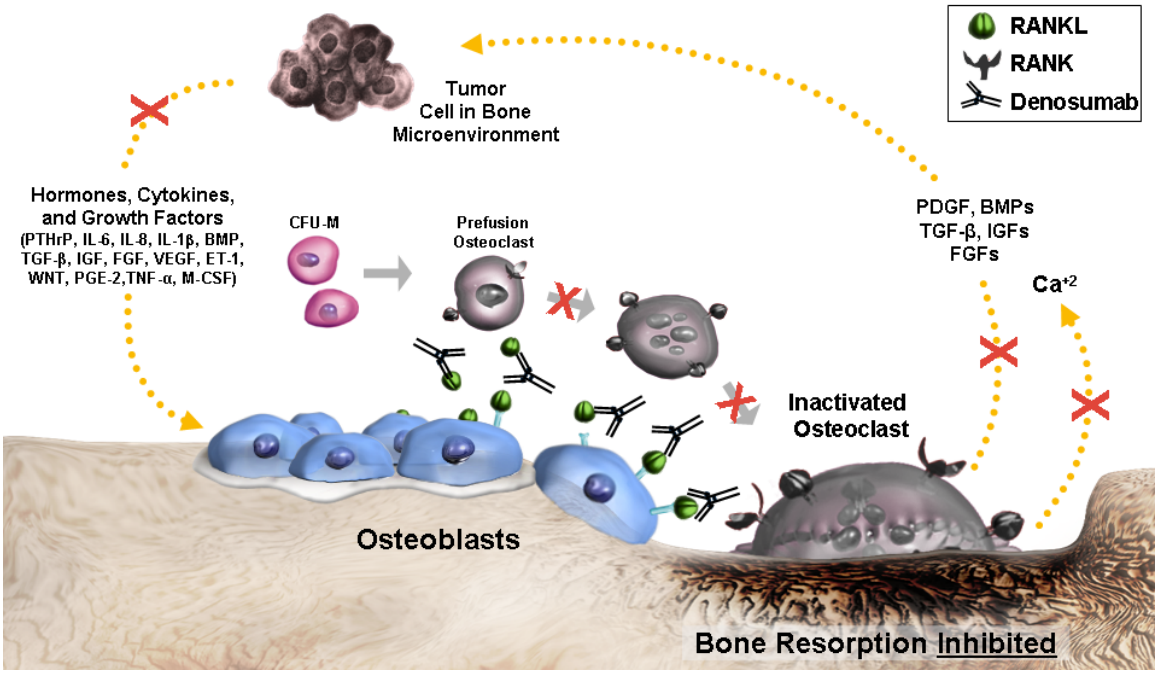
2. Scientific discussion

2.1. Introduction

Bone metastases occur in more than 1.5 million patients with cancer worldwide and can result in severe clinical sequelae such as pathological fracture, radiation to bone, spinal cord compression, or surgery to bone. These events are collectively defined as *skeletal-related events (SREs*). At present, several bisphosphonates are approved on indications related to prevention of skeletal related events or treatment of osteolytic lesions in patients with advanced cancer and skeletal metastasis: pamidronate, clodronate, ibandronic acid and zoledronic acid (ZOL). Of these drugs, ibandronic acid and ZOL have been approved via the centralised procedure. Bisphosphonates are associated with an increased risk of renal impairment and are not recommended for patients with a glomerular filtration rate below 30 ml/min. Further, the most potent bisphosphonates used for this indication are administered as an intravenous infusion.

Denosumab is a fully human monoclonal antibody of IgG_2 subtype, capable to inhibit the receptor activator of nuclear factor-κB (RANK) Ligand on bone cells. This antibody binds with high affinity and specificity to RANKL, thereby neutralising the ligand and inhibiting the differentiation of immature cells into osteoclasts. RANKL is a member of the tumour necrosis (TNF) group of proteins and is an essential factor for formation, activation and survival of osteoclasts. Osteoclasts are the cells responsible for bone resorption while osteoblasts are bone forming cells. Osteoprotegrin (OPG) is the naturally occurring soluble decoy receptor that binds to and blocks the action of RANKL. OPG binding to and blocking the action of RANKL leads to an increase in bone mass. Inhibition of RANKL is a possible intervention point to interfere with conditions with increased bone resorption. See figure 1.

Figure 1. Mechanism of action for denosumab



BMP = bone morphogenetic proteins, Ca2+ = calcium, CFU-M = macrophage colony-forming unit; ET1 = endothelin-1, FGF = fibroblast growth factors, IGF = insulin-like growth factors, IL-1 (IL-6, IL-8) = interleukin-1 (-6, -8), M-CSF = macrophage colony-stimulating factor, PDGF = platelet-derived growth factor; PGE2 = prostaglandin E2, PTHrP = parathyroid hormone-related peptide, RANKL = RANK ligand, TGF b = transforming growth factor b, TNFa = tumour necrosis factor a; VEGF = vascular endothelial growth factor; WNT = wingless-type protein-1

There are no regulatory guidelines specific to the proposed indication within the EU, however relevant sections of the current EMA CHMP guideline on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95/Rev.3) were considered during the evaluation. The study designs were also consistent with the underlying principles outlined in FDA's recently issued draft guidance document entitled "Guidance for Industry: Non-Inferiority Clinical Trials" (FDA, 2010). Scientific advice was received from EMA in 2005 and in 2009, see table 1 below.

Table 1. Summary of key interactions with health authorities for the denosumab clinical program

Date	Agency	Guidance
Dec 2005	EMEA - ScAWG	Scientific advice from this Group regarding the pivotal phase 3 clinical trials was integrated into the development program. The study designs and planned statistical analyses for advanced cancer studies (including two phase 3 studies evaluating the effect of denosumab on SREs in prostate cancer patients [20050103] and breast cancer patients [20050136]) in support of the targeted indication were discussed. Recommendations based on the CHMP advice were generally followed as discussed above this table and summarized in Section 4.1.
Jul 2009	EMEA	Legal, regulatory, and procedural aspects of the proposed MAA were discussed with the EMEA in this pre-submission meeting. The EMEA agreed to the proposed structure and content of the clinical sections, including the provision of the Summary of Clinical Safety from the separate standalone denosumab MAA in patients with PMO or bone loss associated with HALT (also referred to as the Bone Loss MAA – PROLIA). Agreement was reached on various review aids relating to overlap of data between the current Advanced Cancer MAA and the Bone Loss MAA. It was agreed that a separate risk management plan will be provided for the current Advanced Cancer MAA.
Feb 2010	EMEA PDCO	The EMEA Decision under Article 25 of Regulation (EC) No. 1901/2006 as amended for the denosumab PIP (EMEA-000145-PIP01-07-M02) was issued on 04 February 2010 (P/14/2010). There are no recommendations to conduct pediatric studies related to patients with multiple myeloma [PDCO Class Waiver]. The conduct of pediatric clinical studies in the PIP indication of prevention of SREs in pediatric patients with bone metastases is deferred [deferral status]. The required nonclinical commitments have been completed and a PIP compliance procedure has been completed.

Scientific advice was also received from Health Canada, from the FDA and from Japanese authorities.

Previously, a separate stand alone marketing authorisation application (MAA) was submitted in January 2009 via the Centralised Procedure and the corresponding Commission decision was granted on 26 May 2010 for the use of denosumab (Prolia) in the following indications:

- *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 (see section 5.1). In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.*

The current denosumab (XGEVA) MAA concerns another indication (*wording applied for by the applicant*):

- *Prevention of skeletal related events in adults with advanced malignancies involving bone*

which is submitted as a complete stand alone application via the centralised procedure, under Article 8 (3) of Directive 2001/83/EC of regulation (EC) No 726/2004, as amended. The application concerns a biotech medicinal product according to Article 3(1), Annex 1 of regulation (EC) No 726/2004.

Further, as part of the XGEVA MAA, the Applicant requested the extension by 1 year of the 10-year period of marketing protection for denosumab, according to Articles 10(1) of Directive 2001/83/EC, as amended, and 14(11) of Regulation (EC) 726/2004. The grounds for this request are that the Applicant considers the prevention of skeletal related events in adults with advanced cancer involving bones to represent a new therapeutic indication for denosumab, compared to the authorised indications for Prolia, and a significant clinical benefit in comparison with existing therapies for this indication. Both Prolia and the present MAA for XGEVA fall under the concept of a "global marketing authorisation" within the meaning of Article 6(1) of Directive 2001/83/EC, as amended.

According to Article 8 of Regulation (EC) No 1901/2006, given that the XGEVA MAA falls under a "global marketing authorisation" with Prolia, a paediatric investigation plan for denosumab for this actual indication in all age subsets of the paediatric population has been agreed. In accordance with the requirements of Article 23 of Regulation (EC) No 1901/2006 and the EMA Procedural Advice for Validation of New Marketing Authorisation Application-Extension/Variation Application and Compliance Check with an Agreed PIP (EMEA/553631/2007), a PIP Decision with number (P/14/2010) has been issued. PDCO Compliance Report and cover letter referred to are: EMA/153223/2010 and EMA/184624/2010. The indications of treatment of postmenopausal osteoporosis and treatment of multiple myeloma fall within the scope of the decision on class waivers (EMEA/245439/2008).

2.2. Quality aspects

2.2.1. Introduction

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

XGEVA drug product is supplied as a sterile, preservative-free solution for administration by subcutaneous injection. Three drug product presentations of denosumab have been developed to support different indications and posology: two for the Bone Loss program, i.e. a 60 mg vial (60 mg/mL 1.0 mL) and a 60 mg PFS (60 mg/mL 1.0 mL) presentations and one 120 mg (70 mg/mL 1.7 mL deliverable volume) for the advanced cancer program. The presentations for bone loss were subject of an independent Marketing Authorisation under the invented name of Prolia. The 120mg presentation corresponds to the current marketing authorisation application. All presentations are based on the same acetate-sorbitol formulation, which has been used throughout development.

The commercial manufacturing process is identical between the Bone Loss and Advanced Cancer programs. As a result, a significant overlap exists within the Chemistry, Manufacturing and Controls Module between the two independent applications. Some minor corrections and changes have been implemented within the drug substance sections of the Advanced Cancer application and the drug product sections are new, because of a higher strength compared to Prolia.

Since both vial presentations, 60 and 70 mg/mL, and the 60 mg/mL PFS presentation, were developed in parallel and share common features, studies performed with the 60 mg/mL (1.0 mL) presentations provide data considered supportive of the approval of the 70 mg/mL (1.7 ml) vial presentation. For this reason, certain data (eg, Formulation Development) generated from the 60 mg/mL (1.0 mL) vial and 60 mg/mL (1.0 mL) PFS presentations are provided within the application, in addition to full manufacturing and quality information for the 70 mg/mL vial presentation.

Most of the formal CMC quality commitments/follow-up measures (FUMs) resulting from the review of the Bone Loss MAA (Prolia) are equally applicable for the advanced cancer application.

2.2.2. Active Substance Manufacture

Description of the drug substance

The same drug substance is used for both the bone loss marketing authorisation (Prolia) and the advanced cancer application (XGEVA), and the drug substance sections of the two dossiers are essentially identical, except for some updates that are acceptably addressed.

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 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 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, viral inactivation and filtration steps: Protein A chromatography, low pH 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 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 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 denosumab 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.

2.2.3. Finished Medicinal Product

Composition, pharmaceutical development

The Xgeva drug product is supplied as a sterile, preservative-free solution, intended for delivery by subcutaneous injection. The strength is 120 mg (70 mg/mL, 1.7 mL deliverable volume).

The qualitative composition of the drug product includes: denosumab, sorbitol, glacial acetic acid, 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.

Translucent particles have been found in aged containers in the inventory of the clinical material, as was also identified and described in the Bone loss MAA. 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 addition to the 100% inspection of vials made at manufacture, further control, using semi-quantitative criteria, are in-place for evaluation of particle content. Moreover, the applicant has also committed, as for the Bone loss MAA, to further characterise the effect of formulation parameters, including polysorbate addition, on the propensity for low-level particle formation, this both in the 60 mg/mL and the 70 mg/ml vial formulations, and to undertake further studies on alternative formulations.

Throughout the development, process changes and introduction of new manufacturing sites have been made as was already addressed in the Bone loss MAA. The higher concentration and larger fill volume used for the Advanced cancer program is the major difference between the two quality dossiers of both marketing authorisations and is the primary subject of the comparability exercise in this application.

The overall strategy for demonstrating drug product comparability was based on the requirements outlined in ICH guideline Q5E, Comparability of Biotechnological/Biological Products. Comprehensive studies were conducted to demonstrate drug product comparability between 1) sourcing of drug substance, 2) the two strengths and 3) the manufacturing sites for drug product. The comparability program included the assessment of process comparability, batch analyses, forced degradation and stability studies, and clinical outcomes.

In addition to establishing analytical comparability for the formulation modification, Amgen has conducted open-label randomized single-dose bioequivalence studies. Clinical comparability between the administration of a 70 mg/mL vial and two 60 mg/mL vials was demonstrated in bioequivalence Study 20060446. Additional clinical experience with the different presentations was conducted. The results met the predefined criteria for bioequivalence.

In conclusion, the comparability was satisfactory demonstrated.

Manufacture

The manufacturing process is a standard aseptic process. The containers of drug substance are thawed, filtered and filled into vials. Critical parameters and in-process controls are acceptably described and justified, and the manufacturing process is acceptably validated.

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

Control of drug product

The proposed specification limits are the same as for the Bone loss MAA (Prolia). They are primarily based on the batch and stability data derived from the batches derived from a drug substance manufacturing process. This is considered acceptable, taking into account that the applicant has committed to reconsider and propose narrower limits, as appropriate, when maore batch data is gathered. This is in line with the commitments made for the Bone loss MAA.

The strategy of setting specifications is considered acceptable.

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.

The stability program currently consists of 10 Vial lots (primary, commercial and supporting lots) of the 70 mg/mL strength stored at the recommended storage temperature of 5°C. Data supporting a proposed 36 month shelf life for 70 mg/mL vials stored at the recommended storage condition of 5°C has been submitted.

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 the non-enveloped viruses.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The different aspects of the chemical, pharmaceutical and biological documentation are in compliance with existing guidelines.

The manufacture of the drug substance have been adequately described, controlled and validated. The drug substance has been well characterised with regard to its physicochemical and biological characteristics and appropriate specifications have been set.

The manufacturing process of the drug product has been satisfactorily described and validated. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics. The quality of the drug product is controlled by adequate test methods and specifications.

The viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The applicant is recommended to undertake some minor quality issues having no impact on the benefit-risk balance of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, the application for XGEVA is considered approvable.

2.3. Non-clinical aspects

2.3.1. Introduction

Denosumab represents an antiresorptive therapy for osteoporosis targeting the ligand for receptor activator for nuclear factor-κB (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. Denosumab is a fully human IgG2 mAb and does not recognise rodent RANKL but recognizes and neutralizes RANKL in non-human primates, and the cynomolgus monkey was identified as a relevant non-clinical species. The main studies in relation to the indication postmenopausal osteoporosis were conducted in ovariectomized animals and one toxicology study with bone efficacy endpoints was performed in normal cynomolgus monkeys, using both males and females. The pharmacology of denosumab with respect to osteoporosis and treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures has been reviewed during the evaluation of the first denosumab MAA for Prolia and is only briefly considered in the present report.

Imbalances in the RANK/RANKL/OPG system have been implicated in a variety of pathophysiological conditions including osteoporosis, multiple myeloma, and breast malignancy. Osteoclastic activity in bone metastasis is increased with stimulation of the RANK/RANKL pathway as a main driver. Bone metastasis may be characterised as either osteoblastic and/or osteolytic and in both cases dysregulation of normal bone remodelling processes occurs. Osteoclast activity and subsequent osteolysis as central components in metastatic bone disease thus indicate a role of therapeutics that target RANK/RANKL/OPG system. Literature data is extensive with respect to studies implicating RANKL in bone metastasis induced by different tumour types. RANKL may be produced by tumour cells themselves and then bind to its cognate receptor, RANK that has been shown to be expressed also at the surface of cancer cells. In rodent models of bone metastasis representing osteolytic, osteoblastic and/or mixed osteolytic/osteoblastic lesions, inhibition of RANKL has been shown to prevent tumour induced osteolysis and to delay progression of skeletal tumours

Denosumab was granted an initial marketing authorisation under the invented name Prolia in May 2010 for the treatment of osteoporosis in postmenopausal women at increased risk of fractures and

treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. The recommended posology for these indications is 60 mg subcutaneously every 6 months corresponding to approximately Cmax values of 6.94 µg/ml and $AUC_{0\text{-}6\ months}$ of 10752 µgxh/ml.

With reference to the indication applied for as part of the current XGEVA MAA "*prevention of skeletal related events in adults with advanced malignancies involving bone*", the compound is intended to be administered subcutaneously once every 4 weeks at a dose of 120 mg. In a 6-month period this dose is 12 times greater that the previously approved dose for osteopososis and corresponds to an $AUC_{0\text{-}4weeks}$ of 723 µgxday/ml at steady state. The mean Cmax at a dose of 120 mg was approximately 27 µg/ml.

The excipients selected for the drug product are not considered to be of any toxicological interest. It is stated that the drug product and drug formulation manufactured at different sites have been shown to be bioequivalent.

The dose selection and the dosing schedule in the non-clinical pharmacology and toxicology studies were based on considerations of dose-response activity, identification of systemic effects and a no-observed-effect-level and were also planned in view of the circulating half-life of denosumab and the potential for immunogenicity in the test species. In studies with a longer duration of treatment doses were adjusted upwards to accommodate for the immune response to the drug in order to maintain adequate exposure to active drug.

The majority of non-clinical studies submitted with the XGEVA MAA have already been assessed by the CHMP in the context of the osteoporosis indication for Prolia and therefore the present report focuses on the additional primary pharmacology studies conducted in support of the new XGEVA indication. These studies used OPG-Fc as an inhibitor of RANK in different murine models of bone metastasis. The sections on pharmacokinetics and toxicology are in principle the same as included in the previous non-clinical report for Prolia with no new data included, but are discussed in relation to the higher dose and the increased frequency of dosing relevant for the present indication.

Pivotal toxicology studies, including safety pharmacology and studies on cross-reactivity were conducted in accordance with GLP principles with some minor deviations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro primary pharmacodynamic studies

In vitro studies have shown that denosumab binds with high affinity to huRANKL (Kd $3x10^{-12}$M) but not to muRANKL. The binding affinity of denosumab to huRANKL was comparable to that of huOPG-Fc, with similar Kd values, thus these data support the use of huOPG-Fc as a surrogate molecule in mechanistic studies. The relative affinity of denosumab for huRANKL versus other TNF family members, TNF-α, TNF-β, TRAIL and CD40L, was assessed in competitive binding assays. Denosumab did not bind to these TNF family members, indicating specificity to target. *In vitro* osteoclastogenic response in murine leukemic monocyte macrophage cell line was inhibited with an IC_{50} of 1.64 ng/ml. Osteoclastogenesis was not inhibited in a system with non-adherent murine bone marrow cells cocultured with murine ST2 stromal cells as a source of murine RANKL. Osteoclastogenesis in these non-adherent murine bone marrow cells stimulated with recombinant human RANKL was inhibited with denosumab with an IC_{50} of 10^{-14} M, while no effects were detected on osteoblast proliferation.

Endothelial apoptosis is an important regulator of angiogenesis and OPG has been reported to block endothelial cell apoptosis through binding TRAIL. Increased tumour cell apoptosis has also been reported in the literature as a consequence of RANK inhibition. Inhibition of RANKL has been shown to reduce skeletal tumour progression in models in which tumour induced neovascularisation is associated with progression of the skeletal tumour and is responsive to anti-angiogenic therapies. Contradictory effects of OPG-Fc on angiogenesis were reported in a model of neovascularisation in rat corneal disk implant model. As multiple signalling pathways, including recruitment of specific proteins, activation of transcription factors, cascades of mitogen activated protein kinases and induction of Akt activation, are involved in RANK/RANKL system a dynamic dominance of one or two systems may confound identification of a potential angiogenic interaction depending on the model used.

In vivo primary pharmacodynamic studies

A fracture healing study in male huRANKL KI mice 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.

In relation to the indication postmenopausal osteoporosis ovariectomized cynomolgus monkeys were used in studies of a somewhat short duration of 16 months which corresponds to 4 remodelling cycles in both monkeys and humans. A dose of 25 or 50 mg/kg/month for 12 or 16 months decreased biochemical markers of bone turnover compared to ovariectomized or sham controls. These doses also prevented the ovariectomized induced decreases in trabecular and cortical bone mass at the lumbar spine, femur, proximal tibia and distal radius and showed positive gains in bone mass. Disproportionate increases in bone strength relative to bone mass were observed at lumbar spine and femoral neck, suggesting treatment improved bone quality. The pharmacologic effects of transitioning from a bisphosphonate, alendronate, to denosumab were evaluated in a 12-month study in ovariectomized cynomolgus monkeys. Pretreatment with alendronate for 6 months did not negatively modify the response of denosumab (25 mg/kg/month). Transition to denosumab seemed to further increase bone mineral density of the whole body, lumbar spine and distal radius compared to 12 months of alendronate treatment.

Since denosumab is a fully human antibody, an immunogenic response was expected in cynomolgus monkeys. Anti-drug-antibodies were detected more frequently at low doses than at high doses, most likely due to high serum denosumab concentrations interfering with detection of anti-drug antibodies at the higher doses.

The pharmacology of RANKL inhibition in relation to bone lesions induced by a range of metastatic tumours was studied in rodent models (mostly females) using a recombinant form of OPG (OPG-Fc) and also a recombinant form of RANK-Fc. The mechanism of action of denosumab is similar to osteoprotegerin, which is the endogenous soluble decoy receptor that binds to and blocks the action of RANKL. Human RANKL appears to be able to activate murine RANK resulting in increased bone resorption and hypercalcemia and human OPG-Fc was selected to be used as a surrogate in studies of pharmacodynamics of denosumab. Inhibition of RANKL reduced bone lesions and delayed formation of *de novo* bone metastasis in these models, but had no effect on non-skeletal tumour burden. The latter might have to be interpreted with caution in the light of the use of bone-tropic tumour cell lines. The utilized rodent models may therefore not adequately reflect on non-skeletal metastasis.

Skeletal tumour growth was reduced and the effects appeared additive when combined with anticancer therapies such as docetaxel. In a model of hormone and carcinogen induced mammary tumourigenesis inhibition of RANKL resulted in reduction of epithelial proliferation and cyclin D1 expression.

In mouse models of bone metastasis induced by intracardial injection of human tumour cells representing breast, prostate and lung cancer OPG-Fc administration reduced radiologically detectable lesions and reduced skeletal tumour burden assayed by hind limb bioluminescence index. Survival of tumour bearing mice was prolonged. Progression of mixed osteolytic/osteoblastic bone metastasis in athymic nude mice seemed to be reduced by OPG-Fc either alone or in combination with tamoxifen and skeletal tumour volume was reduced with the combination resulting in a greater tumour growth inhibition than with the compounds administered alone.

In a prostate cancer bone metastasis (PC3) model in mice primarily characterised by osteolytic reaction but with some blastic reaction, OPG-Fc at 3.0 mg/kg subcutaneously 3 times a week with and without docetaxel at 5 or 10 mg/kg reduced radiologically detectable osteolytic lesions. Osteoclast activity as reflected in serum TRAP5b was reduced by OPG-Fc, only. Further, reductions of progression of skeletal tumours growth, skeletal tumour area and hind limb tumour burden were reported after treatment with OPG-Fc. Similar effects were recorded in the non-small cell lung cancer bone metastasis models that included use of H1299 to produce osteolytic lesions. These models mainly include xenograft but some data are also available in syngeneic models. In syngeneic mouse models using multiple myeloma cells recombinant OPG prevented bone loss and lytic lesion likely due to reduction of tumour induced osteoclast formation.

Data in the literature reviewed by the applicant is also consistent with surrogate recombinant forms of OPG and RANK-Fc having a suppressive effect on the progression of tumours of bone such that inhibition of osteoclasts results in effects on osteolytic, mixed osteolytic/osteoblastic and osteoblastic lesions in rodent models. While these data taken together support a role of the system and by inference of denosumab, in prevention of skeletal related events, no conclusion on the most appropriate dose and frequency of dosing is possible based on non-clinical studies.

The influence of RANKL inhibition on *mammary tumourgenesis* was investigated in mice, which overexpress RANK (introduced via MMTV, murine mammary tumour virus), and WT mice after hormonal stimulation and chemical tumour-induction. The study results support the assumption that RANKL inhibition opposes mammary tissue proliferation and the development of mammary neoplasia in WT mice and RANK overexpressing MMTV mice.

The predominant histotype of tumour in MMTV-RANK mice was adenocarcinoma, which reflected an increase in incidence relative to wild type mice. Treatment of MMTV-RANK mice with RANK-Fc decreased the proportion of adenocarcinomas to wild type level, but did not affect the exhibition of other histotypes. In WT mice RANK-Fc reduced tumour burden independent of the histotype.

Literature data reviewed by the applicant provide further support for a preventive effect of RANKL-blockade on non-skeletal tumour metastasis. Those results were obtained in spontaneous metastasis models, using either orthotopic injection of tumour cells or transgenic models, and addressed tumour entities relevant for the proposed indication of this MAA. Additionally, reference is made to in vitro study results indicating an effect of RANKL on several factors involved in migration, angiogenesis and invasion in studies, which utilized cell lines of breast cancer, melanoma, prostate and ostesosarcoma origin.

Table 5. Summary of primary pharmacodynamic studies performed with denosumab

Type of study (Report No)	**Test system (method, cell line, species/strain)**	**Noteworthy findings**
MDA231-F11 Luc Bone metastasis model (R2006160)	Female athymic nude mice, 10/group (OPG-Fc, 0.3, 3.0 mg/kg 2x/week, SC started day 0)	OPG-Fc at 3.0 mg/kg reduction of tumour burden BLI. OPG-Fc at 0.3 and 3.0 mg/kg reduced osteolysis dose-dependently.
MDA231-F11 Luc	Female athymic nude mice, 10/group (OPG-Fc,	OPG-Fc (0.3, 3.0 mg/kg) reduced tumour

Bone metastasis model (R2006161)	0.3, 3.0 mg/kg 2x/week, SC started day 7)	burden BLI of bone metastasis. OPG-Fc (0.3, 3.0 mg/kg) reduced osteolysis dose-dependent. OPG-Fc (3 mg/kg) prolonged survival
Established bone metastasis model in mouse (R20080161) Growth of MCF-7 cells	Female athymic nude mice, 10/group (Tamoxifen 0.1, 0.5 mg 5x/week IP, starting day 7 continued to day 32, OPG-Fc, 3 mg/kg, 3x/week SC starting day 5 continued to day 31)	Tamoxifen; Hind leg limb tumour burden reduced. OPG-Fc: histological skeletal tumour burden reduced and delay in hind limb tumour growth by BLI. Osteolytic lesions reduced by OPG-Fc.
Established bone metastasis model in mouse (R20080162) Growth of MCF-7 cells	Female athymic nude mice, 10/group (Tamoxifen 0.1, mg 5x/week IP, starting day 7 continued to day 32, OPG-Fc, 3 mg/kg, 3x/week SC, Combination tamoxifen and OPG-Fc 5x/week, starting day 5 continued to day 39)	Additive effects of the combination tamoxifen and OPG-Fc resulting in significant reduction in hind limb tumour burden. OPG-Fc alone significantly reduced osteolytic lesions.
MDA231-F11 Luc Bone metastasis model (R20070953)	Female athymic nude mice, 20/group (OPG-Fc, 0.3, 3.0 mg/kg 3x/week, SC started day -7 continued until day 21)	Pretreatment at 3 mg/kg significantly delayed onset of bone metastasis measured by B LI. Tumour induced osteolysis was dose dependently prevented.
PC-3 prostate cancer bone metastasis (R20080083)	Male athymic nude mice, 8/group (OPG-Fc, 3.0 mg/kg 3x/week, SC, docetaxel 5 or 10 mg/kg 1x/week x2 treatments IP, combination OPG-Fc and docetaxel started day 11 post tumour implantation)	Docetaxel significantly decreased hind limb BLI and histological tumour burden at 10 mg/kg. OPG-Fc reduced skeletal tumour area and progression of lytic lesions. The combination OPG-Fc docetacxel significantly reduced skeletal tumour burden.
Bone metastasis of human non-small cell lung (H1975 cell line) (R20070963)	Female athymic nude mice, 9-10/group (OPG-Fc, 3.0 mg/kg 3x/week, SC started day 1 or day 7 of tumour cell inoculation, animals sacrificed day 27)	Reduction of skeletal tumour burden by histology and prevention of osteolytic lesion formation.
Bone metastasis of human non-small cell lung (H1299 cell line) (R20080310)	Female athymic nude mice, 9-10/group (OPG-Fc, 3.0 mg/kg 3x/week, SC started day 1 or day 7 or 8 of tumour cell inoculation, animals sacrificed day 27)	OPG-Fc initiated either early (day 1) or late (day 7-8) reduced skeletal tumour burden by histology and prevented osteolytic lesion formation.
Bone metastasis of human non-small cell lung (H1299 cell line) (R20080331)	Female athymic nude mice, 10/group (OPG-Fc, 3.0 mg/kg 3x/week, SC, docetaxel 35 or 50 mg/kg, 1x/week x 2 treatments IP, or combination OPG-Fc and docetaxel started day 5 post tumour implantation, animals sacrificed day 22)	OPG-Fc and docetaxel alone or in combination significantly decreased hind limb BLI and histological skeletal tumour area and progression of lytic lesions.
Bone metastasis of human non-small cell lung (H1299 cell line) (R20080332)	Female athymic nude mice, 7-8/group (OPG-Fc, 3.0 mg/kg 3x/week, SC, docetaxel 15 mg/kg, 1x/week x 2 treatments IP, or combination OPG-Fc and docetaxel started day 7 post tumour implantation, animals sacrificed day 23)	OPG-Fc and docetaxel alone or in combination significantly decreased hind limb BLI and histological skeletal tumour area and progression of lytic lesions.
Hormone and carcinogen induced mammary tumourigenesis (R20090211)	C57BL6 and MMTV-RANK female mice 5-51/group. Transgenic mice overexpressing RANK via murine mammary tumour virus long terminal repeat. MPA in combination with DMBA used to induce mammary tumours. Tg and wild type mice were treated with 10 mg/kg muRANK-muFc or PBS simultaneously with the first DMBA treatment.	Inhibition of RANKL (using RANK-Fc) attenuated mammary tumour development after hormone and carcinogen treatment in both MMTV RANK and wild type mice. Reduction in mammary carcinogenesis preceded by a reduction in preneoplasia and reduction in epithelial proliferation and cyclin D1 expression.
Neovascularisation in rat corneal disk implant model of angiogenesis (R2002266)	Rat (Sprague-Dawley) female 8/group. Angiogenesis induced by implanting a VEGF soaked nylon disc into the corneal stroma. OPG-Fc (4 mg/kg/day, SC administered for 7 days)	Treatment with OPG-Fc increased statistically significantly the angiogenic response compared to vehicle treated group. No toxicity was evident.
Neovascularisation in rat corneal disk implant model of angiogenesis (R2002204)	Rat (Sprague-Dawley) female 8/group. Angiogenesis induced by implanting a VEGF soaked nylon disc into the corneal stroma. OPG-Fc (4 mg/kg/day, SC administered for 7 days)	No statistically significant effects on the VEGF induced angiogenic response compared with PBS treated group. No toxicity was evident.

Neovascularisation in rat corneal disk implant model of angiogenesis (R2002267)	Rat (Sprague-Dawley) female 8/group. Angiogenesis induced by implanting a rHu-bFGF soaked nylon disc into the corneal stroma. OPG-Fc (4 mg/kg/day, SC administered for 7 days)	No effects on the bFGF induced angiogenic response compared with PBS treated group. No toxicity was evident.

Effect of OPG-Fc or alendronate on tooth eruption or bone density, geometry and strength in neonatal rats (R20090070)	Rat (Sprague-Dawley) male/female 9-11/group. Vehicle or OPGF-Fc (1, 3, 10 mg/kg) or alendronate (1 mg/kg) SC once weekly for 6 weeks, sacrifice after 10 weeks discontinuation.	10 weeks after discontinuation of a 6 week treatment with OPG-Fc evidence of restoration of bone resorption, partial normalization of bone density, size and strength. Molar eruption (delayed by treatment with OPG-Fc) partial recovery. Alendronate: Increase in bone volume, density and strength unchanged after discontinuation. Molar eruption did not recover within this time frame. Bone size, body weight, molar root development reduced 10 weeks after discontinuation of OPG-Fc or alendronate.
Long bone geometry in 1 and 2 month transgenic rats overexpressing soluble RANKL inhibitor OPG during growth and development (R20090069)	Rat (Sprague-Dawley) male/female 3-9/group.	Overexpression of OPG from a prenatal stage and throughout the first 2 months of life resulted in changes in bone density, geometry and femur bending strength described as neutral or favourable, no consistent changes in material properties.
Dose dependent effects of OPG-Fc on tooth eruption, bone growth and bone strength in neonatal rats (R20090282)	Rat (Sprague-Dawley) male/female 3-10/group. Vehicle or OPG-Fc at 3, 10 mg/kg weekly for 6 weeks SC.	Dose-dependent reduction on bone resorption resulting in osteopetrosis-like changes at 10 mg/kg (increases in bone density, reduced bone growth and weight gain and impaired tooth eruption). Structural parameters overall unchanged or improved whereas intrinsic (material) strength parameter toughness significantly reduced in femurs. OPG-Fc adm. resulted in thickened and disorganized growth plate morphology.

Secondary pharmacodynamic studies

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 3rd molars and 84% of 2nd molars. In a recovery study effects of OPG-Fc (1, 3, 10 mg/kg) and alendronate (1 mg/kg) were compared. Although discontinuation resulted in some reversibility of effects, the delay in molar eruptions was coupled to malocclusion and bone size, body weight and molar root development were significantly reduced after 10 weeks.

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. Considering the mechanism of action of denosumab, potential effects on immunomodulation and immunosuppression cannot be ruled out, see further conclusion on toxicology below.

RANK/RANKL have been shown to be involved in the control of body temperature at several key brain regions (Hanada et al, 2009), with impairment of the RANK/RANKL system leading to ablation of the fever response to infection in rodents and in humans. Since denosumab is a monoclonal antibody, it would not be expected to cross the blood brain barrier and mediate a central effect. This may however be different in advanced tumour patients, where some tumours with bone involvement may also develop metastasis in the brain leading leakage of the blood-brain-barrier. In addition, the target population can be expected to experience a higher degree of infections, which may first become clinically apparent through fever.

Safety pharmacology programme

The safety pharmacology package included two studies on cardiovascular endpoints, one of these was incorporated in a toxicology study in accordance with ICH S6 and ICH S7A. Also, visual observations of respiration rate and cage observations of general appearance and behaviour were performed. According to the guideline, clinical observation of animals is generally not adequate to assess respiratory function, thus these parameters should have been quantified by appropriate methodologies. However, since no indication of denosumab to affect respiratory function was noted, the current study is considered sufficient. A small amount of denosumab is shown to pass the blood-brain barrier but no denosumab-related behavioural changes were observed during cage observations. Some findings of isolated cases of slight bradycardia, fused P-T wave, tachycardia and a run of four ventricular premature complexes were noted, but not considered to be treatment related. There is also some clinical data that address these aspects.

Table 6. Summary of safety pharmacology studies performed with denosumab

Type of study	**Test System (method, cell line, species/strain)**	**Noteworthy finding**	**Report No**
Effects of denosumab on blood pressure, heart rate and ECG activity	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 4 ventricular premature complexes (VPCs) approximately 45 minutes postdose. Stress was not considered as the cause. The absorption of denosumab is very slow (expected peak plasma levels occurring between 48 and 72 hours following sc administration). The exposure of this animal to denosumab was expected to be very low at 45 minutes postdosing. Therefore, the single episode of VPCs that occurred in this animal was not considered to be related to treatment with denosumab.	101606
Effects of denosumab on blood pressure and ECG	Male and female cynomolgus monkey (n=3/group, 3 months recovery n=2/group, SC injection, 0, 1, 10 and 50 mg/kg once/month for 6 or 12 months)	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 single animals. These findings were not considered to be related to the administration of the test material, as there were similar findings observed pre-dose, during treatment and during the recovery period and in control animals. However, one male animal showed a bradycardia and a fused P-T wave in Week 25 of study. Since this animal at this time generally showed poor physical condition (diarrhea, low food consumption, body weight loss, low body temperature), this finding was considered to be due to the general health status of the animal rather than being compound related. Two male animals died in the high dose group. One of these animals had among other findings, cardiac pathology. According to the Applicant these deaths were not related to treatment. See further the toxicology section.	102090 (tox study)
Effects of denosumab on respiration rate	Male cynomolgus monkey (n=3/group, single SC injection, 0, 0.3, 3, and 30 mg/kg	No treatment related changes in respiration rate were observed. There were similar variations in respiration rates across all groups and over time.	101606

Clinical signs (cageside observations)	Male cynomolgus monkey (n=3/group, single SC injection, 0, 0.3, 3, and 30 mg/kg	No treatment related cageside observations were observed.	101606

Pharmacodynamic drug interactions

No specific preclinical studies have been conducted addressing drug interactions, which is considered acceptable. In the switch study performed in ovariectomized cynomolgus monkeys pretreated with the bisphosphonate alendronate no adverse effects on the pharmacodynamic activity were noted.

2.3.3. Pharmacokinetics

Analysis

Denosumab in serum was quantified by ELISA methods. The limit of quantification was approximately 0.78 and the analytical range from 0.781 to 10 ng/ml. The method in principle measured free denosumab, i.e. not bound to RANKL.

Absorption

Table 7. Single dose pharmacokinetic parameters of denosumab in different species

Study	Species (n)	Dose (mg/kg)/Route	Cmax, C_0 (µg/ml)	AUC $_{0\text{-inf}}$ (µgxh/ml)	CL, CL/F (ml/h/kg)	Vss (ml/kg)	Tmax (h)	$t_{1/2}$ (h)
101494	Mouse (M)	1, SC	23.1	15600	0.0642	NA	72	444
		0.1, IV	3.91	1680	0.0594	43.5	NA	420
		1, IV	31.9	18100	0.0553	40.2	NA	463
		10, IV	511	128000	0.0778	48.6	NA	461
101002	Rat (M/F)	1 SC	6.87	1970	0.507	NA	72	106
		O.0628 IV	1.97	201	0.318	98.6	NA	240
		1 IV	22.9	3580	0.287	107	NA	270
		10 IV	318	41800	0.242	97.2	NA	290
101398	Monkey (F)	0.0016 SC	0.00433	0.301	10.6	NA	10.7	41.9
		0.0053 SC	0.0229	1.64	6.15	NA	18.7	35.8
		0.0848 SC	0.728	126	0.808	NA	56	24.1
		1.0 SC	16.5	3940	0.298	NA	96	28.9
		3.0 SC	35.8	8790	0.353	NA	64	29.5
		0.0016 IV	0.0625	0.763	4.40	51.4	NA	8.37
		0.0053 IV	0.243	4.77	2.10	45.1	NA	14.3
		0.0848 IV	3.72	189	0.542	38.4	NA	36.9
		1.0 IV	35.9	3590	0.310	30.7	NA	19.3
		3.0 IV	105	12400	0.277	31.2	NA	27.5
101606	Monkey (M/F)	0.3 SC	2.89	NA	NA	NA	96	NA
		3 SC	29.2	NA	NA	NA	96	NA
		30 SC	291	NA	NA	NA	96	NA
	Human (M/F)	120 mg SC	27	7232[a)]			7-10 d	

NA =not applicable. a) $AUC_{0\text{-}4\ weeks}$ µxday/ml

In mouse and rat non-linear pharmacokinetics of denosumab were evident after intravenous doses. In mouse and rat the terminal half-life ranged from 19 to 11 days. In monkey non-linear pharmacokinetics both after subcutaneous and intravenous administration were reported over a dose range of 0.0016 to 1 mg/kg, but approximately linear at 1 to 3 mg/kg. The volume of distribution was similar to plasma volume indicating limited distribution. At doses of 0.0848 mg/kg and above almost all animals developed antibodies to the test substance and this was not route dependent. Early development of antibodies correlated with increased clearance at doses above 0.0848 mg/kg.

Table 8. Single dose pharmacokinetic parameters of denosumab in mouse

Study	Species (n)	Dose (mg/kg)/Route	Cmax, C_0 (µg/ml)	AUC $_{0\text{-inf}}$ (µgxh/ml)	CL, CL/F (ml/h/kg)	Vss (ml/kg)	$t_{1/2\,z}$ (h)
106893	Mouse (M/F), neonatal Fc(FcRn)KO	0.1, IV 1.0 IV	2.55 21.7	48.5 455	2.06 2.20	52.3 58.6	18.1 20.2
	Wild-type	0.1 IV 1.0 IV	2.21 20.8	685 6910	0.146 0.145	39.3 46	489 506
106892	Mouse (M/F), huRANKL	0.1 IV	2.19	127	0.786	56.9	34.2
	Wild-type	0.1 IV	2.6	839	0.119	70.7	371

KO=knock-out

In both FcRn KO and wild-type mice approximate dose-proportionality (from 0.1 to 1 mg/kg) was recorded. The results indicated that elimination and distribution is influenced by FcRn.

Denosumab does not cross-react with mouse or rat receptor activator for nuclear factor κB ligand (RANKL), but is stated to bind and inactivate the cynomolgus monkey RANKL. Pharmacokinetics were also determined in transgenic mouse expressing a chimeric form of RANKL. In these mice an accelerated rate of elimination was evident compared to wild-type mice also consistent with that binding of denosumab to huRANKL plays a significant role in the elimination of the antibody.

Distribution

Distribution of ^{125}I-denosumab was determined by quantitative whole body autoradiography in cynomolgus monkey (104105) given a single subcutaneous dose of 0.1 or 1 mg/kg. Radioactivity was quantifiable in almost all analyzed tissues at 12 and 120 hours post-dose. Highest levels were detected at the dose site and thyroid at both dose levels and in both genders. At the 1 mg/kg dose, highest levels, excluding dose site and the thyroid, were reported in the gastric mucosa, blood, lung, liver and cervical lymph nodes in males and females and in males also stomach contents, mesenteric lymph nodes, prostate and stomach. Further, in females high levels were detected in axillary lymph nodes, ovary and nasal turbinates. Radioactivity was detected in testis suggesting that drug derived radioactivity may cross the blood-testis barrier. Low levels were also detected in cerebrum, cerebellum and medulla indicating that very low levels may cross blood/brain barrier. No specific uptake or sequestration in bone was reported.

In a study in female monkeys (104192) given single subcutaneous doses of 0.1 or 1 mg/kg of ^{125}I denosumab, a wide distribution of radioactivity was evident. Highest levels were detected at dose site skin, thyroid/parathyroid, serum, axillary lymph nodes, inguinal lymph nodes, blood, spleen and ovaries. At the dose of 1 mg/kg, radioactivity was quantifiable in all tissues analyzed at 672 hours post dose and in half of tissues at 1344 hours postdose. Highest label was found at injection site, thyroid/parathyroid, axillary lymph nodes, serum, blood, ovaries and lungs.

Systemic exposure increased greater than dose proportional so that for a 10-fold increase in dose a 26-fold increase in systemic exposure was noted.

In the embryo-fetal development study fetal serum samples collected at the cesarean section had quantifiable levels of denosumab indicating that the substance crosses the placental barrier.

Metabolism

Denosumab is a monocloncal antibody. 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, at acidic pH in the endosome prior to releasing the antibody at the cell surface. The role of FcRn was studied using FcRn knock-out mice. Compared with wild-type mice a much shorter elimination half-life, that was similar to the half-life reported for a murine antibody, was recorded in FcRn knock-out mice and data indicated that FcRn protects denosumab from elimination and so influences tissue distribution.

Excretion

Table 9. Excretion of total

Study	Species	Dose/Route (mg/kg)	Urine (%) (0-672 h)	Faeces (%) (0-672 h)	Total (0-672 h)
104192	Monkey (F) (cynomolgus)	0.1 SC 1.0 SC	80-95 76-79*	1.8-3.1 1.1-2.8*	92-106 83-89*

* values refer to 1344 hours post dose

All animals in study 104192 developed antibodies. In the 0.1 mg/kg group Cmax values ranged form 487 to 847 ng/g equivalents ^{125}I-denosumab and from 4670 to 8330 ng/g equivalents ^{125}I-denosumab in the 1 mg/kg. Radioactivity was slowly excreted and acid-precipitable radioactivity in urine ranged from 3.4 to 25% and generally from 20 to 60% in faeces. Data indicate that drug derived radioactivity was excreted mainly as free iodide or small iodinated peptide fragments.

Pharmacokinetic drug interactions

No specific studies were conducted, which is acceptable.

Other pharmacokinetic studies

The pharmacokinetics of denosumab manufactured by 2 different processes (CP1 and CP2) were determined in monkey (cynomolgus females) given subcutaneous doses of 0.1 mg/kg. Of 16 monkeys 13 developed antibodies. In the subset (3-5 monkeys at 336 hours) that did not develop antibodies, mean Cmax and $AUC_{0\text{-}336h}$ values were less than 23 and 16% different, respectively. Changes in bone turnover markers were similar with denosumab manufactured by the 2 different processes.

In a 12 month monkey study (106564) it was concluded that previous treatment with alendronat did not markedly affect the pharmacokinetics of denosumab.

2.3.4. Toxicology

Single dose toxicity

No specific single dose toxicity was conducted which is 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 (see further safety pharmacology section above).

Repeat dose toxicity

Table 10. Overview of monkey studies

Study ID	Species/Sex/ Number/Group	Dose (mg/kg)/ Route	Duration	Major Findings
101447 (SBL 39-50)	Monkey (cynomolgus), (6 M+6F)	0, 0.1, 1, 10, SC 10, IV Once per week (total of 4 doses)	1 month (3M+3F)+ 13 week recovery (3M+3F)	No sign. effects on clinical signs, body weight, food intake, ophthalmology, hematology, urinalysis or histopathology. Dose-dependent osteocalcin. **≥0.1 mg/kg**: ALP↓. Serum NTx ↓ **≥1 mg/kg**: serum Ca^{++}↓ (M), total+cortical BMD proximal tibia ↑ (M), distal radius BMD ↑ (M during recovery) **10 mg/kg**: serum Ca^{++} (M), thyroid w. ↑ (IV, F), cortical BMD distal radius ↑ (IV, M-during recovery)
102090 (1052-011)	Monkey (cynomolgus) (8M+8F)	0, 1, 10, 50, SC Once per month (total of 13 doses)	6 or 12 months 13 week recovery (2M+2F)	**All groups**: Clinical signs: Occasional diarrhea, low food intake, hair loss, sticky fur, soft faeces. **≥10 mg/kg**: ALP↓, enlarged epiphyseal growth plate, decreased chondroclasis, decreases of osteoclasts and osteoblasts. Trabecular and total bone mineral density –radius, total bone mineral content-tibia ↑. OSCL, NTx/UCRT, SCRL ↓ from week 13. **50 mg/kg**: 2 deaths (M), inorganic P↓, Ca^{++}↓ (slightly M), bone mass ↑ (by DXA and/or pQCT), femur diaphysis, lumbar spine biomechanical strength ↑

The decreases in total alkaline phosphatase and serum calcium (males) in the 1 month study (101447) were in accordance with the pharmacological activity. In addition to changes included in the table above, one high dose male and high dose female in the intravenous group had occult blood in urine at week 4. This was also reported for one low dose female. A slight decrease in erythrocytes, hematocrit value and haemoglobin values was noted in the treated groups, but changes were small and judged toxicologically insignificant. In males, at the 10 mg/kg intravenous dose an increase in CPK was recorded during recovery while there was a general trend for a decrease in females. At the high dose in males reticulocytes seemed increased during treatment and then subsequently decreased during the recovery period. A slight equivocal trend for an increase in platelets at the high doses was noted.

Histopathological examinations showed an apparent increased incidence of mononuclear cell infiltration in kidney in high dose treated males and females, but changes were slight or very slight. Bone parameters assessed in the study showed a tendency for increases in total and cortical bone mineral density (measured by peripheral quantitative computed tomography) at the proximal tibia in males given 1 mg/kg or higher. Bone mineral density at the distal radius was increased at 1 mg/kg subcutaneously in males during recovery. Cortical bone mineral density at the distal radius was increased at 10 mg/kg intravenously in males during recovery. Bone resorption as reflected by serum cross-linked N-telopeptides was decreased (60 to 80%) at all dose levels. Osteocalcin levels were 15 to 45% below baseline values from day 3 to day 56. Serum osteocalcin and NTx levels were decreased in all treatment groups dose-dependently. Decreases in NTx levels occurred before decreases in osteocalcin and this was taken to indicate that denosumab is predominantly an inhibitor of bone-resorption.

In the high dose intravenous group one female had bilateral ovarian cysts subsequently identified as oviduct cysts. The microscopic changes were overall within the background range and not considered toxicologically significant. Overall denosumab produced expected pharmacological effects, increases in bone mineral density in males together with a decrease in serum alkaline phosphatase, Ca, NTx and osteocalcin levels. The NOAEL was considered 10 mg/kg.

On day 28, antibody positive animals were 100%, 67%, 33% and 25% for the 0.1, 1, 10 mg/kg subcutaneous and 10 mg/kg intravenous groups, respectively. On day 14, 58% (7 animals) were antibody positive in the 0.1 mg/kg group and 1 animal in the 1 and 10 mg/kg groups SC. During recovery 100% of treated animals were positive except in the 10 mg/kg intravenous group where 67% were antibody positive. Antibody incidence increased during the recovery period. Following the first subcutaneous dose the maximum plasma levels were 1.51, 14.0 and 155 at the dose of 0.1, 1 and 10 mg/kg and occurred at 72, 92 and 108 hours post-dose respectively.

Table 11. Plasma level estimates week 4

Dose (mg/kg)	**Cmax (µg/ml)**	**$AUC_{(0-168)}$ (µgxhr/ml)**	**$AUC_{(0-168)}$/D(µgxhr/ml/µg/kg))**	**Tmax (hr)**
0.1 (SC)	11.3	349	3490	26.9
1 (SC)	27.5	3410	3410	30.7
10 (SC)	302	42000	4200	35
10 (IV)	663	68600	6860	4

There was no evidence of exposure in control animals.

Exposure decreased during recovery in animals that developed antibodies.

Table 12. Plasma level estimates day 21 in antibody positive and antibody negative animals

Dose (mg/kg)	**Cmax (µg/ml)**	**$AUC_{(0-t)}$(µgxhr/ml)**
10 (SC) pos	25.7	33000
10 (SC) neg	30.7	60000
10 (IV) pos	59.7	54800
10 (IV) neg	72.9	82500

A total of 8 males and 8 females per group were used in the 6 and 12 month study (102090) and 3 animals/sex/group were necropsied week 25 and week 53 of study. The recovery group included 2 animals/sex/group and these were sacrificed week 66. Administration was once per month. Clinical signs, body weight, food intake, ophthalmology, cardiovascular parameters or clinical pathology did not seem affected by treatment. Incidences of diarrhea occurred, apparently at a higher incidence than the overall incidence at the testing facility, but were comparable across groups. At interim kill as well as terminal kill there was a trend for increased heart organ weight in males (statistically significant), but not females.

One male (403) exhibited bradycardia and a fused P-T wave week 25 of study, but as signs of poor physical condition were also noted this change was not judged related to treatment. Evaluation of sperm motility or morphology indicated no relevant effects of denosumab. Total white blood cell count was significantly higher in high dose females week 52 and there was a trend for higher values at earlier timepoints. In addition, there were statistically significant changes in a few haematology and clinical chemistry parameters, e.g. calcium levels were slightly decreased at the high dose in males. No dose response was evident and may be difficult to define also in view of development of antibodies. Denosumab did not appear to have any effect on the immune system, but inter animal variations in immunoglobulin levels and lymphocyte subset occurred. Lymphocytes (%) exhibited a trend for decrease in the high dose group compared with predose values. Immunogenicity of denosumab was reflected in 100%, 50% and 13% of monkeys having binding antibodies in the 1, 10 and 50 mg/kg group, respectively. Corresponding numbers for neutralizing antibodies were 81%, 50% and 47%. Immunophenotyping indicated a tendency in high dose females for elevated CD4+ T-helper cells at week 25, but this finding was not confirmed later. The change was ascribed a minor relevance, but could be consistent with a potential of denosumab to interfere with the immune system under certain circumstances. Determination of immunoglobulin levels indicated a decrease in IgM in males at week 25 and 52, but changes were not statistically significant and were not evident in females. Also in males, NK/B cell determination week 25, both $CD3^-$ $CD16^+$ (also week 52) and $CD3^+$ $CD16^+$, exhibited an increase, but this was not statistically significant and a slight decrease were noted in females.

Bone turnover markers in serum and urine were decreased by denosumab and returned to near baseline at the end of the 3 month non-treatment period. The marker OSCL was decreased from doses of at 10 mg/kg and from week 13. The bone resorption marker SCRL and NTx/UCRT ratio was decreased from week 13 from doses of 10 mg/kg. Histopathological investigations of tibia, sternum and femur showed decreases in osteoblasts and osteoclasts, decreased chondroclasis at the epiphyseal growth plate with increased thickness of the epiphysis at doses of 10 mg/kg or higher in the 6 month study.

Two males in the high dose group died, one on day 76 and the other on day 289. The weight of evidence suggested the cause of death being unrelated to treatment with denosumab. Haematology parameters did not suggest immunosuppression. Histopathology showed evidence of cardiac inflammation in the male monkey that died on day 76, but similar changes were also noted in a control monkey. The monkey that was euthanized day 289 was diagnosed with intestinal inflammation and signs were indicative of an acute exacerbation of pre-existing parasitic intestinal infection. Overall it cannot be excluded that treatment created favourable conditions for an adverse progression of a sub-symptomatic existing disease.

The NOAEL for the study was considered 50 mg/kg.

Table 13. Plasma level estimates in Anti-AMG162 antibody positive animals following the 13 subcutaneous dose

Dose (mg/kg)	Cmax (µg/ml)	AUC(0-τ) (µgxhr/ml)	AUC(0-τ)/D(µgxhr/ml/mg/kg))	Tmax (hr)
1	ND (0)	ND (0)	ND (0)	ND (0)
10	1.79 (2)	75.7 (2)	0.00757 (2)	36 (2)
50	32.8 (1)	2660 (1)	0.0531 (1)	24 (1)

Number of animals in parenthesis. ND=not determined

Table 14. Plasma level estimates in Anti-AMG162 antibody negative animals following the 13 subcutaneous dose

Dose (mg/kg)	Cmax (µg/ml)	AUC(0-τ) (µgxhr/ml)	AUC(0-τ)/D(µgxhr/ml/mg/kg))	Tmax (hr)
1	ND (0)	ND (0)	ND (0)	ND (0)
10	115 (4)	48200 (4)	4.82 (4)	24 (4)
50	666 (7)	268000 (7)	5.37 (7)	48 (7)

Number of animals in parenthesis. ND=not determined

At the dose of 1 mg/kg all animals had antibodies. Development of anti AMG162 antibodies correlated with a marked reduction in serum levels and systemic exposure. With increasing dose the incidence of animals with anti-AMG 162 antibodies decreased. Neutralizing antibodies were detected in 23 of 47 dosed animals in week 12 but of the 23 animals followed to week 52, 15 maintained neutralizing antibodies. Denosumab exhibited thus immunogenicity in the cynomolgus monkey.

No specific toxicity of denosumab was reported in the monkey studies. In the 12 month study the most common histopathological finding was listed as inflammatory cell foci in various organs such as kidney, liver as well as brain. In addition at the terminal kill that included 3 animals/sex/group, there was 2 cases of brain inflammation, one male at 1 mg/kg and 1 female at 10 mg/kg. Further, there were occurrences of haemorrhages in various organs, primarily the liver and caecum, at the interim and terminal kill, respectively. The relation to treatment of these findings is difficult to assess also due to differences in site, the magnitude (sligtht, moderate etc) and possible relation to production of antibodies. It may be noted that the 2 deaths at the high dose were males while no deaths were reported in the 16 month monkey bone study that included female animals although similar doses were used.

Binding antibodies in the 1, 10 and 50 mg/kg groups were reported to 100%, 50% and 13% and corresponding incidences of neutralizing antibodies to 81%, 50% and 47%, respectively. This pattern is a confounding factor in the interpretation of data.

Toxicokinetics

Toxicokinetic data is presented in relation to relevant studies.

Interspecies comparison

Table 15. Interspecies comparison

Species/Study	**Dose* (mg/kg)**	**Cmax (µg/ml)**	**$AUC_{0\text{-}tau}$ (µgxh/ml)**	**$C_{max\ animal}/C_{max\ human}$ AUC_{animal}/AUC_{human}**
Monkey (cynomolgus) (102090)-12 month	10	115	48200	4 -
	50	666	268000	25 -
Monkey (cynomolgus) (103981)-16 month	25	222	101000	8 -
	50	413	171000	15 -
Monkey (cynomolgus) (102842)-Embryo-fetal toxicity	12.5	282	41000	10 -

* The proposed human dose is 120 mg subcutaneously/4 weeks and the corresponding $AUC_{0\text{-}4\ weeks}$ 723 µgxday/ml and the Cmax 27 µg/ml. The AUC for a 6 month interval was approximated by multiplying by 26 and 6 for weekly (102842) and monthly (102090 and 103981) dosing, respectively.

The Applicant proposes that the NOAEL in monkey toxicology studies is 50 mg/kg. This is questionable also in view of the 2 deaths at the high dose, both males, and the level of confidence that can be attributed to such a NOAEL seems uncertain. Nothwithstanding, it seems that monkeys were sufficiently exposed in toxicology studies. Comparison based on AUC values has not been included in the table above as the unit (day) in the cited human $AUC_{0\text{-}4\ weeks}$ of 723 µgxday/ml is immediately comparable or translated into the 6 month data.

Genotoxicity

No specific 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 specific 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.

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 related to altered immunolopgy that could be critical in cancer pathogenesis.

Reproduction Toxicity

Table 16. Summary table of performed studies.

Study type/ Study ID / GLP	**Species; Number/ sex/group**	**Route & dose**	**Study design**	**Major findings**
Fertility early embryonic development (1052-013)	Monkey (cynomolgus) (6 F)	SC, 0, 2.5, 5, 12.5 mg/kg	Once/week through 2 menstrual cycles until day 20 post-mating	No effect on fertility. Control, low and mid dose, 2 of 6 animals mated. At high dose, 5 of 6 animals pregnant.
Embryo-foetal (102842)	Monkey (cynomolgus) (16 F)	SC, 0, 2.5, 5, 12.5 mg/kg	Once/week, gestation day 20 to 50	No effect clinical sign, body weight. No effect fetal organ, placental weight, external, visceral or skeletal examinations of foetuses.

Fertility and early embryonic development

After multiple doses a decrease in exposure was noted in 4/6, 3/6 and 2/6 animals in the low, mid and high dose groups, respectively, likely due to development of antibodies. The low dose was selected to provide approximately x3 exposure margins to expected clinical exposure and was considered the lowest dose possible to give and maintain exposure.

A specific male fertility study was not conducted, but male fertility parameters, including assessment of sperm concentration and morphology, were monitored in the 12 month monkey study. No evidence of an effect on testes was reported.

Table 17. Mean toxicokinetic parameters for denosumab in fertility study

Dose (mg/kg)	**Cmax (µg/ml)**	**AUC(0-τ) (mgxhr/ml)**	**tmax (hr)**
2.5	48.8 (after 1st dose) 26.5 (prior to 1st mating) 121 (prior to 2nd mating)	6.77 (after 1st dose) 4.22 (prior to 1st mating) 17.6 (prior to 2nd mating)	72 (after 1st dose) 24 (prior to 1st mating) 64 (prior to 2nd mating)
5	79 (after 1st dose) 115 (prior to 1st mating) 163 (prior to 2nd mating)	11.7 (after 1st dose) 16.4 (prior to 1st mating) 16.9 (prior to 2nd mating)	72 (after 1st dose) 24 (prior to 1st mating) 24 (prior to 2nd mating)
12.5	186 (after 1st dose) 476 (prior to 1st mating) 727 (prior to 2nd mating)	26.9 (after 1st dose) 67.8 (prior to 1st mating) 85.5 (prior to 2nd mating)	72 (after 1st dose) 24 (prior to 1st mating) 8 (prior to 2nd mating)

The dose number prior to first mating was 11, 9 and 10 for the low, mid and high dose groups respectively. The dose number prior to the second mating was 18, 17 and 20 for the low, mid and high dose groups respectively.

Embryo-fœtal development

A study in pregnant cynomolgus monkey was conducted to evaluate the potential embryonic and teratogenic effects of denosumab. Treatment was not associated with any signs of histopathological alterations (thymus, spleen and Peyer's patches examined histologically in fetuses). Fetal spleen mean weight showed a trend for a decrease with increasing dose, however, no statistically significant differences were evident. There was no evidence of toxicity in maternal animals. The incidence of prenatal loss was 3 of 16 in control and 1 of 16 in the low dose group. There were 3 abortions in the control group between days 25 and 66 of gestation and 1 in the low dose group between days 33 and 38 of gestation. One fetal death occurred day 86 in the mid dose group. This was considered incidental.

Toxicokinetics indicated a moderate accumulation over the 5 weekly doses. Denosumab was detected in 70% of fetal serum samples (collected at cesarean section) indicating the compound crosses the

placental barrier. Anti-denosumab antibodies developed in 66% of treated animals and 34% developed neutralizing antibodies. Neutralizing antibodies were found in 53%, 38% and 13% of serum samplesf rom low, mid and high dose, respectively. Non-neutralizing (35%) and neutralizing (16%) antibodies were detected in fetal samples also indicating that denosumab crossed the placental barrier. One monkey in the control group had quantifiable serum denosumab concentrations.

Table 18. Mean toxicokinetic parameters for denosumab in embryotoxicity study

Dose (mg/kg)	**Cmax (µg/ml)**	**AUC(0-τ) (mgxhr/ml)**	**Tmax (hr)**
2.5	1-25.9 5-42.7 *(5-58.8(-), 28.5 (+))*	1-3.59 5-5.78 *(5-8.8 (-), 3.14 (+))*	1-120 5-24 *(5-24 (-), 48 (+))*
5	1-56.6 5-94.1 *(5-114 (-), 61.2 (+))*	1-7.46 5-11.9 *(5-15.5 (-), 5.95 (+))*	1-120 5-24 *(5-16 (-), 24 (+))*
12.5	1-122 5-291 *(5-282 (-), 356 (+))*	1-16.7 5-41.4 *(5-41 (-), 43.9 (+))*	1-120 5-24 *(5-24 (-), 24 (+))*

Values are following the first (1-) and 5th (5-) subcutaneous dose and corresponding values for *neutralizing antibody negative (-)* and *positive (+)* monkey are in parenthesis).

Reproduction toxicology studies were conducted in the monkey, only. This is acceptable in view of the species selectivity of denosumab. Further, literature data are in line with the fact that deficiency of RANK/RANKL has an impact on the development of the lactating mammary gland. While constitutive deficiency of RANK/RANKL and inhibition of the same may not be directly comparable, the issue has been adequately addressed in section 4.6 of the SmPC.

Prenatal and postnatal development, including maternal function

No specific studies were conducted and this is acceptable in view of considerations on use of animals and there being no cause of concern identified in other studies. A study (R220080340) in the preweaning rat may though have been considered in this context.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No specific studies were conducted and this is justified with reference to the indication not including patients less than 9 years old and the age of monkeys used in the toxicology programme.

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.

Other toxicity studies

Antigenicity

No specific studies were conducted. Antigenicity was assessed in the general toxicity studies. At all doses a high incidence of binding and/or neutralizing antibodies were detected. Denosumab was associated with immunogenicity in monkey. In humans very low incidence of production of anti drug antibodies has been reported (see clinical section).

Immunotoxicity

No specific studies were conducted. Under the conditions in chronic toxicity studies and in the chronic bone quality pharmacology studies no significant adverse effects on immunology parameters

monitored were recorded. However, the potential for unwanted effects of denosumab on immune function is not clear. Also based on theoretical considerations on the role of OPG/RANKL in osteoimmunology, dysregulation, modulation, toxicity cannot be ruled out and collectively the data indicate that a concern for interference with immune pathways of regulatory importance cannot be dismissed.

Dependence

No specific studies were conducted. Denosumab has not been shown to interact with receptors known to be involved in dependence.

Metabolites

No specifc studies have been conducted, which is considered acceptable.

Studies on impurities

No specific studies have been conducted, which is considered acceptable.

Other studies

Three studies addressing the potential for cross-reactivity were conducted.

Table 19. Cross-reactivity studies with denosumab

Study ID	Study type	Noteworthy findings
101758	Cross-reactivity with cynomolgus monkey and human tissues. 1, 10 µg/ml. Spleen, lymph node, thymus, tonsil, bone marrow, thyroid, bone, human bone, human lymph node	Membrane staining of lymphocytes lining the periphery of the paracortex in monkey. Human fetal bone and human lymph nodes positive. Non-specific staining in multiple tissues.
101348	Cross-reactivity with normal human tissues 1, 10 µg/ml.	Immunoreactivity in lymph node from 1 donor. Weak-moderate staining of few-moderate lymphocytes lining the periphery of the paracortex. Unconclusive.
102700	Cross-reactivity with monkey, rat and rabbit tissue, 3 animals/species. 5, 25 µg/ml.	Monkey: Lymph nodes, spleen and GALT. Rat: Light to moderate staining in chrondrocytes and the margins of the surrounding lacunae in the auricular cartilage. Rabbit: Lymph nodes, spleen and GALT

Studies were conducted according to principles of GLP with some exceptions.

2.3.5. Ecotoxicity/environmental risk assessment

Denosumab is a human monoclonal antibody with an approximate molecular weight of 147 kilodaltons. It is a sequence of amino acids and a protein and in accordance with the CHMP guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00) is exempt from testing because of the chemical structure.

2.3.6. Discussion on non-clinical aspects

Pharmacodynamics

The additional pharmacology studies both *in vitro* and *in vivo* provide evidence that denosumab has expected effects relevant to the indication prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours. The dosing schedule for this indication differs from that in osteoporosis in that a higher frequency and a higher dose is employed. 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.

Pharmacokinetics

Levels of denosumab in serum from mouse, rat and monkey were measured by an ELISA method that, in principle, determined free (not bound to RANKL) denosumab. Pharmacokinetics and disposition following subcutaneous or intravenous administration of single and multiple (only in monkey) doses of denosumab were investigated in mouse, rat and cynomolgus monkey, species also used in toxicology studies. 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-lifes were 19 days in mouse and 11 days in rat.

In the cynomolgus monkey pharmacokinetics were linear over an intravenous 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. Following subcutaneous doses of 0.0016 to 1 mg/kg, non-linearity was evident while approximately linear pharmacokinetics were recorded at a dose range of 1 to 3 mg/kg. 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 ^{125}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. 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 the potential to cross the blood/brain barrier, the blood/testis barrier as well as the placental barrier. 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 (e.g. membrane, soluble) does not appear to be available. Literature data indicate that RANKL may be produced by tumour cells themselves, for example in multiple myeloma, prostate cancer, or human neuroblastoma. Further, osteosarcoma cells have been reported to express the functional receptor RANK at the cell surface.

Denosumab is a monocloncal 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.

The monkey was determined to be the most suitable species to use in toxicology studies based on pharmacology and pharmacokinetics. Toxicokinetic data showed no significant differences in exposure in male and female animals. 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

Denosumab is a fully human monoclonal antibody (IgG2) with affinity and specificity for the human receptor activator of nuclear factor κB ligand that may bind and inactivate RANKL similarly to the endogenous osteoprotegerin. The potential for toxicity of denosumab after repeated administrations and monitoring of standard parameters was evaluated in monkey as denosumab only recognizes RANKL in nonhuman primates. In addition some data from knock-out mice are also considered from the toxicological point of view. OPG/RANKL interactions have been implicated in a variety of disease activities also including liver and vascular systems.

In monkey, subcutaneous doses up to 10 mg/kg once weekly and 50 mg/kg given once per month were administered for durations up to 12 months. No specific single dose toxicity studies were conducted, but no remarkable observations were recorded after the first dose in the repeated dose toxicity studies. The intended human dose is 120 mg given subcutaneously every 4 weeks corresponding to an $AUC_{0\text{-}4\ weeks}$ of 752 µg*day/ml and in most cases doses used in toxicology studies represented high multiples of expected human exposure. However, the development of neutralizing and/or binding antibodies in subsets of animals, resulting in greatly reduced exposure, was a confounding factor. There were no remarkable changes in clinical parameters, serum biochemistry, or histopathological effects in any of the studies, but bone turnover markers in serum and urine were decreased as were calcium levels (in males). Clinical data indicate cataracts as common eye disorders, but no treatment related ocular changes were reported after ophthalmological examinations in monkey. In the 12 month monkey study, 2 deaths at the high dose occurred. The overall conclusion was that deaths were not related to treatment, one diagnosed with possibly cardiac inflammation and the other death linked to acute exacerbation of pre-existing parasitic intestinal infection. However, it does not seem completely justified to exclude a possibility of involvement of an induced dysregulation of immune function in these findings. Of note is that the 2 deaths were both males. No deaths were recorded in the 16 month bone study that utilized female animals only. Further, clinical data have indicated a higher incidence of infections in subsets of denosumab treated patients.

No specific data on local tolerance is available, but clinical data are expected to be sufficient to assess any possible local reactions.

The pharmacological target of denosumab indicates that a potential for adverse effects may also involve osteoimmunological pathways. No specific studies on potential for immunotoxicity have been conducted. From data in the literature it appears 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. Data on potential effects of RANKL inhibition on the immune system are though conflicting. In rodent models using the endogenous RANKL inhibitor osteoprotegerin, a modest stimulation of production of antigen specific antibodies against T cell dependent and independent antigens has been reported. Denosumab and the natural ligand exhibited a similar range of binding affinities in *in vitro* studies. *In vitro,* osteoprotegerin had modest T cell co-stimulatory properties. To the extent these results with endogenous inhibition by osteoprotegerin can be extrapolated to inhibition by denosumab in primate/humans it would appear that cellular responses are not affected while antigen specific humoral responses may be stimulated. Although no relevant effects were

reported in infection models that assessed host response to Bacillus-Calmette-Guerin or influenza virus infection, such studies have limitations and an interference with the immune response e.g. under conditions of a pre-altered immune system cannot be fully ruled out. Denosumab may be considered a multifunctional molecule in the sense that antibodies have a potential to activate FcR bearing cells as well as primary target cells. An antibody can act as a bridge bringing different cells into close contact by virtue of engaging an antigen recognizing part and engaging Fc receptors on different cells via its Fc part also indicating a potential for additional cellular activation.

Due to the species specificity of denosumab, toxicity studies in rodents were not conducted, however reference is made to data obtained in knock-in mouse as well as rodent studies using osteoprotegerin instead of denosumab. Although ablation of RANKL and inhibition of the RANK/RANKL pathway can be expected to differ, such data may provide indications of potential for undesirable effects due to interference with this signalling system involving diverse pathways. These studies were focussed on the primary pharmacological effect and no specific toxicity, with the exception of expected effects (defects in tooth eruption, lymph node genesis, mammary gland and lymphocyte development as well as disturbances in T cell/dendritic cell interactions), was reported. Denosumab appears thus to include several features that preclude a reliable risk assessment from the non-clinical point of view: species-specificity, immunogenicity, immune system target, target in systems with potential for large biological amplification *in vivo*, multifunctional agent (Fc binding domain) and cell associated target. Taking these issues into consideration denosumab toxicity may be accepted as sufficiently investigated and at this point of time clinical experience may be expected to be extensive, although with a different posology. In similarity to some intravenous bisphosphonates, use of denosumab in the clinic has been associated with incidences of osteonecrosis of the jaw (ONJ). The mechanism of ONJ has not been established, but a role of inhibition of osteoclastic activity has been discussed. Bisphosphonates reportedly alter this activity by interfering with osteoblast production of mediators of osteoclastogenesis. There are studies indicating that some bisphosphonates may alter production of RANKL and OPG contributing to a microenvironment that favours inhibition of bone resorption and ONJ. Osteoblastic activity is coupled to osteoclastic activity and oversuppression of bone turnover may result. Antiangiogenetic properties may also be involved in the process. Further, in this context the issue whether a similar "osteolytic targeting" of denosumab and bisphosphonates (that may have a prolonged half-life) could also have implications on safety aspects such as ONJ, in the event bisphosphonate therapy is followed by denosumab administration.

A cross-reactivity study using a human tissue panel was conducted, but was inconclusive.

The potential for reproduction toxicity of denosumab was evaluated in monkeys. Fertility and early embryonic development did not appear to be influenced by weekly subcutaneous doses of denosumab up to 12.5 mg/kg. However, this may be attributable to study design. Denosumab treatment was applied from GD20-GD50, during the time of organogenesis when the placenta however is not permeable for monoclonal antibodies. With caesarean section being on day 100, there likely has not been enough drug exposure of the foetus for an effect to show. Evaluation of sperm motility and flow cytometric data on testicular tissue in the 12 month monkey toxicity study did not indicate adverse effects of denosumab. 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.

A further study of reproductive toxicity in an "enhanced pre/post natal design" (with exposure at the relevant time period) in the Cynomolgus monkey is currently undertaken and the results will become available in the end of 2011. These study results should be submitted as a FUM with the consequence that in case of safety signals, appropriate changes will be implemented in the SmPC.

Studies using various rodent models of RANKL inhibition during early and rapid bone growth concluded that denosumab administration, particularly at younger ages, high doses or prolonged durations, has the potential to negatively influence long bone growth, geometry or strength in children.

No specific studies on the potential for genotoxicity and carcinogenicity have been conducted and the lack of studies has been justified and is generally consistent with applicable guidelines. Denosumab is not likely to have any primary genotoxic/carcinogenic potential, but a potential to interfere with the immune system cannot be discounted and the available studies that address these issues seem limited. 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.

2.3.7. Conclusion on the non-clinical aspects

The majority of non-clinical studies submitted with the application have already been assessed in the context of the osteoporosis indication for Prolia and the present report focuses on the additional primary pharmacology studies conducted in support of the new indication. These studies used OPG-Fc as an inhibitor of RANK in different murine models of bone metastasis. The sections on pharmacokinetics and toxicology are in principle the same as in the previous non-clinical report for Prolia with no new data included, but are discussed in relation to the higher dose and the increased frequency of dosing relevant for the present indication. In a 6-month period the dose is 12 times greater than the previously approved dose for osteopososis and corresponds to an $AUC_{0\text{-}4weeks}$ of 752 µgxday/ml. The Cmax at a dose of 120 mg was approximately 11 µg/ml. Comparison of exposures achieved in non-clinical studies and the expected clinical values at the new dose and new dosing frequency indicate considerable margins of exposure although the development of anti denosumab antibodies is a confounding factor.

The additional pharmacology studies both *in vitro* and *in vivo* provide evidence that denosumab has expected effects relevant to the indication prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours. Considering the mechanism of action of denosumab, potential effects on immunomodulation and immunosuppression cannot be ruled out.

Safety pharmacology studies revealed no major cause for concern. RANKL is expressed in several tissues. OPG mRNA is highly expressed in e.g. heart. Secondary pharmacology studies did not indicate any specific unwanted activity of inhibition, but studies were focused on immune and bone issues. One incidence of heart inflammation was an equivocal finding in a monkey study and a trend for an increase in heart weight in males was noted in earlier studies.

Based on the review of the non-clinical data provided, the MAA for XGEVA is considered approvable.

2.4. Clinical aspects

2.4.1. Introduction

Denosumab is a fully human monoclonal antibody of IgG_2 subtype, inhibiting the receptor activator of nuclear factor-κB (RANK). Inhibition of RANKL is a possible intervention point to interfere with conditions with increased bone resorption.

Previously, a separate stand alone MAA was submitted in January 2009 via the Centralised Procedure and the corresponding Commission decision was granted on 26 May 2010 for the use of denosumab (Prolia) in the following indications:

- *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 (see section 5.1). In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.*

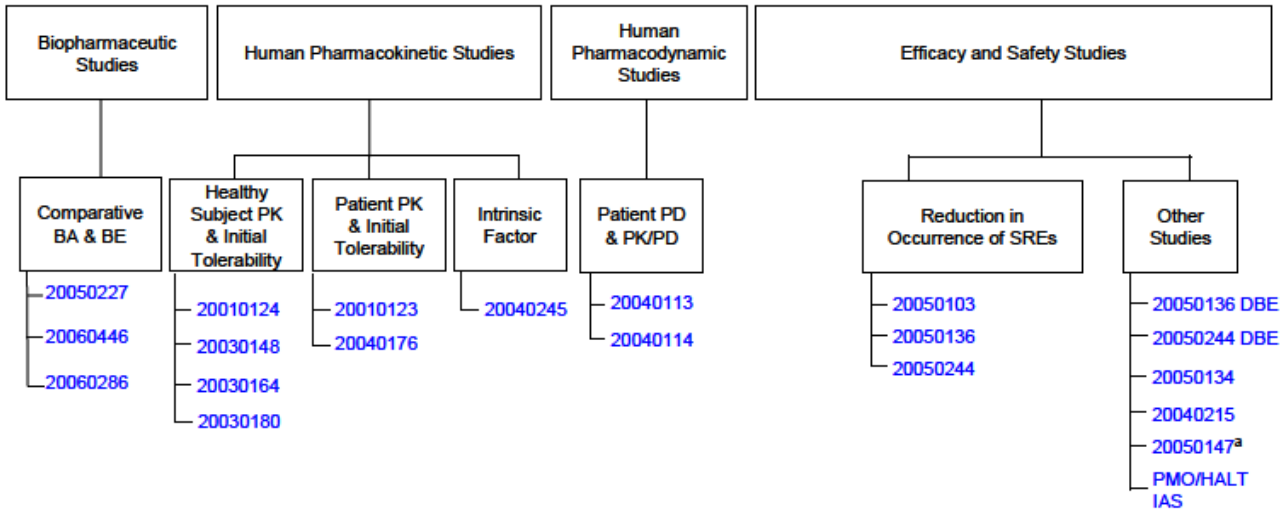
The current XGEVA MAA concerns another indication *(wording applied for)*:

- *Prevention of skeletal related events in adults with advanced malignancies involving bone.*

Seventeen of the 18 clinical studies supporting this marketing application contributed data on the safety, tolerability, PK, and PD profiles for denosumab (Figure 2). The remaining study (20050147) also assessed these parameters but is ongoing and blinded; therefore, PK and PD data are not yet available.

Seven of the 18 studies were primarily designed as phase 1 clinical pharmacology studies to assess healthy volunteer PK and initial tolerability (Studies 20010124, 20030148, 20030164, and 20030180), patient PK and initial tolerability (Studies 20010123 and 20040176), or intrinsic factor PK (renal impairment, Study 20040245). Two of the 18 studies were phase 2 studies designed to assess patient PD and PK/ PD (Studies 20040113 and 20040114); one (20040114) was an extrinsic factor study (previous IV bisphosphonate use), and the other (20040113) was a dose-ranging study. The remaining 9 studies were primarily designed to address other objectives.

Fig 2. Organogram of denosumab clinical studies in this application



[a] blinded demographic and safety data only

BA = bioavailability, BE = bioequivalence, DBE = double-blind extension, HALT = hormone ablation therapy, IAS = integrated analysis of safety, PD = pharmacodynamics, PK = pharmacokinetics, PMO = postmenopausal osteoporosis, SRE = skeletal-related event.

The phase 2 dose-ranging Study 20040113 forms the rationale for the proposed dose regime. It was designed to evaluate 5 SC denosumab dosing regimens of 30, 120, and 180 mg Q4W and 60 and 180 mg Q12W and an IV bisphosphonate comparator in 255 subjects with breast cancer and bone metastases. The 120 mg Q4W dose was selected as the phase 3 dosing regimen because it was well-tolerated, resulted in high serum denosumab levels throughout the dosing interval, and achieved maximal suppression of uNTx/Cr over the entire dosing interval in a high proportion of subjects.

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.

2.4.2. Pharmacokinetics

The data provided for the PK analysis of this application are mainly identical to those assessed for the MAA for Prolia (denosumab). Since the outcome of the assessment of these data is still valid and supported by the CHMP, the relevant studies have not been assessed again and regarding these trials the following PK information reflects the previous CHMP assessment of the relevant paragraphs as far as applicable for the different dosing regimen proposed in the current application.

In addition the applicant has provided data from PK substudies in the pivotal phase III trials 20050103, 20050136, and 20050244 to allow for an assessment of PK parameters of the 120 mg Q4W dosing regimen in the target population. PK data from Study 20050244 and Study 20050136 have been included in the population pharmacokinetic model.

Absorption

The only study where denosumab was given both IV and SC was a Phase 1, dose-escalation (0.01, 0.03, 0.1, 0.3, 1.0, and 3.0 mg/kg) study (20010124) in postmenopausal women between the ages of 40 and 70 years old. Twelve single-dose cohorts with 8 subjects per cohort randomized to either denosumab or placebo (3:1 ratio) were evaluated. Six cohorts received a single SC injection and six cohorts received a single IV injection.

Following both IV and SC administration, denosumab demonstrated dose-dependent, nonlinear PK. Mean SC CL/F and mean IV CL observed at 0.01 mg/kg were 9.8-fold and 4.4-fold greater, respectively, than mean CL/F and CL at 3 mg/kg.

Table 20. Relative exposure following SC and IV administration.

Dose (mg/kg)		0.01		0.03		0.1		0.3		1.0		3.0	
Parameter	Units	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
RE	% Dose	35.6	NA	62.8	NA	60.6	NA	63.6	NA	77.9	NA	74.8	NA

Based on the Population PK analysis of the 120 mg Q4W dosing PK data the absolute bioavailability was estimated to be 62%, in line with the estimate of 61% for the 60 mg/Q6M dosing, findings in the Study 109957 population PK analysis for the Q6M dosing, and 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

The 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 (3.96 L/66 kg), indicating limited extravascular distribution, as expected for a monoclonalantibody.

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 the fact that renal function did not affect the PK of denosumab.

The initial phase 1 studies of denosumab in healthy postmenopausal women, healthy men ≥ 50 years of age, and subjects with advanced cancer and bone metastasis (Studies 20010123, 20010124, 20030148, 20030164, and 20030180) explored a wide range of weight-based SC doses (0.01 to 3.0 mg/kg). An additional phase 1 study in Japanese subjects (Study 20040176) assessed single fixed doses of 60 and 180 mg and 3 fixed doses of 180 mg Q4W. A phase 2 study, Study 20040113, explored a wide range of fixed SC doses (30 to 180 mg) and dosing intervals (Q4W and Q12W) in subjects with breast cancer and bone metastasis.

The results of these assessments consistently show that denosumab displays nonlinear clearance across a wide dose range. However, non-linear clearance is observed primarily at lower doses (0.03-0.3) mg/kg. An indication of less nonlinear PK is seen in doses over 60 mg/kg which is consistent with the proposed saturation of the target mediated elimination. At the 1.0-mg/kg and the 3.0-mg/kg SC doses, which are in the proximity of the 120-mg dose applied for, CL/F was around 0.07-0.1 mL/h/kg.

The corresponding mean half-life value that described the disposition of denosumab over a large proportion of exposure ($t_{1/2,\beta}$) was approximately 30 days, which is similar to that observed for other monoclonal antibodies.

Consistent with these data which indicate approximately dose-proportional increases in exposure with weight-based doses above 1.0 mg/kg, mean C_{max} and $AUC_{0\text{-}tau}$ values increased approximately 3.8- to 4.0-fold for a 3-fold increase in fixed dose from 60 to 180 mg in Japanese subjects with breast cancer and bone metastasis in Study 20040176 and increased approximately 5.8- to 6.5-fold for a 6-fold increase in fixed dose from 30 to 180 mg in subjects with breast cancer and bone metastasis in Study 20040113

Dose proportionality and time dependencies

Dose proportionality

The initial phase 1 studies of denosumab in healthy postmenopausal women, healthy men ≥ 50 years of age, and subjects with advanced cancer and bone metastasis (Studies 20010123, 20010124, 20030148, 20030164, and 20030180) explored a wide range of weight-based SC doses (0.01 to 3.0 mg/kg) with intensive PK sampling. The results of these assessments consistently show that denosumab displays nonlinear PK across a wide dose range. At doses at or above a dose of 60 mg (approximately 1.0 mg/kg), however, an indication of less nonlinear PK is seen.

Time dependency

Time dependency could be assessed based on data from study 20040114 which was a phase 2, multicenter, randomized, open-label, active-controlled, parallel-group, multi-dose (up to week 25) study in subjects with advanced cancer. One group received denosumab 180 mg SC Q4W and limited PK sampling was performed after the first dose up to study week 32. An approximate 2-fold accumulation (1.7- to 2.3-fold) was observed for the denosumab 180-mg Q4W group following the third and fifth doses.

Denosumab does not seem to exhibit time dependent PK. The accumulation ratio is in line with the expected accumulation ratio based on single dose PK data.

Intra- and inter-individual variability

Inter-individual variability is approximately 40% in C_{max} and AUC. Data on intra-individual variability has not been presented.

Pharmacokinetics in target population

Sparse pharmacokinetic sampling was performed primarily for POP-PK analysis in the pivotal phase 3 studies of subjects with advanced malignancies involving bone (breast cancer, prostate cancer, other solid tumors, and multiple myeloma) (Studies 20050136, 20050244, and 20050103). These data allow comparison of trough denosumab serum concentrations at 1, 3, and 6 months (during 120 mg denosumab Q4W dosing) between these subjects and subjects with advanced breast cancer in the phase 2 dose-ranging study (Study 20040113) and healthy adults in Study 20060446. Study 20060446 was considered appropriate for comparison purposes (month 1 only; single dose) because this study used the proposed clinical dose of 120 mg denosumab and enrolled a relatively large sample size (116 healthy adult men and women) for a phase 1 study with intense pharmacokinetic sampling.

The advanced cancer population in Study 20050244 included subjects with multiple myeloma, non-small cell lung cancer, and a range of other solid tumors (breast cancer and prostate cancer were excluded). Because of the large number of different solid tumor types and the small number of subjects per tumor type, comparisons of exposure between all individual tumor types in this study were not performed; only data for subjects with multiple myeloma are assessed separately.

Median trough serum denosumab concentrations at month 1 after a 120 mg dose differed by < 52% between subjects with solid tumors (breast, prostate, and other solid tumors) and healthy adults (men and women), with extensive overlap in the 10th to 90th percentile ranges. In addition, median trough serum denosumab concentrations at month 6 differed by < 23%, respectively, between subjects with breast cancer (Studies 20040113 and 20050136), subjects with prostate cancer (Study 20050103), and subjects with other solid tumors (Study 20050244), with notable overlap observed in the 10th to 90th percentile ranges.

These results indicate that disease status (i.e., breast cancer, prostate cancer, other solid tumors) does not markedly affect the pharmacokinetic profile of denosumab. No conclusion can be drawn regarding multiple myeloma in this comparison due to limited patient numbers.

Population PK model

The population pharmacokinetic model provided in this application is mainly in line with the population PK Study 109957 for the Q6M dosing with the exception of the addition of data from the phase III pivotal Studies 20050244 and 20050136. The primary objectives were to quantitatively characterise the pharmacokinetics after IV and SC administration to healthy subjects, postmenopausal women with low BMD or osteoporosis, and subjects with cancer, to quantify intra-subject variability, and to evaluate the influence of patient- and treatment-related covariates on variability. The population PK analysis was performed using NONMEM.

The analysis included serum denosumab concentration-time data from 20 clinical studies, including healthy subjects, postmenopausal women with low BMD or osteoporosis, and subjects with cancer. Denosumab was administered as a single IV dose (N = 36) or as single or multiple SC doses

(N = 2279) ranging from 0.01 to 3 mg/kg or 6 to 210 mg fixed dose administered Q4W, Q3M, or Q6M for up to 48 months. Index and Test data subsets were prepared and used to develop and evaluate the model, respectively. The Index data consisted of 9 phase I studies (20010123, 20010124, 20030148, 20030164, 20040176, 20050227, 20050241, 20060286, 20060446), 6 phase II studies (20010223, 20040113, 20040114, 20040215, 20050134, 20050172) and 3 phase III studies (20030216, 20040132, 20040135) and included 23,857 denosumab serum concentrations from 2158 subjects. The Test data included data from 2 additional phase III studies (20050244, 20050136) and consisted of 746 serum concentrations from 157 subjects with cancer. The final model was fit to a combined dataset of the Index plus Study 20050136 in order to obtain final population estimates of PK parameters. The final model was fit to the total combined dataset of Index plus Test in order to update the population estimates of clearance for subjects with solid tumours and multiple myeloma, needed due to addition of Study 20050244 to the dataset. The Final dataset included 24603 serum concentrations from 2315 subjects, including 495 healthy subjects, 1069 postmenopausal women with low BMD or osteoporosis, and 751 subjects with cancer. The mean (range) age and body weight were 58 (18 to 87) years and 69 (36 to 174) kg, respectively; 361 (15.6%) were male. Most subjects, 1800 (77.8%), were white; 271 (11.7%), 162 (7.0%), 63 (2.7%), and 19 (0.8%) were Asian, Hispanic, black, and "other", respectively. Data of phase III Study 20050103 were not available at the time of analysis. A two-compartment PK model with linear distribution to the peripheral compartment and parallel linear and nonlinear elimination was selected. The non-linear elimination was described by the capacity-limited binding of denosumab to RANKL using the quasi-steady-state approximation of the target-mediated drug disposition model. The model was parameterised in terms of clearance and volume of distribution, which were allometrically scaled on the basis of body weight using 1.0 as exponents for both types of parameters. For SC dosing, the addition of absolute bioavailability and a first-order rate constant for absorption allowed the model to describe data for this route of administration.

The model estimate for absolute bioavailability was 62% and for mean absorption half-life 3.14 days with rate and extent of absorption being similar across doses evaluated. The volume of distribution was similar to blood volume and linear clearance was estimated to be 3.1 mL/hr/66 kg. At doses $\geq$ 60 mg or $\geq$ 1 mg/kg pharmacokinetics are essentially linear with dose. With 120 mg Q4W the estimated target occupancy at steady state exceeded 98% for a typical subject during the entire inter-dose interval. No evidence of time-dependent kinetics was found for up to 48 months. Simulation predicted a 186% accumulation at steady state with 120 mg Q4W.

In the covariates analyses gender and previous bisphosphonate treatment had no relevant impact on PK parameters. Body weight was identified as the covariate with the largest effect on pharmacokinetics. The between-subject variability ranged from 34% to 53%.

Table 21: Population Pharmacokinetic Parameters of Denosumab

Parameters	Units	Typical Value	Factor [b]	95%CI
Linear Clearance (CL) [a]	mL/hr/66kg	3.08		2.97 - 3.18
- Multiple Myeloma		-	1.71	1.68 - 1.74
- Breast Cancer		-	1.15	1.11 - 1.2
- Aromatase Inhibitors Therapy		-	0.795	0.714 - 0.876
- Prostate Cancer		-	1.30	1.14 - 1.46
- Giant Cell Tumor		-	1.28	1.15 - 1.41
- Other Solid Tumors		-	1.39	1.38 - 1.39
- Black		-	1.21	1.12 - 1.3
- Hispanic		-	1.24	1.17 - 1.31
Central Volume (V_c) [a]	mL/66kg	2660		2540 – 2770
- Black			0.91	0.792 - 1.03
Inter-compartmental Clearance (Q) [a]	mL/hr/66kg	39.5	-	37.8 - 41.2
Peripheral Volume (V_p) [a]	mL/66kg	1300	-	1280 – 1330
Absorption Rate (k_a) [a]	1/hr	0.00921	-	0.00859 - 0.00982
- Age power [c]		-0.556	-	-0.658 – (-0.454)
- Reference Age [c] (AGE_{ref})	years	69.8	-	60.4 - 79.1
Bioavailability (F_{SC})	%	62.1	-	60.5 - 63.7
Baseline RANKL Concentration (R_{max})	ng/mL	590	-	564 – 617
Quasi-Steady-State Constant (K_{SS})	ng/mL	185	-	173 – 198
RANKL Degradation Rate (k_{deg})	1/hr	0.00148	-	0.00142 - 0.00153
Complex Internalization Rate (k_{int})	1/hr	0.00651	-	0.00618 - 0.00684
Between Subject Variability (Variance [CV%])				
Linear Clearance (ω^2_{CL})		0.115 [CV=34.0%]	-	0.108 - 0.123
Clearance-Volume Correlation [R] (ω_{CL} ω_{Vc})		0.0857 [R=0.559]	-	0.0763 - 0.0951
Central Volume (ω^2_{Vc})		0.204 [CV=45.2%]	-	0.188 - 0.22
Baseline Target Concentration (ω^2_{Rmax})		0.19 [CV=43.6%]	-	0.172 - 0.209
Absorption Rate (ω^2_{Ka})		0.279 [CV=52.8%]	-	0.257 - 0.301
Residual Variability:				
High concentrations (phase I studies)	%	9.68	-	9.6 - 9.76
High concentrations (phase II-3 studies)	%	25.6	-	25.4 - 25.8
Low concentrations	%	141	-	138 – 144
Transition from low to high concentrations	ng/mL	56	-	53.5 - 58.4

[a] For a typical subject: 66 kg, 70 years of age, healthy, white
[b] Magnitude of the covariate effect: factor by which the typical value is multiplied
[c] Absorption rate declined with age. The multiplicative factor was $(Age/AGE_{ref})^{Age\ Power}$ up to $Age=AGE_{ref}$ and remained constant at $Age > AGE_{ref}$

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

Following administration of 120 mg SC median denosumab AUC and C_{max} values were < 23% and < 16% different, respectively, between healthy adult men and women, and extensive overlap in the interquartile ranges was observed (see below). Thus, despite a slightly higher average body weight for men (mean 83.1 kg vs. 71.2 kg), no notable differences in exposure were observed. The results do not indicate clinically relevant gender differences in the pharmacokinetics of denosumab.

Race

Because of the limited number of non-white subjects compared with white subjects in Studies 20060446 and 20040113, the assessment of denosumab exposure by race across all studies was evaluated in the POP-PK analysis. Blacks and Hispanics, but not Asians, had approximately 21% to 24% higher denosumab linear clearance relative to whites. The population PK analysis is considered sufficient to conclude that no clinical significant effects on the systemic exposure of denosumab were identified with respect to race (Blacks, Hispanics, Asians and Whites explored).

Weight

Exposure based on AUC and C_{max} tended to be lower for heavier subjects following a 120 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 III studies.

Weight significantly affected the pharmacokinetics of denosumab and one might question the choice of a flat dose instead of a weight based dose from a pharmacokinetic perspective. However, the applicant has justified the flat dose regime based on the lack of correlation between weight and pharmacodynamic markers observed throughout several 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 III studies.

No relationship was apparent between age and exposure to denosumab, based on AUC in healthy adults aged 18 to 82 years.

Children

The applicant has obtained necessary decisions for the paediatric development of denosumab (P/14/2010). There are no recommendations to conduct paediatric studies related to patients with multiple myeloma (Class Waiver). The conduct of paediatric clinical studies in the paediatric indication of prevention of SREs in patients with bone metastases is deferred. The required non-clinical commitments have been completed and a PIP compliance procedure concluded that the applicant is currently compliant with the agreed PIP.

Pharmacokinetic interaction studies

No formal drug interaction studies were performed because denosumab is a monoclonal antibody not eliminated via hepatic metabolic mechanisms and the interaction potential is considered to be low. The impact of previous bisphosphonate treatment on the pharmacokinetics of denosumab was assessed in

Study 20050241 in which pharmacokinetics of denosumab were not altered in subjects who transitioned from alendronate to denosumab. Further, for subjects with advanced breast cancer there seems to be no difference in denosumab PK based on type of concomitant cancer therapy (i.e. chemotherapy [with or without hormone therapy] or hormone therapy).

Effects of immunogenicity on the pharmacokinetics of denosumab

Clinical studies showed a low immunogenicity incidence. Overall, 0.4% of 3508 denosumab-treated subjects in the studies included in this filing were positive for binding antibodies at any time point, and, in most of these subjects, the antibodies were transiently detected. In addition, neutralizing antibodies have not been detected in any subject. Based on the low number of subjects with antibodies, no conclusion on antibodies´ impact on denomsumab PK may be drawn.

Exposure relevant for safety evaluation

Mean (SD) C_{max} and AUC were 27100 (14800) ng/ml and 723 (684) µg*day/ml, respectively, at steady state following multiple 120 mg SC doses.

2.4.3. Pharmacodynamics

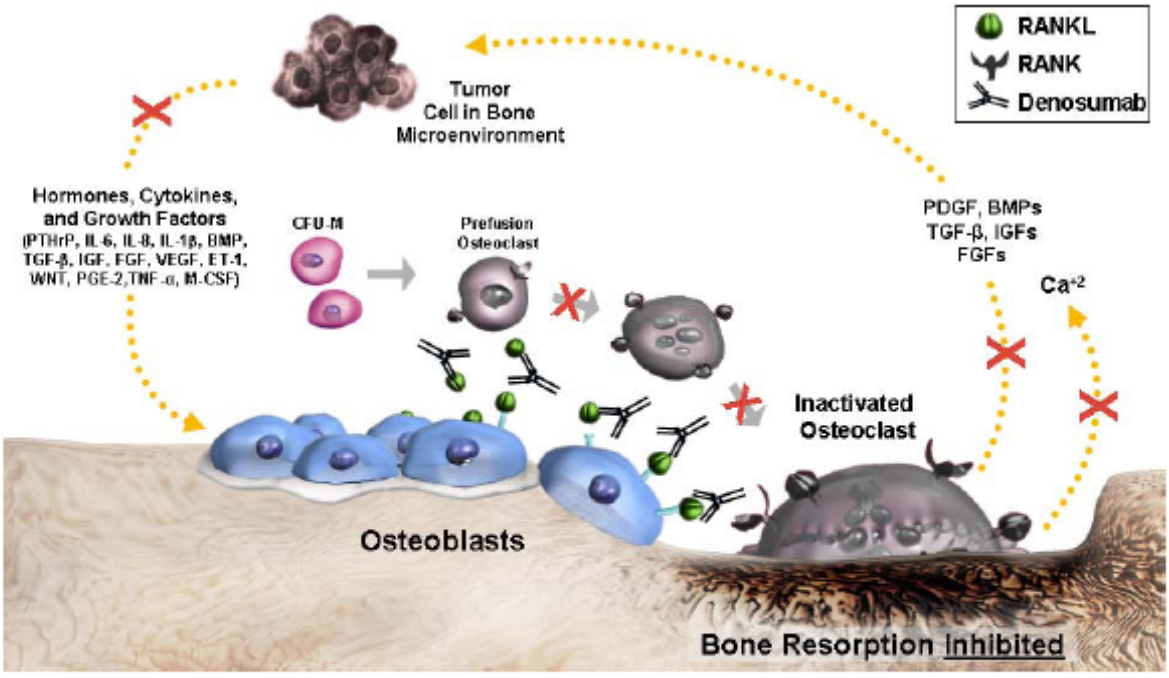
Mechanism of action / Primary pharmacology

In preclinical studies, denosumab has been shown to block the formation, activation, and survival of osteoclasts in vitro and to reduce bone resorption in vivo (see Non-Clinical section above).

Pharmacodynamic data for this application are presented from the two dose-finding studies 20040113 and 20040114.

Denosumab is a fully human monoclonal IgG_2 antibody. It binds with high affinity to human receptor activator of nuclear factor-κB ligand (huRANKL), a member of the tumour necrosis factor (TNF) family of proteins. RANKL is essential for the formation, function and survival of osteoclasts, the one and only cell type responsible for bone resorption. As denosumab is highly specific to huRANKL, it does not bind to other TNF family member proteins such as TNFα, TNFβ, CD40 ligand, and TNF related apoptosis inducing ligand (TRAIL). The binding of denosumab to huRANKL prevents it from activating its only known receptor, receptor activator of nuclear factor-κB (RANK), on the surface of osteoclasts and their precursors. Prevention of RANKL-RANK interaction results in reduced osteoclast numbers and function, with consequent decreased bone resorption, and increased bone mass and bone strength.

Fig 3. Mechanism of action for denosumab



BMP = bone morphogenetic proteins, Ca2+ = calcium, CFU-M = macrophage colony-forming unit; ET1 = endothelin-1, FGF = fibroblast growth factors, IGF = insulin-like growth factors, IL-1 (IL-6, IL-8) = interleukin-1 (-6, -8), M-CSF = macrophage colony-stimulating factor, PDGF = platelet-derived growth factor; PGE2 = prostaglandin E2, PTHrP = parathyroid hormone-related peptide, RANKL = RANK ligand, TGF b = transforming growth factor b, TNFa = tumor necrosis factor a; VEGF = vascular endothelial growth factor; WNT = wingless-type protein-1

Secondary pharmacology

No dose related adverse effects were seen with respect to blood pressure or ECG (Qt intervals) in phase 1 or phase 2 clinical studies.

Inactivation of RANKL by denosumab could theoretically result in elevated "free" or circulating levels of *osteoprotegerin* (OPG, the endogenous RANKL inhibitor). The effect of denosumab, as compared with IV bisphosphonates, on levels of OPG was evaluated in studies 20040113 and 20040114. No differences were found in OPG levels between denosumab and IV bisphosphonates.

Antidenosumab antibodies were rarely seen, were never neutralising and no dose relationship was seen for the existence of such antibodies.

No dose relationship for denosumab was seen in phase 2 or 3 studies, with mandatory calcium and vitamin D supplementation, for the development of hypocalcemia. In these studies, denosumab

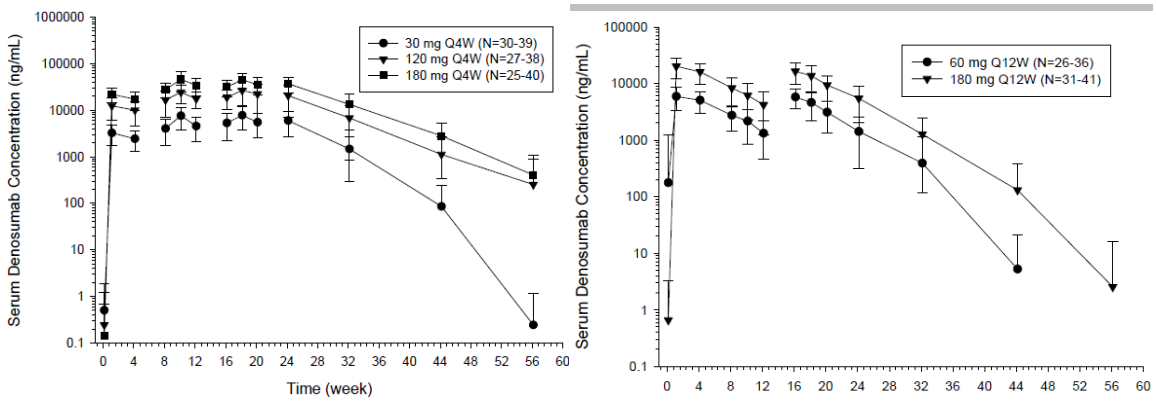
administration was associated with transient decreases in serum calcium, which were most often not clinically significant (i.e. median serum calcium decreases from baseline < 5%).

Selection of dose regimen

N-telopeptide (NTX), serum C-telopeptide (CTX1), and bone-specific alkaline phosphatase (BSAP) were selected as pharmacodynamic endpoints in the clinical pharmacology studies with denosumab. The choice of urinary NTX as a main pharmacodynamic variable for the clinical studies has been supported by data from the literature, from phase 1 studies and from registrational studies with the comparator zoledronic acid. The applicant has submitted a PK-PD analysis characterizing the time course of uNTx/Cr as a function of denosumab serum concentrations.

Study 20040113 was a dose-finding phase 2 study, entitled "A Randomized, Active-controlled Study of AMG 162 in Breast Cancer Subjects With Bone Metastasis Who Have Not Previously Been treated With Bisphosponate Therapy". The primary study objective was to evaluate the effect of different doses and schedules of denosumab compared to IV bisphosphonate every 4 weeks on the percentage change from baseline in urinary N-telopeptide (uNTx) at week 13 in this category of patients. 240 patients were enrolled, 40 in each treatment group.

Fig 4 Mean (±SD) serum denosumab concentration-time profiles after SC denosumab
A. 30, 120, or 180 mg Q4W denosumab **B.** 60 and 180 mg Q12W



Based on the results from this study, the dose 120 mg and the dosing interval every 4 weeks was selected for the phase 3 studies. The 120 and 180 mg doses did not significantly differ with respect to maximum serum concentration of uNTx/Cr achieved. The 12 week dosing interval did not maintain maximal suppression of uNTx/CCr over the whole dosing interval in most patients and the dosing interval of 4 weeks was therefore selected for the continued clinical development of the drug. The choice of dosing schedule for phase 3 studies is sufficiently supported.

Study 20040114 was a randomised open-label active-controlled phase 2 study in patients (n=111) with advanced cancer being treated with intravenous bisphosphonates. The primary objective for the initial 25 weeks treatment phase was to determine the effectiveness of denosumab in reducing uNTx/Cr to below 50 nM/mM in subjects with bone metastases of solid tumours (exept lung cancers) and in subjects with multiple myeloma and bone disease.

A cutoff level of uNTx/Cr value 50 nM/mM as a prognostic tool, as used in study 0040114, has been used in studies with zoledronic acid and is justified from zoledronic study data and from the literature. Denosumab, in different doses, was initiated directly after bisphosphonate therapy and was compared

to continued treatment with the same IV bisphosphonate. The proportion of subjects with uNTx/Cr < 50 nM/mM at week 13 was significantly greater in the combined denosumab group compared with the IV bisphosphonate group. Further, denosumab treatment resulted in significantly more patients treated with denosumab than with zoledronic acid reaching this level of uNTx after 25 weeks of treatment and those patients who reached the cutoff level did so significantly quicker in the denosumab treated groups than in the group treated with zoledronic acid. More patients treated with denosumab every 4 weeks than patients treated every 12 weeks reached the cutoff uNTx/Cr level.

Pharmacokinetic and pharmacodynamic comparisons between studies 20040114 (bisphosphonate-experienced subjects) and 20040113 (bisphosphonate-naïve subjects) indicated that prior exposure to IV bisphosphonates does not affect the pharmacokinetics or pharmacodynamics of denosumab in subjects with advanced breast cancer. Data from these studies suggest that the type of concomitant cancer therapy (chemotherapy with or without hormone therapy) or hormone therapy alone in subjects with advanced breast cancer does not affect the pharmacokinetics or pharmacodynamics of denosumab in subjects with advanced cancer.

In clinical studies for the bone loss indication, with denosumab 60 mg every 6 months, previous treatment with bisphosphonates had no influence on the pharmacodynamic effects of denosumab as assessed by sCTx1. It is not clear from denosumab studies in advanced cancer with skeletal metastases whether previous bisphosphonate treatment could alter the safety of denosumab, in particular with respect to the potential to develop osteonecrosis of the jaw.

Pharmacodynamic interactions with other medicinal products or substances

No formal pharmcodynamic interaction studies have been performed, which is acceptable.

Genetic differences in PD response

The issue of genetic polymorphism in the human RANKL system as a possible explanation to the variation in the response to denosumab has not been investigated by the applicant, which is acceptable.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The majority of the PK studies submitted have already been assessed during the evaluation of the osteoporosis indication as part of the MAA for Prolia. The new assessment has focused on the higher dose/frequency of administrations for XGEVA as compared to Prolia.

A total of 17 of the 18 clinical studies supporting this MAA contributed data on the safety, tolerability, and pharmacokinetic profiles for denosumab.

The bioanalytical methods used in the studies performed seems adequately validated.

A comprehensive comparability program has demonstrated that the formulations intended to be marketed are bioequivalent, in terms of PK and PD, to the formulation used in the pivotal phase III studies. Regarding the quality part of the comparability program, the reader is referred to the quality AR.

Data from a wide range of weight-based SC doses (0.01 to 3.0 mg/kg) and data from fixed SC doses (30 to180 mg) consistently show that denosumab displays nonlinear pharmacokinetics across a wide dose range. However, at doses at or above a dose of 60 mg (approximately 1.0 mg/kg), an indication of less nonlinear pharmacokinetics was seen.

The influence of site of injection on the pharmacokinetics of denosumab has been studied and administrations in thigh, abdomen or back of arm are comparable from a PK point of view. No in vitro permeability studies have been performed. The time for denosumab reaching the maximum concentration in serum occurred in a median time of 7-10 days (range: 3 to 21 days) following a single 120 mg SC dose.

Two mechanisms of elimination for denosumab are suggested, one mechanism that predominates at low doses or serum concentrations and becomes saturated as serum levels increase and another nonsaturable mechanism that governs the rate of denosumab elimination at higher doses or serum concentrations. The saturable mechanism of elimination is likely related to denosumab binding to RANKL and elimination of the antibody-RANKL complex. The nonsaturable mechanism of denosumab elimination is likely nonspecific catabolism in cells of the reticuloendothelial system. The high molecular weight (approximately 150 kD) of denosumab precludes renal excretion as a route of elimination.

For 1.0-mg/kg and the 3.0-mg/kg SC doses, which are in the proximity of the 120-mg dose applied for, clearance was around 0.07-0.1 mL/h/kg. The corresponding mean half-life value that described the disposition of denosumab over a large proportion of exposure ($t_{1/2,\beta}$) was approximately 30 days. The distribution of denosumab is similar to the volume of plasma (3 l) which is expected as for drugs with high molecular weight. Protein binding has not been determined.

Weight significantly affected the pharmacokinetics of denosumab with higher exposures in patients with low weight compared to patients with higher weight. The applicant justified the flat dose regime based on the lack of correlation between weight and pharmacodynamic markers observed throughout several studies. Furthermore, efficacy data presented by weight quartiles supported efficacy over the weight distribution.

No notable differences in mean exposure were observed due to gender and age.

Blacks and Hispanics, but not Asians, had approximately 21% to 24% higher denosumab linear clearance relative to whites, changes that are considered to be clinically insignificant.

One study in patients with impaired renal function was performed. The pharmacokinetic profile of denosumab was not notably affected by varying degrees of renal function (mild kidney disease with CrCL 50 to 80 mL/min), moderate kidney disease with CrCL 30 to 49 mL/min), severe kidney disease with (CrCL < 30 mL/min, and ESRD). No study in hepatically impaired subjects has been performed which is acceptable for a monoclonal antibody.

No formal interaction studies have been performed which is acceptable as the interaction potential is considered low. However, the impact of previous bisphosphonate treatment on the pharmacokinetics of denosumab was assessed via studies 20040113 and 20040114. There were no strong indications that trough serum concentrations of denosumab were altered in subjects with previous bisphosphonate treatment. Similarly, based on studies 20040113 and 20050136, no large differences in trough serum concentrations of denosumab depending on type of concomitant cancer therapy (i.e. chemotherapy [with or without hormone therapy] or hormone therapy) for subjects with advanced breast cancer could be observed.

Clinical studies showed a low immunogenicity incidence. Overall, 0.4% of greater than 3508 denosumab-treated subjects in the studies included in this filing were positive for development of binding antibodies.

Regarding exposure relevant for safety evaluation, mean (SD) C_{max} and AUC were 27100 (14800) ng/ml and 723 (684) µg*day/ml, respectively, at steady state following multiple 120 mg SC doses.

Pharmacodynamics

Denosumab inhibits the bone degrading activity of osteoclasts by inhibiting RANKL, thus reducing the degradation of bone. This inhibition of osteoclastic bone resorption differs from the mechanism of action for bisphosphonates. Doses and treatment scheduled selected for phase 2 trials are well founded in the phase 1 trials. The 120 and 180 mg doses did not significantly differ with respect to maximum serum concentration achieved of uNTx/Cr. The 12 week dosing interval did not maintain maximal suppression of uNTx/Cr over the whole dosing interval in most patients and the dosing interval of 4 weeks was therefore selected for the continued clinical development of the drug. The choice of dosing schedule for phase 3 studies has been sufficiently supported.

The choice of urinary NTX as the main pharmacodynamic variable for the clinical studies has been adequately supported by data from the literature, from phase 1 studies and from registrational studies with the comparator ZOL. A cutoff level of uNTX/Cr value < 50 nM/mM as a prognostic tool, as used in study 0040114, has been used in studies with ZOL and is justified from these studies and from literature data. Using this tool, significantly more patients treated with denosumab than with ZOL reached the level of uNTX < 50 nM/mM after 25 weeks of treatment. Those patients who reached the cutoff level did so significantly quicker in the denosumab treated groups than in the group treated with ZOL.

Levels of OPG or development of antidenosumab antibodies were not affected by different denosumab doses. No dose relationship for the development of hypocalcemia was seen in phase 2 or 3 studies, with mandatory calcium and vitamin D supplementation.

In clinical studies for the bone loss indication, with denosumab 60 mg every 6 months, previous treatment with bisphosphonates had no influence on the pharmacodynamic effects of denosumab as assessed by sCTx1. It is not clear from denosumab studies in advanced cancer with skeletal metastases whether previous bisphosphonate treatment could alter the safety of denosumab, in particular with respect to the development of osteonecrosis of the jaw (ONJ).

The applicant has submitted a PK-PD analysis characterizing the time course of uNTx/Cr as a function of denosumab serum concentrations, which is acknowledged. The analysis is considered supportive to the clinical data. However, since no claims are made based on this analysis no thorough assessment has been done.

2.4.5. Conclusions on clinical pharmacology

In conclusion, the pharmacokinetic profile of denosumab is very well characterized.

Adequate data on PD effects of denosumab at the suggested dosage has been presented to support an indication in the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours in patients with advanced malignant disease involving bone.

2.5. Clinical efficacy

Seven of the 18 studies submitted with this application were conducted in subjects with advanced malignancies. Eight additional studies were conducted to provide pharmaceutical and clinical

pharmacology data and also information on the initial efficacy and tolerability of the drug. The remaining 3 studies were conducted in patient populations outside the indication for this application (treatment of patients with multiple myeloma or giant cell tumour or prevention of bone metastases in patients with hormone-refractory prostate cancer at high risk for developing bone metastases).

2.5.1. Dose response study(ies)

Studies 20040113 and **20040114,** discussed above under clinical pharmacology, are the dose response studies for this application.

2.5.2. Main study(ies)

The three pivotal studies for the indication "Prevention of skeletal related events in adults with advanced malignancies involving bone" are:

A. Study **20050136**, in patients with breast cancer and bone metastases (n = 2046);

B. Study **20050103**, in men with hormone refractory prostate cancer and bone metastases (n = 1901);

C. Study **20050244**, in patients with advanced solid malignant tumours (excluding breast cancer and prostate cancer) and bone metastases, or with multiple myeloma (n = 1776).

These 3 studies had a common study design, with only minor differences. The common study design is described below while specific details for each of the 3 studies are described separately for each study, together with the individual study results. A short summary of pooled efficacy and safety data from all 3 studies will also be provided

Table 22. Pivotal clinical studies with denosumab in advanced malignancies involving bone

Study No.	Study Design	Study Population	Study Objectives	Region	Number of Randomized Subjects	Duration of Treatment
20050136	Phase 3, randomized, double-blind, active-controlled	Adult (men included) with histologically or cytologically confirmed breast adenocarcinoma; current or prior radiographic (ie, x-ray, CT, or MRI) evidence of at least 1 bone metastasis	Primary: to determine if denosumab was noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE Secondary: to determine if denosumab was superior to zoledronic acid with respect to the first on-study SRE and the first-and-subsequent on-study SRE (using multiple-event analysis), and to assess the safety and tolerability of denosumab compared to zoledronic acid	North America, Europe, Latin America, Japan, India, Australia, South Africa	2046 (1026 denosumab 120 mg Q4W, 1020 zoledronic acid)	Event driven: double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~745 subjects experienced an initial on-study SRE, followed by a 2-year survival follow-up period or a 2-year open-label extension period[b].
20050244	Phase 3, randomized, double-blind, active-controlled	Adult with histologically or cytologically confirmed advanced cancers including solid tumors (excluding breast and prostate), multiple myeloma, and lymphoma; current or prior radiographic (ie, x-ray, CT, or MRI) evidence of at least 1 bone metastasis (or lytic bone lesion from multiple myeloma)	Primary: to determine if denosumab was noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE Secondary: to determine if denosumab was superior to zoledronic acid with respect to the first on-study SRE and the first-and-subsequent on-study SRE (using multiple-event analysis), and to assess the safety and tolerability of denosumab compared to zoledronic acid	North America, Europe, Latin America, India, Australia, South Africa	1776 (886 denosumab 120 mg Q4W, 890 zoledronic acid)	Event driven: double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~745 subjects experienced an initial on-study SRE, followed by a 2-year survival follow-up period.
20050103	Phase 3, randomized, double-blind, active-controlled	Adult men with histologically confirmed prostate cancer; current or prior radiographic (ie, x-ray, CT, or MRI) evidence of at least 1 bone metastasis; documented failure of at least one hormonal therapy as evidenced by a rising PSA[a]; serum testosterone level of < 50 ng/mL due to either surgical or chemical castration	Primary: to determine if denosumab was noninferior to zoledronic acid with respect to the first on-study occurrence of an SRE Secondary: to determine if denosumab was superior to zoledronic acid with respect to the first on-study SRE and the first-and-subsequent on-study SRE (using multiple-event analysis), and to assess the safety and tolerability of denosumab compared to zoledronic acid	North America, Europe, Latin America, India, Australia, South Africa, New Zealand	1901 (950 denosumab 120 mg Q4W, 951 zoledronic acid)	Event driven: double-blind treatment phase with primary analysis phase determined by the anticipated date on which ~745 subjects experienced an initial on-study SRE, followed by a 2-year survival follow-up period or a 2-year open-label extension period[b].

CT = computed tomography; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; SRE = skeletal-related event

[a] defined as 3 consecutive determinations, taken at least 2 weeks apart from one another. The third measurement must be ≥ 0.4 ng/mL and be taken within 8 weeks prior to randomization

[b] For subjects at all study centers, except in the United Kingdom and Czech Republic, the open-label phase is being conducted under the respective protocol number (20050136 or 20050103); in the United Kingdom and Czech Republic, the open-label extension phase is being conducted under protocol number 20080540 per Health Authority request.

Methods

Study Participants

Study participants were in all three studies patients with advanced cancer and bone metastasis.

Study **20050136** included patients with breast cancer (males were also included).

Study **20050103** included patients with hormone refractory prostate cancer and documented failure of at least 1 hormonal therapy (surgical or chemical castration), as evidenced by a rising PSA *and* serum testosterone level of < 50 ng/dL due to either surgical or chemical castration

Study **20050244** included adults with advanced solid malignant tumours (excluding breast cancer and prostate cancer) or with multiple myeloma or lymphoma.

Important inclusion and exclusion criteria

In all 3 studies, subjects were also requested to have ≥ 1 bone metastasis and ECOG performance status 0, 1, or 2. Creatinine clearance was to be no less than 30 mL/min for included patients (as calculated according to the Cockroft-Gault equation) and albumin-adjusted serum calcium was to be ≥

2.0 mmol/L (≥ 8.0 mg/dL) and ≤ 2.9 mmol/L or ≤ 11.5 mg/dL. Life expectancy less than 6 months and prior history or current evidence of osteonecrosis/osteomyelitis of the jaw were exclusion criteria in all 3 studies. Among other exclusion criteria were current or prior IV bisphosphonate administration and current or prior oral bisphosphonate treatment for bone metastasis.

Treatments

Subjects received either denosumab 120 mg, i.e. 120 mg SC Q4W or ZOL, 4 mg IV Q4W. Subjects with creatinine clearance < 30 ml/min were excluded, in accordance with the product information for Zometa. The ZOL dose was adjusted for patient with impaired renal function, in accordance with the product information for Zometa.

Calcium supplementation of ≥ 500 mg calcium and ≥ 400 IU vitamin D was strongly recommended, unless the subject had hypercalcemia.

Investigators were permitted to prescribe anticancer therapy (chemotherapy or hormonal therapy) and other concomitant medication or treatment that they deemed necessary to provide adequate care, except bisphosphonates or unapproved medicinal products or devices. Bone marrow transplantation was permitted, if indicated.

Study subjects were required to visit the clinic once a month for study purposes in addition to receiving standard of care evaluation and treatment of the underlying cancer, which included regular evaluation of disease progression.

Study procedures

No interim analysis was done for these studies. Results from the extended double-blind treatment phase and the open-label treatment phase, when completed, will be reported separately. The studies had an external, unblinded data monitoring committe (DMC), with members chosen for their expertise in oncology or bone disease.

Pain endpoints were included in these studies, using validated pain score scales and recording of analgesic use. These patient-related outcomes (PRO) were recorded at baseline and then at every study visit.

Anti-denosumab antibody testing was done at day 1 and at weeks 25, 49 and 97, at end of study, and at follow-up.

Objectives

The pivotal clincial studies were designed to investigate if denosumab was noninferior (primary endpoint) or superior (secondary endpoint, tested after noninferiority has been demonstrated) to ZOL with respect to preventing or delaying the time to first on-study occurrence of a SRE and whether denosumab was superior to ZOL in delaying the time to first and subsequent on-study SRE. Within each pivotal study, the planned sample size was sufficiently powered to detect noninferiority of denosumab to ZOL for the endpoint of time to first on-study SRE and to detect superiority of denosumab to ZOL for at least 1 of the 2 secondary endpoints (time to first on-study SRE; time to first-and- subsequent on-study SRE). The duration of the primary blinded treatment phase supporting the primary analysis was event driven.

Outcomes/endpoints

The primary endpoint in the phase 3 studies was time to first on-study SRE; this endpoint was also evaluated in the integrated analysis.

Definition of skeletal related-events, SRE

In the pivotal studies, SRE is defined as one or more of these local, irreversible events:

- pathologic fracture;
- radiation therapy to bone;
- surgery to bone, or spinal cord compression.

This definition of SREs for the primary efficacy analyses is the same that was used in the registration studies supporting the approval of ZOL, in this indication.

Hypercalcemia of malignancy (HCM) is pathogenetically related but was considered to be a systemic and potentially reversible event and was therefore not considered to be a component of the SRE in the denosumab pivotal studies. In contrast, correction of tumour-induced hypercalcemia was the primary endpoint in several Zometa studies.

Disease progression and Overall Survival

Data on disease progression was collected at the monthly visits and assessed as objective endpoints in each study by 3 measures: (1) *disease progression in bone* (determined by blinded, central radiology reads from one reviewer using predominantly Q12W skeletal surveys), (2) *overall disease progression* (determined by the investigator throughout the study and reported on a specific case report form that required documentation of the methods used to determine disease progression), and (3) *overall survival* determined throughout the study. *Time to disease progression in bone* and *Time to overall disease progression* were also recorded in the pivotal studies. In the prostate cancer study 20050103, change from baseline in PSA values measured Q12W by central laboratory was also included to evaluate disease progression. Events of disease progression were recorded on the specifically designed CRF and not at as a separate adverse event(AE). If an AE indicative of initial disease progression was reported, a matched entry was also reported on the disease CRF.

Table 23. Key endpoints for clinical efficacy in pivotal studies

Endpoint	Level of Endpoint in Individual Studies (20050136, 20050244, and 20050103)
Time to first on-study SRE (noninferiority)	Primary
Time to first on-study SRE (superiority)	Secondary
Time to first-and-subsequent on-study SRE (multiple-event analysis)	Secondary
Time to first on-study SRE or HCM	Exploratory
Time to first on-study radiation to bone	Exploratory
Time to first on-study pathological fracture[a]	-
Skeletal morbidity rate	Exploratory
BPI-SF "worst" pain	
"Worst" pain score	Exploratory
Time to > 4-point score[b]	Exploratory
Time to > 4-point score (subjects with baseline score ≤ 4-points)[c]	-
Time to ≥ 2-point increase from baseline[b]	Exploratory
Time to ≥ 2-point decrease from baseline	Exploratory
Proportion of subjects with ≥ 2-point decrease from baseline	Exploratory
Analgesic use	
Analgesic score	Exploratory
Overall survival time	Exploratory
Time to disease progression in bone	Exploratory
Time to overall disease progression	Exploratory

BPI-SF = Brief Pain Inventory – Short Form; HCM = hypercalcemia of malignancy; SRE = skeletal-related event
[a] Integrated analysis only; for each individual study homogeneity testing was done for time to first on-study SRE (superiority analysis) by type (spinal cord compression, surgery to bone, pathological fracture, and radiation to bone)
[b] Ad hoc for the integrated analysis
[c] Ad hoc for Studies 20050136 and 20050244 and the integrated analysis

Sample size

Study 20051003: A sample size of 1870 subjects and 745 subjects experiencing ≥ 1 SRE was calculated to provide adequate statistical power to detect that: a) denosumab is noninferior to ZOL for time to first on-study SRE with a true hazard ratio (HR) of 0.9, based on a synthesis approach designed to demonstrate that denosumab preserves ≥ 50% of the effect of ZOL compared with placebo (90% power); and b) denosumab is superior to ZOL for at least 1 of the 2 secondary endpoints (first on-study SRE and time to first-and-subsequent SRE) with a true HR of 0.8 and a correlation coefficient of 0.6 between these 2 endpoints (90% power). Data from Novartis Study 039 comparing ZOL with placebo in subjects with prostate cancer was used to obtain the treatment effect of ZOL relative to placebo.

Study 2005136: planned sample size of 1960 subjects and 745 subjects experiencing ≥ 1 SRE was calculated to provide adequate statistical power to detect that: a) denosumab is noninferior to ZOL for time to first on-study SRE with a true HR of 0.9, based on a synthesis approach designed to demonstrate that denosumab preserves ≥ 50% of the effect of ZOL compared with placebo (97% power), and b) denosumab is superior to ZOL for at least 1 of the 2 secondary endpoints first on-study SRE and time to first-and-subsequent SRE with a true HR of 0.8 and a correlation coefficient of 0.6 between these 2 endpoints (90% power). This study was designed to assess noninferiority with respect to time to first on-study SRE, historical data from the literature were used to estimate the HR of placebo compared with the active control ZOL. Because limited data comparing ZOL against placebo

were available, calculation of the combined estimate of ZOL´s effect relative to placebo was based on a 3-step approach.

Study 20050244: A planned sample size of 1690 subjects and 745 subjects experiencing ≥ 1 SRE was considered provide adequate statistical power to detect that: a) denosumab is noninferior to ZOL for time to first on-study SRE with a true HR of 0.9, based on a synthesis approach designed to demonstrate that denosumab preserves ≥ 50% of the effect of ZOL compared with placebo (97% power); and b) denosumab is superior to ZOL for at least 1 of the 2 secondary endpoints with a true HR of 0.8 and a correlation coefficient of 0.6 between these 2 endpoints (90% power). This study was designed to assess noninferiority with respect to time to first on study SRE and historical data from the literature were used to estimate the HR of placebo compared with the active control ZOL. As limited data comparing ZOL against placebo were available, calculation of the combined estimate of ZOL's effect relative to placebo was based on a 3-step approach.

Randomisation

Subjects were randomised in a 1:1 ratio to receive either denosumab or ZOL according to study schedule.

Table 24. Stratification factors for each phase 3 study

	Study		
Stratification Factor	20050136	20050244	20050103
Previous SRE (yes or no)	x	x	x
PSA (< 10 ng/mL or ≥ 10 ng/mL)			x
Current chemotherapy (defined as within 6 weeks before randomization) (yes or no)	x		x
History of systemic anti-cancer therapy (eg, chemotherapy, biologic therapy, or hormonal therapy; yes or no)		x	
Prior oral bisphosphonate use (yes or no)	x		
Region (Japan or other countries).	x	x[a]	
Tumor type (non-small cell lung cancer or multiple myeloma or other)		x	

PSA = prostate-specific antigen, SRE = skeletal related events
[a] Study 20050244 was planned to be a global study. However, Japan was not actually one of the participating countries so stratification by region was not necessary.

Blinding (masking)

The primary blinded treatment phase lasted until the date when approximately 745 subjects were anticipated to have experienced an on study SRE, which was the primary analysis date cutoff date. Even after this date, subjects continued on blinded investigational product until the primary efficacy and safety analysis were completed – this was the *extended blinded treatment phase*. After completing the blinded treatment phase, subjects in studies 20050136 and 20050103 were offered to receive open-label denosumab 120 mg SC Q4W for up to 2 years or until denosumab is available commercially (whichever will occur first). The open-label phase is conducted under the parent protocol number (20050136 or 20050103) except in the United Kingdom and in the Czech Republic. These two countries have requested a special protocol number for the open label extension phase; this protocol number is

20080540. No open-label extension phase was initiated in study 20050244 because superiority was not met in this study.

Those subjects in studies 20050103 and 20050136 who did not enrol into the open-label extension phase and all subjects in study 20050244 were to be followed for survival for 2 years after the last dose of blinded investigational product.

Statistical methods

The analyses of the primary and secondary endpoints were conducted hierarchically. The significance level for the analysis of the primary endpoint was 0.05. The secondary efficacy endpoints were tested only when the null hypothesis of the primary endpoint was rejected at a significance level of 0.05. The secondary efficacy endpoints were tested simultaneously using the Hochberg procedure. A synthesis approach was used for the noninferiority test for the primary endpoint. This synthesis approach assumed constancy from study to study for the estimate of the historical active-control effect (ie ZOL effect on time to first on-study SRE). The study was designed to require preservation of at least 50% of the effect of ZOL on time to first on study SRE. The 50% effect preservation level was chosen to lead to a statistically robust study design and to ensure that noninferiority could not be claimed if denosumab had a clinically meaningful inferior effect relative to ZOL.

The estimated HR and SE from the Cox model (with treatment groups as the independent variable and stratified by the randomisation stratification factors) were combined with the historical estimate and SE of ZOL's effect relative to placebo, to determine whether or not denosumab is noninferior to ZOL. If denosumab was found to be noninferior to ZOL, then the results of the Cox model described for the primary endpoint were used directly in a Wald test to determine whether or not denosumab is superior to ZOL.

If denosumab was found to be noninferior to ZOL, an Andersen and Gill model with robust variance estimate stratified by the randomisation stratification factors was used for a superiority test of denosumab compared with ZOL in time to first and subsequent on study SRE, which accounted for both the absolute number of SREs and the timing between 2 consecutive events. A Nelson-Aalen estimate of cumulative mean number of SREs over time was plotted for each treatment arm.

Exploratory endpoint: Proportion of subjects with an SRE by weeks 49 and 73 and by the primary analysis cut-off date. This was the primary endpoint in Novartis ZOL 039 study.

Results

Participant flow

The median period for on-study assessments was between 7 and 17 months in the 3 studies; maximum duration of treatment was 30 - 41 months. By the primary analysis data cutoff date, 69.4 % of denosumab- treated and 70.4 % of ZOL-treated patients had discontinued study treatment. Death accounted for 27.2 % of discontinuations in the denosumab group and for 26.4 % of discontinuations in the ZOL group. Study consent was withdrawn for 13.6 % of patients in the denosumab group and for 14.8 % of patients in the ZOL group. Disease progression caused study discontinuation for 12.8 % of denosumab patients and for 11.9 % of ZOL patients. A lower percentage of subjects in study 20050136 than in the two other studies discontinued the study. Most subjects who discontinued the investigational product (70.0 % denosumab and 71.0 % ZOL) also discontinued the study.

Dropout rates were high, varying between 54 and 80% in the different treatment arms in the studies. This is not higher than is often seen in oncology studies in these categories of patients. Dropouts were

evenly distributed between study arms. The high dropout rate is explained by the severeness of the disease in these patient categories, patients with advanced malignancies and skeletal metastasis. Death (17 – 35 %) and progression of disease (12 – 14 %) were the most common underlying reasons causing study dropout.

Baseline data

In general, baseline characteristics for study populations were balanced in the denosumab pivotal studies.

Table 25. Baseline demographics, full analysis set, pivotal studies for denosumab

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N = 1020)	Denosumab 120 mg Q4W (N = 1026)	Zoledronic Acid 4 mg Q4W (N = 890)	Denosumab 120 mg Q4W (N = 886)	Zoledronic Acid 4 mg Q4W (N = 951)	Denosumab 120 mg Q4W (N = 950)	Zoledronic Acid 4 mg Q4W (N = 2861)	Denosumab 120 mg Q4W (N = 2862)
Sex - n (%)								
Female	1011 (99.1)	1018 (99.2)	338 (38.0)	298 (33.6)	0 (0.0)	0 (0.0)	1349 (47.2)	1316 (46.0)
Male	9 (0.9)	8 (0.8)	552 (62.0)	588 (66.4)	951 (100.0)	950 (100.0)	1512 (52.8)	1546 (54.0)
Ethnic group / race - n (%)								
White or Caucasian	813 (79.7)	822 (80.1)	770 (86.5)	770 (86.9)	810 (85.2)	829 (87.3)	2393 (83.6)	2421 (84.6)
Black or African American	25 (2.5)	26 (2.5)	29 (3.3)	20 (2.3)	35 (3.7)	38 (4.0)	89 (3.1)	84 (2.9)
Hispanic or Latino	59 (5.8)	59 (5.8)	36 (4.0)	49 (5.5)	57 (6.0)	45 (4.7)	152 (5.3)	153 (5.3)
Asian	37 (3.6)	32 (3.1)	44 (4.9)	36 (4.1)	26 (2.7)	22 (2.3)	107 (3.7)	90 (3.1)
Japanese	69 (6.8)	70 (6.8)	1 (0.1)	3 (0.3)	0 (0.0)	0 (0.0)	70 (2.4)	73 (2.6)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	0 (0.0)

Table 9, ctd

Ethnic group / race - n (%)								
Native Hawaiian or Other Pacific Islander	1 (<0.1)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	2 (<0.1)	2 (<0.1)
Other	16 (1.6)	16 (1.6)	8 (0.9)	8 (0.9)	22 (2.3)	15 (1.6)	46 (1.6)	39 (1.4)
Age (years)								
n	1020	1026	890	886	951	950	2861	2862
Mean	56.6	56.8	60.6	59.3	71.0	70.5	62.6	62.1
SD	11.6	11.5	10.7	11.4	8.4	8.7	12.1	12.2
Median	56.0	57.0	61.0	60.0	71.0	71.0	63.0	63.0
Q1, Q3	49.0, 65.0	49.0, 65.0	53.0, 69.0	52.0, 67.0	66.0, 77.0	64.0, 77.0	54.0, 72.0	54.0, 71.0
Min, Max	24, 90	27, 91	22, 87	18, 89	38, 91	40, 93	22, 91	18, 93
Age group - n (%)								
< 50 years	287 (28.1)	275 (26.8)	128 (14.4)	160 (18.1)	5 (0.5)	9 (0.9)	420 (14.7)	444 (15.5)
≥ 50 years	733 (71.9)	751 (73.2)	762 (85.6)	726 (81.9)	946 (99.5)	941 (99.1)	2441 (85.3)	2418 (84.5)
Geriatric age group - n (%)								
≥ 65 years	266 (26.1)	275 (26.8)	336 (37.8)	299 (33.7)	735 (77.3)	697 (73.4)	1337 (46.7)	1271 (44.4)
≥ 75 years	63 (6.2)	61 (5.9)	74 (8.3)	74 (8.4)	347 (36.5)	338 (35.6)	484 (16.9)	473 (16.5)

Table 26. Baseline disease characteristics and disease history, full analysis set, pivotal studies for denosumab

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N = 1020)	Denosumab 120 mg Q4W (N = 1026)	Zoledronic Acid 4 mg Q4W (N = 890)	Denosumab 120 mg Q4W (N = 886)	Zoledronic Acid 4 mg Q4W (N = 951)	Denosumab 120 mg Q4W (N = 950)	Zoledronic Acid 4 mg Q4W (N = 2861)	Denosumab 120 mg Q4W (N = 2862)
ECOG at study entry - n (%)								
0	488 (47.8)	504 (49.1)	236 (26.5)	240 (27.1)	426 (44.8)	418 (44.0)	1150 (40.2)	1162 (40.6)
1	444 (43.5)	451 (44.0)	492 (55.3)	508 (57.3)	460 (48.4)	464 (48.8)	1396 (48.8)	1423 (49.7)
2	82 (8.0)	68 (6.6)	157 (17.6)	136 (15.3)	65 (6.8)	68 (7.2)	304 (10.6)	272 (9.5)
3	2 (0.2)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)	1 (<0.1)
Missing	4 (0.4)	2 (0.2)	5 (0.6)	2 (0.2)	0 (0.0)	0 (0.0)	9 (0.3)	4 (0.1)
Tumor type - n (%)								
Breast Cancer	1020 (100.0)	1026 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1020 (35.7)	1026 (35.8)
Prostate Cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	951 (100.0)	950 (100.0)	951 (33.2)	950 (33.2)
Multiple Myeloma	0 (0.0)	0 (0.0)	93 (10.4)	87 (9.8)	0 (0.0)	0 (0.0)	93 (3.3)	87 (3.0)
Other	0 (0.0)	0 (0.0)	797 (89.6)	799 (90.2)	0 (0.0)	0 (0.0)	797 (27.9)	799 (27.9)
Time from initial cancer diagnosis to first bone metastasis (months)								
n	1020	1026	885	884	951	948	2856	2858
Mean	52.73	52.83	14.30	13.30	42.53	43.33	37.43	37.45
SD	58.80	58.17	31.98	28.67	47.76	51.88	50.67	51.35
Median	35.44	32.81	2.86	2.07	24.48	24.49	16.52	16.62
Q1, Q3	8.64, 75.50	7.00, 78.65	0.03, 14.52	-0.03, 15.03	1.74, 71.56	2.00, 64.79	0.95, 57.26	0.89, 54.74
Min, Max	-4.7, 343.9	-2.1, 393.5	-38.2, 390.9	-16.2, 263.6	-16.9, 248.0	-12.2, 481.8	-38.2, 390.9	-16.2, 481.8
Time from first bone metastasis to randomization (months)								
n	1020	1026	886	884	951	949	2857	2859
Mean	5.70	5.90	4.71	4.36	13.18	12.06	7.88	7.47
SD	12.77	11.63	10.44	10.75	20.56	18.34	15.71	14.37
Median	2.02	2.10	1.84	1.74	5.19	3.94	2.30	2.17
Q1, Q3	1.08, 4.95	1.02, 5.13	0.89, 4.07	0.92, 3.78	1.31, 16.10	1.22, 15.67	1.05, 7.62	1.02, 7.10
Min, Max	0.1, 191.0	0.0, 138.1	0.1, 129.7	0.1, 152.2	0.0, 156.7	0.0, 207.3	0.0, 191.0	0.0, 207.3
Number of metastatic lesions in bone (by central read of skeletal survey) - n (%)								
≤ 2	780 (76.5)	784 (76.4)	746 (83.8)	749 (84.5)	623 (65.5)	632 (66.5)	2149 (75.1)	2165 (75.6)
> 2	240 (23.5)	242 (23.6)	144 (16.2)	137 (15.5)	328 (34.5)	318 (33.5)	712 (24.9)	697 (24.4)
Osteolytic/non-osteolytic lesion (by central read of skeletal survey) - n (%)								
Osteolytic	139 (13.6)	152 (14.8)	212 (23.8)	196 (22.1)	39 (4.1)	32 (3.4)	390 (13.6)	380 (13.3)
Non-osteolytic	881 (86.4)	874 (85.2)	678 (76.2)	690 (77.9)	912 (95.9)	918 (96.6)	2471 (86.4)	2482 (86.7)
Osteoblastic/non-osteoblastic lesion (by central read of skeletal survey) - n (%)								
Osteoblastic	285 (27.9)	281 (27.4)	130 (14.6)	151 (17.0)	537 (56.5)	601 (63.3)	952 (33.3)	1033 (36.1)
Non-osteoblastic	735 (72.1)	745 (72.6)	760 (85.4)	735 (83.0)	414 (43.5)	349 (36.7)	1909 (66.7)	1829 (63.9)
Presence of visceral metastases - n (%)	525 (51.5)	552 (53.8)	448 (50.3)	474 (53.5)	181 (19.0)	161 (16.9)	1154 (40.3)	1187 (41.5)
Liver - n (%)	182 (17.8)	211 (20.6)	167 (18.8)	171 (19.3)	20 (2.1)	16 (1.7)	369 (12.9)	398 (13.9)
Lung - n (%)	210 (20.6)	216 (21.1)	162 (18.2)	239 (27.0)	32 (3.4)	26 (2.7)	404 (14.1)	481 (16.8)
Other - n (%)	369 (36.2)	369 (36.0)	340 (38.2)	319 (36.0)	153 (16.1)	141 (14.8)	862 (30.1)	829 (29.0)

Altogether, demographic characteristics were balanced between the denosumab and zoledronic acid study groups in the three pivotal studies. Baseline characteristics differed between studies in several aspects. The study population in 20050103 was older than the populations in the two other studies (71 years in the former study; 57 and 56 years in the two latter studies, respectively), consistent with the incidence peaks for the different diseases occurring at different ages.

In the pooled study data, approximately 13 % of subjects in each treatment group had purely osteolytic lesions at baseline. More patients in study 20050103 than in the other two studies had osteolytic bone lesions. Approximately 36 % of subjects in the denosumab group and 33 % of subjects in the ZOL group had purely osteoblastic lesions at baseline in the pooled dataset from the pivotal studies. Fewer patients in study 20050103 than in the other studies had osteoblastic lesions at baseline.

Fewer patients in study 20050103 than in the other studies had visceral metastases. Patients in study 20050103 had a longer period from first bone metastasis to study randomisation than patients in the other two studies.

Approximately 40 % of patients in study 20050244 had non-small cell lung cancer and 10 % had multiple myeloma. The rest of the patient population in this study had a number of other tumour types. Patients in this study were not stratified with respect to tumour type and outcomes with respect to different tumour types could therefore risk to be biased. Patients in study 20050244 had a shorter period of time between initial cancer diagnosis to bone metastasis than patients in the two other studies. Most of the oldest patients were found in study 10050244. Fewer patients in study 20050244 had a low ECOG performance status of 0 or 1 than in the two other studies while more patients in this study had an ECOG performance status of 2.

In the pooled study data, there were 54 % men and 85 % whites in the denosumab study groups and 53 % men, 85 % whites in the zoledronic acid groups. Approximately 44 % of patients in the denosumab groups and 47 % in the zoledronic acid groups were 65 years or older. Approximately 17 % of patients in both treatment groups were 75 years or older.

Table 27. Distribution of primary tumour type, full analysis set, study 20050244

	Zoledronic Acid 4 mg Q4W (N = 890)	Denosumab 120 mg Q4W (N = 886)	All (N = 1776)
NON-SMALL CELL LUNG (NSCLC)	352 (39.6)	350 (39.5)	702 (39.5)
MULTIPLE MYELOMA	93 (10.4)	87 (9.8)	180 (10.1)
RENAL	85 (9.6)	70 (7.9)	155 (8.7)
SMALL CELL LUNG (SCLC)	48 (5.4)	61 (6.9)	109 (6.1)
BLADDER	35 (3.9)	28 (3.2)	63 (3.5)
RECTAL	35 (3.9)	25 (2.8)	60 (3.4)
COLON	29 (3.3)	30 (3.4)	59 (3.3)
UNKNOWN PRIMARY	27 (3.0)	31 (3.5)	58 (3.3)
CERVIX	25 (2.8)	18 (2.0)	43 (2.4)
HEAD AND NECK	19 (2.1)	24 (2.7)	43 (2.4)
GASTRIC	16 (1.8)	19 (2.1)	35 (2.0)
NON-HODGKIN LYMPHOMA	15 (1.7)	17 (1.9)	32 (1.8)
SOFT TISSUE SARCOMA	13 (1.5)	18 (2.0)	31 (1.7)
ENDOMETRIAL	11 (1.2)	16 (1.8)	27 (1.5)
ESOPHAGEAL	15 (1.7)	10 (1.1)	25 (1.4)
OTHER	11 (1.2)	14 (1.6)	25 (1.4)
NEUROENDOCRINE/CARCINOID	10 (1.1)	14 (1.6)	24 (1.4)
MELANOMA	11 (1.2)	12 (1.4)	23 (1.3)
OVARIAN	7 (0.8)	12 (1.4)	19 (1.1)
THYROID	6 (0.7)	7 (0.8)	13 (0.7)
PANCREATIC	8 (0.9)	3 (0.3)	11 (0.6)
RENAL PELVIS AND URETER	5 (0.6)	4 (0.5)	9 (0.5)
GI, OTHER	4 (0.4)	4 (0.5)	8 (0.5)
HODGKIN DISEASE	2 (0.2)	5 (0.6)	7 (0.4)
LIVER	4 (0.4)	1 (0.1)	5 (0.3)
ANAL	2 (0.2)	1 (0.1)	3 (0.2)
TESTICULAR	1 (0.1)	2 (0.2)	3 (0.2)
BILIARY TRACT	1 (0.1)	1 (0.1)	2 (0.1)
SKIN, SQUAMOUS CELL	0 (0.0)	2 (0.2)	2 (0.1)

The proportion of subjects with previous SRE did not differ between treatment groups, and all different SREs had been experienced by the same proportion of patients in both treatment groups. Study 20050103 had less subjects with a history of a previous SRE than subjects in the other two studies.

Numbers analysed

Table 28. Subject disposition, primary advanced cancer, randomised in pivotal denosumab studies

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)	Zoledronic Acid 4 mg Q4W n (%)	Denosumab 120 mg Q4W n (%)
Randomized	1020	1026	890	886	951	950	2861	2862
On study through primary data analysis cut-off date	461 (45.2)	468 (45.6)	178 (20.0)	180 (20.3)	208 (21.9)	228 (24.0)	847 (29.6)	876 (30.6)
Discontinued prior to primary data analysis cut-off date	559 (54.8)	558 (54.4)	712 (80.0)	706 (79.7)	743 (78.1)	722 (76.0)	2014 (70.4)	1986 (69.4)
Received IP	1014 (99.4)	1019 (99.3)	878 (98.7)	878 (99.1)	946 (99.5)	942 (99.2)	2838 (99.2)	2839 (99.2)
Received IP through primary data analysis cut-off date	443 (43.4)	450 (43.9)	168 (18.9)	169 (19.1)	197 (20.7)	217 (22.8)	808 (28.2)	836 (29.2)
Discontinued IP prior to primary data analysis cut-off date	571 (56.0)	569 (55.5)	710 (79.8)	709 (80.0)	749 (78.8)	725 (76.3)	2030 (71.0)	2003 (70.0)

Outcomes and estimation

Primary efficacy results

In **study 20050136**, denosumab was superior to ZOL for the delay or prevention of SREs in subjects with advanced breast cancer. Denosumab significantly reduced the risk of developing a first on-study SRE by 18% compared with ZOL (HR [95% CI] of 0.82 [0.71, 0.95]; $p < 0.0001$ for noninferiority, $p = 0.0101$ [unadjusted and adjusted] for superiority).

In **study 20050103**, denosumab was superior to ZOL for the delay or prevention of SREs in subjects with hormone-refractory (castrate-resistant) prostate cancer and significantly reduced the risk of developing a first on-study SRE by 18% compared with ZOL (HR [95% CI] of 0.82 [0.71, 0.95]; $p = 0.0002$ for noninferiority, $p = 0.0085$ [unadjusted and adjusted] for superiority).

In study **20050244**, denosumab was noninferior to ZOL for the delay or prevention of SREs in subjects with solid tumours (excluding breast and prostate cancer) and bone metastases (including subjects with multiple myeloma). Denosumab reduced the risk of developing a first on-study SRE by 16% compared with ZOL, although the level of reduction did not reach statistical significance for superiority when adjusted for multiplicity (HR [95% CI] of 0.84 [0.71, 0.98]; $p = 0.0007$ for noninferiority, $p = 0.0309$ [unadjusted] and 0.0619 [adjusted] for superiority. Subgroup analysis was done according to tumour type in study 20050244.

Fig 5 a. Time to first SRE, Kaplan-Meier curves, full analysis set, pivotal studies for denosumab

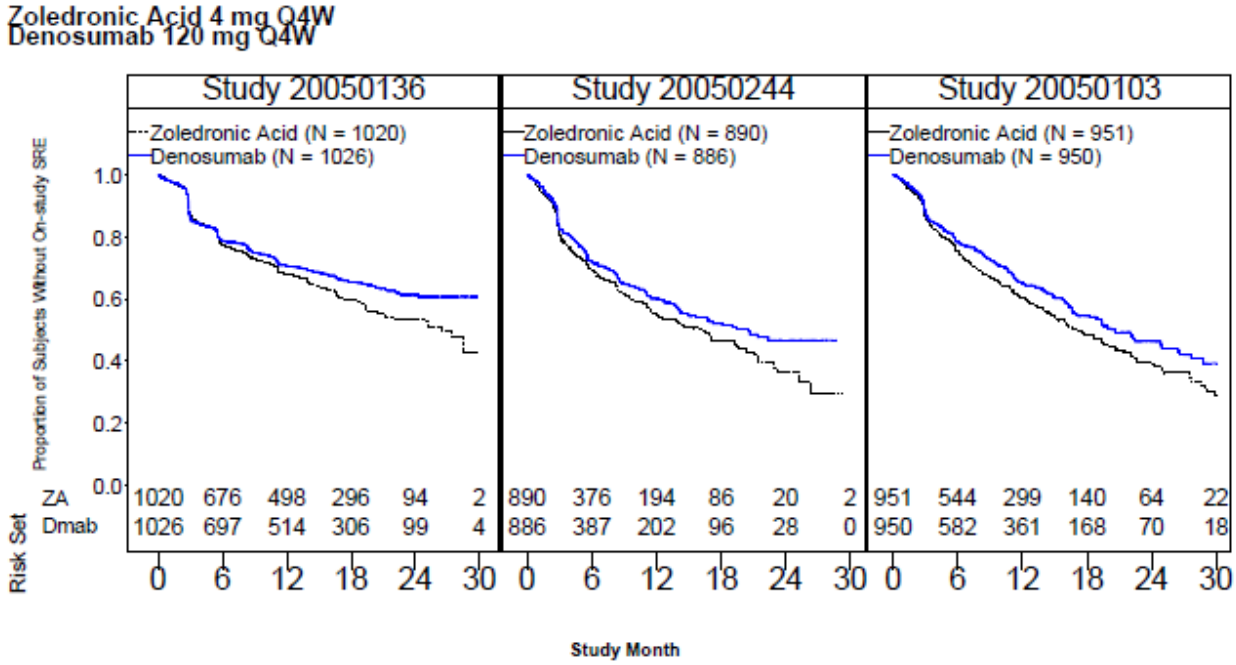


Fig 5 b. Time to first SRE, Kaplan-Meier curve, overall analysis, full analysis set, pivotal studies for denosumab-Amgen

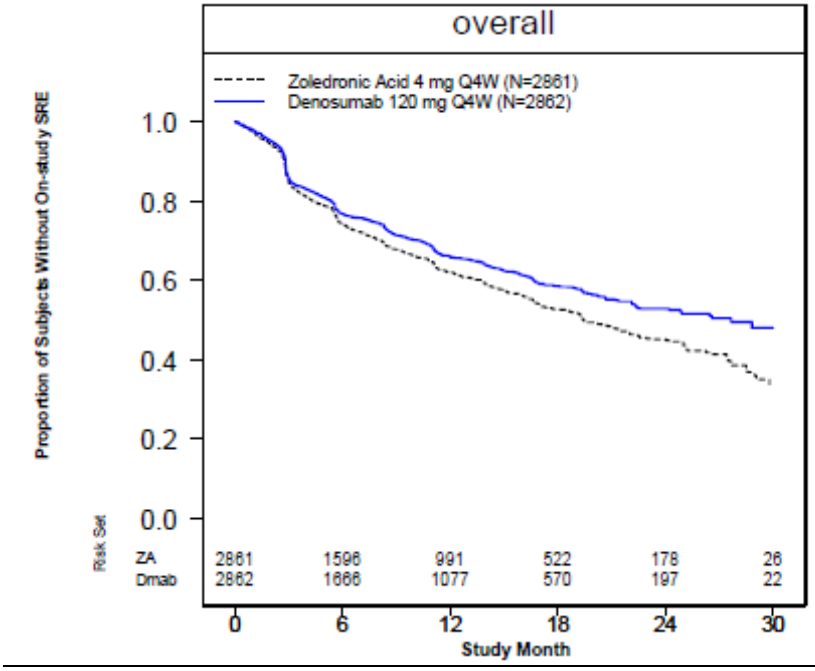


Table 29. Time to first SRE by study, full analysis set, pivotal studies for denosumab

	Crude Incidence	KM Estimate of 25%-tile (Days)		KM Estimate of Median (Days)		Hazard Ratio[a]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Overall (adjusted for study)								
Zoledronic Acid 4 mg Q4W (N = 2861)	1081 (37.8)	175.0	(169.00, 193.00)	592.0	(564.00, 652.00)			
Denosumab 120 mg Q4W (N = 2862)	934 (32.6)	230.0	(184.00, 254.00)	842.0	(737.00, NE)	0.83	(0.76, 0.90)	<.0001
Study 20050136								
Zoledronic Acid 4 mg Q4W (N = 1020)	372 (36.5)	239.0	(179.00, 300.00)	806.0	(666.00, NE)			
Denosumab 120 mg Q4W (N = 1026)	315 (30.7)	268.0	(245.00, 337.00)	NE	(NE, NE)	0.82	(0.71, 0.95)	0.0101
Study 20050244								
Zoledronic Acid 4 mg Q4W (N = 890)	323 (36.3)	130.0	(104.00, 168.00)	496.0	(371.00, 589.00)			
Denosumab 120 mg Q4W (N = 886)	278 (31.4)	164.0	(141.00, 191.00)	625.0	(456.00, NE)	0.84	(0.71, 0.98)	0.0309
Study 20050103								
Zoledronic Acid 4 mg Q4W (N = 951)	386 (40.6)	183.0	(168.00, 215.00)	521.0	(456.00, 592.00)			
Denosumab 120 mg Q4W (N = 950)	341 (35.9)	248.0	(189.00, 288.00)	629.0	(573.00, 757.00)	0.82	(0.71, 0.95)	0.0085
Treatment-by-study interaction[b]								0.9865

N = Number of subjects randomized; KM = Kaplan-Meier; NE = Not estimable
Hazard ratio < 1 favors denosumab.
[a] Based on a Cox proportional hazards model with treatment groups as the independent variable and stratified by study and the randomization stratification factors.
[b] Based on a Cox model adding study-by-treatment and previous SRE-by-treatment interaction to [a].
p-value is for the superiority test of denosumab vs zoledronic acid.

Secondary efficacy results

In **study 20050136**, denosumab significantly reduced the risk of developing a first on-study SRE by 18% compared with ZOL (HR [95% CI] of 0.82 [0.71, 0.95]; p < 0.0001 for noninferiority, p = 0.0101 [unadjusted and adjusted] for superiority).

Denosumab significantly reduced the risk of developing first-and-subsequent on-study SREs by 23% compared with ZOL (rate ratio [95% CI] of 0.77 [0.66, 0.89]; p = 0.0006 [unadjusted] and 0.0012 [adjusted]) (multiple-event analysis).

In **study 20050103**, denosumab significantly reduced the risk of developing a first on-study SRE by 18% compared with ZOL (HR [95% CI] of 0.82 [0.71, 0.95]; p = 0.0002 for noninferiority, p = 0.0085 [unadjusted and adjusted] for superiority).

Denosumab significantly reduced the risk of developing first-and-subsequent on-study SREs by 18% compared with ZOL (rate ratio [95% CI] of 0.82 [0.71, 0.94]; p = 0.0044 [unadjusted] and 0.0085 [adjusted]) (multiple-event analysis).

In **study 20050244**, denosumab reduced the risk of developing a first on-study SRE by 16% compared with ZOL, although the level of reduction did not reach statistical significance for superiority when adjusted for multiplicity (HR [95% CI] of 0.84 [0.71, 0.98]; p = 0.0007 for noninferiority, p = 0.0309 [unadjusted] and 0.0619 [adjusted] for superiority). The results of the secondary endpoint Time-to-first *and subsequent* SRE in the integrated analysis of the 3 pivotal studies were: rate ratio 0.82 (95% CI: 0.75, 0.89); p < 0.0001.

Subgroup analyses were performed for age, gender, race, geographic region and presence of osteolytic metastases. See fig 9 below. The results were consistent between subgroups for the primary efficacy endpoint.

Individual components of the primary endpoint: The individual components of the primary efficacy parameter were further characterised, showing that the frequencies of each component were

consistently in favour of denosumab versus zoledronic acid. The differences between treatment arms with regard to frequency of SRE component were 0.3 % for spinal cord compression, 0.3 % for surgery to bone, 2.7 % for fracture (p =0.009), and 4.0 % for radiation to bone (p < 0.0001).

Exploratory endpoints

Median time to first on study SRE: In **study 20050136**, the median time to first on-study SRE was not reached for denosumab and was 26.4 months (806 days) for ZOL. In **study 20050103**, the median time to first on study SRE was approximately 3 months longer for denosumab compared with ZOL (20.7 months [629 days] vs 17.1 months [521 days]). In **study 20050244**, the median time to first on study SRE was approximately 4 months longer for denosumab compared with ZOL (20.6 months [625 days] vs 16.3 months [496 days]).

Proportion of subjects with skeletal related events: In **study 20050136**, denosumab decreased the proportion of subjects with a first on-study SRE compared with ZOL (5.8% absolute reduction; 30.7% denosumab vs. 36.5% ZOL). In **study 20050103**, denosumab decreased the proportion of subjects with a first on-study SRE compared with ZOL (4.7% absolute reduction; 35.9% denosumab vs. 40.6% ZOL). In **study 20050244**, denosumab decreased the proportion of subjects with a first on-study SRE compared with ZOL (4.9% absolute reduction; 31.4% denosumab vs 36.3% ZOL).

Time to first on study radiation to bone: In **study 20050136**, denosumab also reduced the risk of radiation to bone by 26% compared with ZOL (HR [95% CI] of 0.74 [0.59, 0.94]; p = 0.0121). In **study 20050103**, denosumab also reduced the risk of radiation to bone by 22% compared with ZOL (HR [95% CI] of 0.78 [0.66, 0.94]; p = 0.0071). In **Study 20050244**, denosumab reduced the risk of radiation to bone by 22% compared with ZOL (HR [95% CI] of 0.78 [0.63, 0.97]; p = 0.0256).

Time to first on-study SRE or hypercalcemia of malignancy (HCM): In **study 20050136**, denosumab reduced the risk of developing a SRE or HCM by 18% compared with ZOL (HR [95% CI] of 0.82 [0.70, 0.95]; p=0.0074). In **study 20050103**, denosumab reduced the risk of developing a SRE or HCM by 17% compared with ZOL (HR [95% CI] of 0.83 [0.72, 0.96]; p = 0.0134). In **study 20050244**, denosumab reduced the risk of developing a SRE or HCM by 17% compared with ZOL (HR [95% CI] of 0.83 [0.71, 0.97]; p = 0.0215).

Patient-reported outcomes

BPI-SF "worst pain"

In these studies, worsening in pain represented ≥ 2-point increase from baseline in worst pain score and improvement represented ≥ 2-point decrease from baseline in worst pain score. Worst pain score was > 4 points.

In **study 20050136**, time to worsening in pain (median 259 days denosumab, 226 days ZOL; HR [95% CI] of 0.90; p = 0.0822) and time to moderate or severe pain (median denosumab 88 days; ZOL 64 days; HR [95% CI] of 0.87; p = 0.0094) were delayed for denosumab compared with ZOL. Time to pain improvement was similar for denosumab and ZOL (82 days and 85 days, respectively).

In **study 20050103**, time to worsening in pain (median 145 days for denosumab group and 142 days for the ZOL group; HR [95% CI] 0.97; p = 0.6437), time to moderate or severe pain (median 86 days denosumab and 80 days for the ZOL group; HR [95% CI] 0.93, p = 0.1677), and time to pain improvement (median 113 days for denosumab and 92 days for the ZOL group; HR [95% CI] 0.93; p = 0.3390) were generally comparable between treatment groups. In **study 20050244**, time to worsening in pain (169 days denosumab and 143 days ZOL; HR 0.85; p = 0.0233) and time to moderate or severe pain (median denosumab compared 57 days for denosumab 36 days for ZOL

group; HR 0.91]; p = 0.1092) were delayed for denosumab compared with ZOL. Median time to pain improvement was 85 days for both treatment groups in this study.

Analgesic use

On a scale of 0 (no analgesics) to 7 (> 600 mg OME per day), the mean analgesic score was 1.3 to 1.4 for denosumab and was 1.4 to 1.5 for ZOL at each postdose study visit for the integrated analysis. In each phase 3 study, no significant between-group differences in analgesic use were observed (p = 0.7628, 0.0876, and 0.4641 for studies 20050136, 20050244, and 20050103, respectively). No significant difference in analgesic use in pooled study data was observed between denosumab and ZOL through week 41 (AUC of analgesic score relative to baseline was for denosumab 0.37 and for ZOL 0.37; p = 0.2356).

Quality of life (QoL) and health-related quality of life (HRQL)

In **study 20050136**, the *FACT-B questionnaire* was used. This questionnaire consists of the FACT-G questionnaire, a widely used disease-specific HRQOL instrument, plus additional questions specific to breast cancer. A higher score indicates better health-related quality of life. Mean FACT-B scores were generally similar between treatment groups at baseline and each study visit. The median time to a clinically meaningful decline in the FACT-TOI (ie, ≥ 5-point worsening from baseline) was longer for the denosumab group compared to the ZOL (141 days for denosumab, 114 days for ZOL).

The *EQ-5D* is a widely used, generic HRQOL instrument that allows for estimation of health utility. For both components, the health index and the VAS, a higher score indicates a better health status. At baseline, mean EQ-5D health index scores and VAS scores (64.1 denosumab, 64.5 ZOL) were similar between treatment groups. Both groups demonstrated positive changes from baseline in the mean EQ-5D health state index at most study visits, indicating a maintenance of HRQOL throughout the study. No notable differences in the EQ-5D were observed between treatment groups.

Study 2005103 used the *FACT-P questionnaire* that consists of the *FACT-G questionnaire*, a widely used disease specific HRQOL instrument, plus additional questions specific to prostate cancer. Mean change from baseline in the FACT-G total score, FACT-P total score, physical well-being domain, functional well-being domain, and TOI through week 73 indicated decreasing HRQOL in both treatment groups. A comparison between treatment groups generally showed lower mean decreases in change from baseline in the FACT-G total score in the denosumab group relative to the ZOL group. The denosumab and ZOL treatment groups demonstrated comparable time to a clinically meaningful decline in HRQOL. Mean EQ-5D health index and VAS were similar between treatment groups at baseline. Mean change from baseline for the health index score generally demonstrated a lower decline for denosumab at each study visit, although median scores consistently showed no change from baseline in both treatment groups. No notable differences were observed between treatment groups in mean change from baseline for the VAS. The change in the health index score through week 73 favoured denosumab but the difference was small. The change in the VAS score was similar between treatment groups.

Study 20050244 also used the FACT-G questionnaire for evaluation of QoL. A higher FACT-G score indicates better HRQL. Mean scores generally increased from baseline through week 45 for both treatment groups (50% withdrew due to death, disease progression, or consent withdrawn). The change in each FACT score through week 25 favoured the denosumab group compared with the ZOL group (PWB: p = 0.0004; FWB: p = 0.2121; total score: p = 0.0005). Estimated with the EQ-5D questionnaire, both the denosumab and the ZOL groups demonstrated positive changes from baseline in both the mean EQ-5D health state index and VAS at most study visits. No notable differences in the EQ-5D were observed between treatment groups.

The time to pain improvement (i.e. ≥ 2 point decrease from baseline in BPI-SF worst pain score) was similar for denosumab and zoledronic acid in each study and the integrated analyses. In a post-hoc analysis of the combined dataset, the median time to worsening pain (> 4-point worst pain score) in patients with mild or no pain at baseline was delayed for XGEVA compared to zoledronic acid (198 versus 143 days) (p = 0.0002).

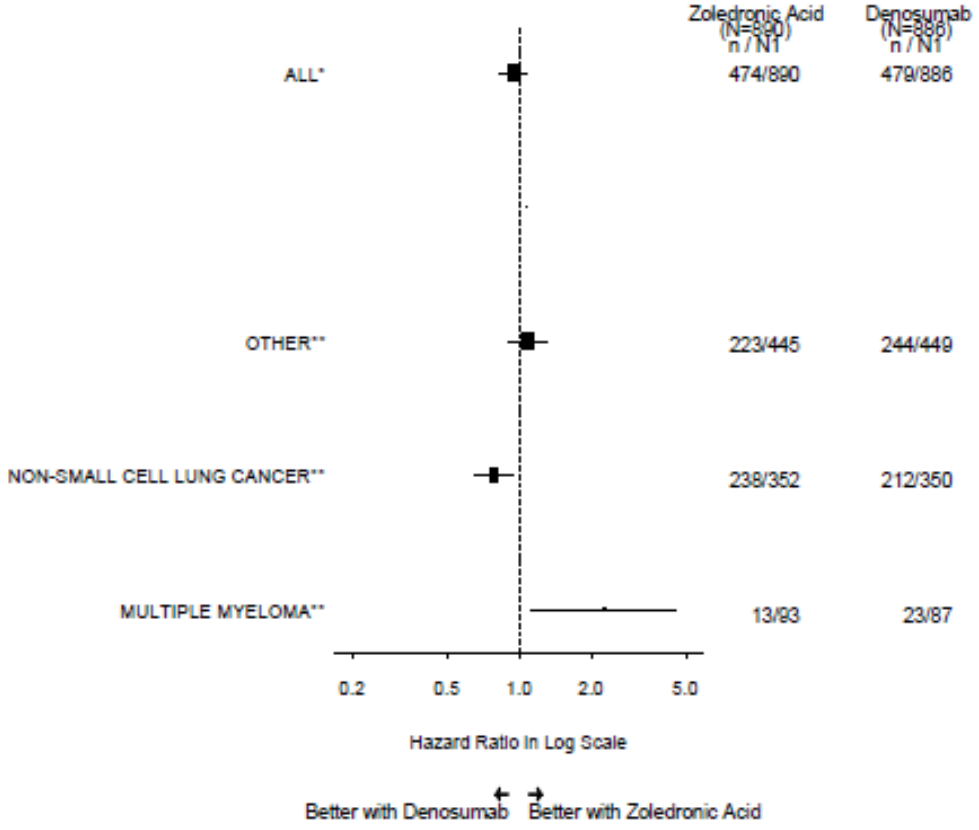
Healthcare utilisation

Healthcare utilisation was lower in the denosumab group than in the ZOL treatment group, probably because fewer patients in this group had skeletal-related events; patients who had a skeletal-related event had greater healthcare resource utilisation. In study 20050103, the mean number of radiation oncology clinic visits was 22% lower in the denosumab group compared to the ZOL group (0.53 and 0.68 visits, respectively).

Overall survival

While total overall survival in **study 20050244** was comparable between treatment arms, as in studies 20050136 and 20050103, a difference was seen in overall survival time between the different cancer types in study 20050244, with a shorter overall survival for multiple myeloma patients.

Fig 6. Forest plot of overall survival analysis by tumour type, study 20050244 full analysis set



N = Number of subjects randomized
N1 = Number of subjects in each tumor type by actual strata; n = Number of deaths;
* Hazard Ratio and 95% CI based on a Cox proportional regression model stratified by Stratification factors
** Hazard Ratio and 95% CI based on a Cox proportional regression model stratified by previous SRE and systemic anti-cancer therapy

After the analysis of results for overall survival in this study, the applicant performed an analysis of factors that might confound the results for overall survival in the subjects with non-small cell lung cancer and multiple myeloma and found the following:

a. At baseline, more subjects in the ZOL group with non-small cell lung cancer had an ECOG score of 2, compared with denosumab (15.7% denosumab, 19.7% ZOL);

b. In the subjects with multiple myeloma, baseline characteristics showed lower disease burden in the ZOL group: the proportion of subjects with stage 1 tumours at diagnosis was higher in the ZOL group (8% denosumab, 14% ZOL);

c. The proportion of subjects with an ECOG score of 0 was higher in the ZOL group (23% denosumab, 32% ZOL) and low baseline renal function (CrCL< 40 mL/min) was higher in the denosumab group (9% denosumab, 2% ZOL)

d. The proportion of subjects who underwent aggressive therapy with stem cell transplant for myeloma either prior to or on-study was higher in the ZOL group (16% denosumab, 25% ZOL)

e. Study withdrawals from study due to consent withdrawn or lost to follow-up were higher in the ZOL group (14% denosumab, 18% ZOL).

Time to first overall disease progression or *Time to first disease progression in bone* did not differ between treatment groups in any of the 3 pivotal studies. However, in study 20050244, disease progression seemed to be enhanced in the small subgroup of multiple myeloma.

Bone turnover markers

In all three studies, the % decrease in the bone turnover markers uNTX/Cr and BSAP were greater ($p < 0.0001$) following 3 months of denosumab treatment compared with ZOL treatment. The decline in uNTX/Cr was more marked than the decline in BSAP. Standard deviations were large. PSA values at baseline were similar between groups in the prostate cancer study. Median change from baseline was 32 ng/mL in the denosumab group and 61 ng/mL in the ZOL group at week 73. The median PSA value was similarly increased relative to baseline in both treatment groups through week 145.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30. Summary of Efficacy for trial 20050136

Title: A Randomised, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects with Advanced Breast Cancer		
Study identifier	20050136	
Design	Phase III, randomized, double-blind, active comparator, multicentre study with open label extension phase	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	34 months (April 2006 to March 2009) not applicable 2 years (open-label extension or survival follow-up)

Hypothesis	The primary hypothesis for this study was that denosumab is noninferior to zoledronic acid on time to first on-study SRE in subjects with advanced breast cancer with bone metastases. The secondary hypotheses (tested only if denosumab was found to be noninferior to zoledronic acid with respect to time to first on-study SRE) were the following. • denosumab is superior to zoledronic acid with respect to time to first on-study SRE • denosumab is superior to zoledronic acid with respect to time to first-and-subsequent on-study SRE (multiple-event analysis)		
Treatment groups	Denosumab		120 mg SC Q4W, 1026 randomised
	Zoledronic acid		4 mg IV Q4W (adjusted for renal function), 1020 randomised
	Not applicable		Not applicable
Endpoints and definitions	Primary: Time to first on-study SRE	Prevention of SREs	Noninferiority compared with zoledronic acid SRE = pathologic fracture, radiation to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression
	Secondary: Time to first on-study SRE	Prevention of SREs	Superiority compared with zoledronic acid
	Secondary: Time to first and subsequent on-study SRE	Prevention of SREs	Superiority compared with zoledronic acid
Database lock	July 2, 2009		

Results and analysis

Analysis description	**Primary analysis**
Analysis population and time point description	Full analysis set which included all randomized subjects Primary analysis data cut-off date (March 6, 2009); date defined by Amgen in anticipation of 745 subjects experiencing an on-study SRE

Descriptive statistics and estimate variability	Treatment group	Denosumab	Zoledronic acid	Not applicable
	Number of subjects	1026	1020	N/A
	Median time to first SRE	Not estimable	806 days	N/A
	95% Confidence Interval	Not estimable, not estimable	666 days, not estimable	N/A
	Mean number of SREs per patient	0.46	0.60	N/A
	variability statistic	N/A	N/A	N/A

Effect estimate per comparison	Primary: Time to first on-study SRE (noninferiority)	Comparison groups	Denosumab vs. zoledronic acid
		Hazard Ratio	0.82
		95% Confidence Interval	0.71, 0.95
		P-value	<0.0001 (unadjusted and adjusted)
	Secondary: Time to first on-study SRE (superiority)	Comparison groups	Denosumab vs. zoledronic acid
		Hazard Ratio	0.82
		95% Confidence Interval	0.71, 0.95
		P-value	0.0101 (unadjusted and adjusted)
	Secondary: Time to first and subsequent on-study SRE (superiority)	Comparison groups	Denosumab vs. zoledronic acid
		Rate Ratio	0.77
		95% Confidence Interval	0.66, 0.89
		P-value	0.0006 (unadjusted) and 0.0012 (adjusted)
Notes	Not applicable		
Analysis description	A second supportive analysis was performed with a data cut-off date of July 20, 2009 (extended double-blind extension phase analysis). Results were consistent with the primary analysis.		

Table 31. Summary of Efficacy for trial 20050244

Title: A Randomised, Double-blind, Multicentre Study of Denosumab Compared with Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Subjects with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma		
Study identifier	20050244	
Design	Phase III, randomized, double-blind, active comparator, multicentre study with double-blind extension phase	
	Duration of main phase:	34 months (June 2006 – April 2009)
	Duration of run-in phase:	not applicable
	Duration of extension phase:	2 years (survival follow-up)

Hypothesis	The primary hypothesis for this study was that denosumab is noninferior to zoledronic acid on time to first on-study SRE in subjects with advanced cancer (excluding breast and prostate cancer) or multiple myeloma and bone metastasis (or lytic bone lesions from multiple myeloma). The secondary hypotheses (tested only if denosumab was found to be noninferior to zoledronic acid with respect to time to first on-study SRE) were the following: • denosumab is superior to zoledronic acid with respect to time to first on-study SRE • denosumab is superior to zoledronic acid with respect to time to first-and-subsequent on-study SRE (multiple-event analysis)		
Treatment groups	Denosumab		120 mg SC Q4W, 886 randomised
	Zoledronic acid		4 mg IV Q4W (adjusted for renal function), 890 randomised
	Not applicable		Not applicable
Endpoints and definitions	Primary: Time to first on-study SRE	Prevention of SREs	Noninferiority compared with zoledronic acid SRE = pathologic fracture, radiation to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression
	Secondary: Time to first on-study SRE	Prevention of SREs	Superiority compared with zoledronic acid
	Secondary: Time to first and subsequent on-study SRE	Prevention of SREs	Superiority compared with zoledronic acid
Database lock	July 29, 2009		

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Full analysis set which included all randomized subjects Primary analysis data cut-off date (April 30, 2009); date defined by Amgen in anticipation of 745 subjects experiencing an on-study SRE			
Descriptive statistics and estimate variability	Treatment group	Denosumab	Zoledronic acid	Not applicable
	Number of subjects	886	890	N/A
	Median time to first SRE	625 days	496 days	N/A
	95% Confidence Interval	456 days, not estimable	371 days, 589 days	N/A
	Mean number of SREs per patient	0.44	0.49	N/A

	variability statistic	N/A	N/A	N/A
Effect estimate per comparison	Primary: Time to first on-study SRE (noninferiority)	Comparison groups	Denosumab vs. zoledronic acid	
		Hazard Ratio	0.84	
		95% Confidence Interval	0.71, 0.98	
		P-value	0.0007 (unadjusted and adjusted)	
	Secondary: Time to first on-study SRE (superiority)	Comparison groups	Denosumab vs. zoledronic acid	
		Hazard Ratio	0.84	
		95% Confidence Interval	0.71, 0.98	
		P-value	0.0309 (unadjusted) 0.0619 (adjusted)	
	Secondary: Time to first and subsequent on-study SRE (superiority)	Comparison groups	Denosumab vs. zoledronic acid	
		Rate Ratio	0.90	
		95% Confidence Interval	0.77, 1.04	
		P-value	0.1447 (unadjusted and adjusted)	
Notes	Not applicable			
Analysis description	A second supportive analysis was performed with an end of study date of October 21, 2009 (extended double-blind extension phase analysis). Results were consistent with the primary analysis.			

Table 32. Summary of Efficacy for trial 20050103

Title: A Randomised, Double-Blind, Multicenter Study of Denosumab Compared with Zoledronic Acid (Zometa) in the Treatment of Bone Metastases in Men with Hormone-Refractory Prostate Cancer		
Study identifier	20050103	
Design	Phase III, randomized, double-blind, active comparator, multicentre study with open label extension phase	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	41 months; May 2006 to October 2009 not applicable 2 years (open-label extension or survival follow-up)

Hypothesis	The primary hypothesis for this study was that denosumab is noninferior to zoledronic acid on time to first on-study SRE in subjects with hormone-refractory prostate cancer with bone metastases. The secondary hypotheses (tested only if denosumab was found to be noninferior to zoledronic acid with respect to time to first on-study SRE) were the following: • *denosumab is superior to zoledronic acid with respect to time to first on-study SRE* • *denosumab is superior to zoledronic acid with respect to time to first-and-subsequent on-study SRE (multiple-event analysis)*		
Treatment groups	Denosumab		120 mg SC Q4W, 950 randomised
	Zoledronic acid		4 mg IV Q4W (adjusted for renal function), 951 randomised
	Not applicable		Not applicable
Endpoints and definitions	Primary: Time to first on-study SRE	Prevention of SREs	Noninferiority compared with zoledronic acid SRE = pathologic fracture, radiation to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression
	Secondary: Time to first on-study SRE	Prevention of SREs	Superiority compared with zoledronic acid
	Secondary: Time to first and subsequent on-study SRE	Prevention of SREs	Superiority compared with zoledronic acid
Database lock	February 4, 2010		

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Full analysis set which included all randomized subjects Primary analysis data cut-off date (October 30, 2009); date defined by Amgen in anticipation of 745 subjects experiencing an on-study SRE			
Descriptive statistics and estimate variability	Treatment group	Denosumab	Zoledronic acid	Not applicable
	Number of subjects	950	951	N/A
	Median time to first SRE	629 days	521 days	N/A
	95% Confidence Interval	573 days, 757 days	456 days, 592 days	N/A
	Mean number of SREs per patient	0.52	0.61	N/A
	variability statistic	N/A	N/A	N/A

Effect estimate per comparison	Primary: Time to first on-study SRE (noninferiority)	Comparison groups	Denosumab vs. zoledronic acid
		Hazard Ratio	0.82
		95% Confidence Interval	0.71, 0.95
		P-value	0.0002 (unadjusted and adjusted)
	Secondary: Time to first on-study SRE (superiority)	Comparison groups	Denosumab vs. zoledronic acid
		Hazard Ratio	0.82
		95% Confidence Interval	0.71, 0.95
		P-value	0.0085 (unadjusted and adjusted)
	Secondary: Time to first and subsequent on-study SRE (superiority)	Comparison groups	Denosumab vs. zoledronic acid
		Rate Ratio	0.82
		95% Confidence Interval	0.71, 0.94
		P-value	0.0044 (unadjusted) 0.0085 (adjusted)
Notes	Not applicable		
Analysis description	No additional analyses were submitted with the MAA.		

Clinical studies in special populations

No specific studies in special populations with clinical endpoints have been performed. One PK study, study 20040245, was performed in renally impaired subjects without advanced malignancy (see discussion on pharmacokinetics above). In this study, the PK profile of denosumab was not notably affected by varying degrees of renal function.

Supportive studies

Study 20050134 is an ongoing open-label multicenter phase 2 trial of denosumab in the treatment of relapsed or plateau-phase multiple myeloma. Study subjects were heavily pretreated. Fifty subjects were planned for enrollment into each cohort. All subjects were to receive 120 mg denosumab SC on day 1 of every 28-day cycle, with additional loading doses on days 8 and 15 of cycle 1. Treatment with denosumab was continued until the investigator's or the sponsor's recommendation for discontinuation, the subject's decision to discontinue for any reason, or disease progression. Serum M-protein levels were measured between days 20 and 23 of each cycle to assess treatment response. Complete, partial, or minimal responses (CR, PR, or MR) were identified using serum M-protein assessments and confirmed based on modified Bladé criteria requiring reductions in serum and urinary M-protein levels, % of plasma cells on bone marrow aspirate or biopsy, and absence of new osteolytic lesions. Progression of disease (PD) was to be confirmed with a repeat investigation at least 4 to 6 weeks after the initial measurement. Subjects with PD discontinued investigational product and had the end-of-study visit completed within days after the last dose of denosumab.

A report containing results from the primary analysis of the study, conducted 168 days after the last enrolled subject initiated treatment with denosumab (equivalent to six 28-day cycles), has been submitted. Fifty-three patients were enrolled in the cohort with *relapsed multiple myeloma*: No subject

had a reduction in Mprotein levels in the range of the predefined overall response rate (CR, PR, and MR). The overall response rate (CR, PR, and MR) was 0%, with an upper confidence bound of 6%. Eleven subjects (21%) maintained stable disease. Bone turnover markers (serum type 1 C-telopeptide, CTx1, and bone specific alkaline phosphatase, BSAP) decreased from baseline after treatment with denosumab. The median (range) % change in serum CTx from baseline was -69.5% (at cycle 4 and 65.8% at cycle 7. The median % change in BSAP from baseline was -33.0% (-73.9% - 33.5%) at cycle 4 and -46.6% (-61.9% - 52.2%) at cycle 7. Bone resorption was suppressed, demonstrating RANKL inhibition. Subjects with *plateau-phase multiple myeloma:* Of 43 subjects, none had a reduction in M-protein levels corresponding to response (CR, PR, and MR). The observed overall response rate (CR, PR, and MR) was 0%, with an upper confidence bound of 7%. Nineteen subjects (46%) maintained stable disease. Levels of serum CTx and BSAP decreased from baseline after treatment with denosumab. The median % change in serum CTx from baseline was -46.5% (-85.5% to 63.5%) at cycle 4 and -49.2% (-87.7% to 32.4%) at cycle 7. The median % change in BSAP from baseline was -12.2% (-43.4% - 68.2%) at cycle 4 and -4.8% (- 58.7% - 51.4%) at cycle 7. Bone resorption was suppressed also in this patient population. Mean serum denosumab concentrations at days 8 and 15 (during the loading dose phase) were similar in relapsed and plateau-phase subjects (19500 vs 16200 and 10800 vs 7980 ng/mL, respectively). Exposures based on C_0 increased with the loading dose regimen and mean serum concentrations at month 1 were approximately 1.2-fold higher than those at expected steady state (achieved by month 2 and later). Mean C_0 up to month 14 ($n \geq 4$ per cohort) were comparable in relapsed and plateau-phase subjects (< 36%), although there was a trend of slightly lower exposure in relapsed subjects. Mean serum C_0 were comparable with a < 2-fold difference, ranging from 14400 to 23600 ng/mL in all subjects through month 16 ($n \geq 6$), indicating that the pharmacokinetics of denosumab did not change with time.

Study 20040215 is an open-label multicenter phase 2 proof-of-concept study in recurrent or unresectable giant cell tumour (GCT) of bone, which is dependent on RANKL for growth. Thirty-seven patients were enrolled. The study report submitted is a primary analysis, including data collected for the treatment period up to 07 April 2008. Denosumab was administered SC at doses of 120 mg Q4W with a loading dose regimen on study days 1, 8, and 15. Study treatment continued until complete tumour resection *or* disease progression *or* investigator's or the sponsor's recommendation for discontinuation *or* the subject's decision to discontinue; or administration of bisphosphonates, calcitonin, or IFN alfa-2a. The *primary objective* was to evaluate response to treatment of denosumab in subjects with recurrent or unresectable GCT. Response was defined as: at least 90% elimination of giant cells relative to baseline, *or* complete elimination of giant cells in cases where giant cells represent < 5% of tumour cells, *or* a lack of progression of the target lesion at week 25 by radiographic measurements in cases where histopathology is not available. Of the 35 subjects included, 86% had a treatment response. Radiographic measurements of changes in longest lesion dimensions were generally consistent with the primary endpoint analysis. The response rate was independent of age or prior bisphosphonate use. uNTX/Cr and serum CTX were consistently suppressed (approximately 80% below baseline) from week 5 onward. Other bone turnover markers (BSAP, osteocalcin, and TRAP-5b) also decreased from baseline and remained below baseline throughout the study. Increased bone calcification and bone repair at the lesion were observed with denosumab treatment. Mean and median C_0 denosumab concentrations at the end of the loading dose were approximately 2-fold those following the first dose, indicating that the loading dose regimen increased systemic exposure to target levels as anticipated. Between Weeks 9 and 49, mean and median C_0 varied by less than 22% and 10%, respectively. Exposures remained stable during the Q4W dosing period.

Study 20050147 is an ongoing phase 3, double-blind, placebo-controlled multicenter study in men with hormone-refractory (androgen-independent) prostate cancer. Subjects (n= 1435) were randomised 1:1 to receive 120 mg denosumab or placebo SCQ4W. Randomisation was stratified based

on PSA criteria and previous or current chemotherapy for prostate cancer. Subjects enrolled in the study will receive investigational product Q4W until 660 subjects have developed bone metastasis or died and the primary efficacy and safety analysis is completed. An interim report, with cutoff date 30 October 2009, has been submitted. The study remains blinded and only safety data up to cutoff date has been evaluated so far. Dropout rate up to cutoff date was 61 %.

2.5.3. Discussion on clinical efficacy

The use of ZOL as comparator in the pivotal studies for denosumab in advanced cancer is supported, as ZOL is widely used and well documented in this indication. Dosing ZOL every 4 weeks is within the labelled dosing interval for the product, therefore this dosing interval is acceptable for the ZOL comparator arm in this application. In the pivotal studies for ZOL, the drug could be administered every 3 or 4 weeks. Data from these studies has not been systematically analysed with respect to whether ZOL was given with 3 or 4 weeks interval. However, it was demonstrated by the applicant that the 4-weekly interval is the most frequently used regimen for ZOL in clinical practice. Theoretically, a longer interval between infusions could reduce chronic toxicity. The arguments presented by the applicant for chosing the dosing interval of 4 weeks are accepted.

Time to first on-study skeletal-related event, SRE, is agreed as the primary efficacy endpoint in the pivotal studies for denosumab. SRE was an important efficacy endpoint also in the pivotal studies for zoledronic acid, however, with the difference that hypercalcemia of malignancy was included in skeletal related events in the zoledronic acid studies. Since denosumab does not have the same calcium lowering effect as zoledronic acid, hypercalcemia is reported separately in the denosumab studies, which is reasonable.

These studies were designed to require preservation of at least 50% of the effect of zoledronic acid on time to first on-study SRE. The zoledronic acid effect level in the placebo was not clearly defined, however, since superiority has been shown in two of three pivotal studies, the non-inferiority criterion is irrelevant and has not been further assessed. Apart from that the statistical methods used are agreed. Patients who dropped out from study were followed for survival only. Otherwise, dropouts were censored at their last measurement.

Denosumab was superior to ZOL in time to first skeletal-related event in women with advanced breast cancer and skeletal metastases, and in men with advanced prostate cancer and skeletal metastases. The applicant has clarified how many of the first on-study SREs that were classifiable as pathological fracture, radiation to bone, surgery to bone and spinal cord compression, respectively. All differences were in favour of denosumab, compared to zoledronic acid, and the difference between treatment groups was statistically significant for fracture and for radiation to bone.

Efficacy results were consistent between studies, independent of some differences in baseline characteristics. In **study 20050136**, the median time to first on-study SRE was not reached for denosumab and was 26.4 months for zoledronic acid. In **study 20050103** the median time to first on study SRE was approximately 3 months longer for denosumab compared with zoledronic acid and in **study 20050244**, approximately 4 months longer for denosumab compared with zoledronic acid. In patients with skeletal metastases and advanced cancer (excluding breast cancer and prostate cancer but including multiple myeloma), denosumab was noninferior to zoledronic acid in time to first skeletal-related event but was close to reaching superiority. Some tumour types were very rare in this study and conclusions can therefore not be drawn on the treatment effect for each of these individual tumour types. For the time to first on-study SRE, superiority was demonstrated for denosumab in studies 20050136 and 10050103 but not in study 20050244. A significant reduction in the risk of first on-study SRE was seen for denosumab in comparison to zoledronic acid in studies 20050136 and 2005103 but

not in study 20050244. The effects seen were independent of subgroup in a number of subgroup analyses.

The terminology used by the applicant in these pivotal studies is somewhat confusing. In oncology studies, the commonly used terms for disease progression are **Time to progression (TTP)** and **Progression-free survival (PFS)**. The applicant has clarified that Overall disease progression excluding death was analogous to the commonly termed endpoint TTP, and that only new bone lesions that were classified as progression in bone events were recorded in the pivotal studies. It was also made clear that the disease progression in bone endpoint assessed the timing of clinical complications from bone metastases and the relation between the SRE and TTP-bone endpoints was adequately discussed. These endpoints are to some degree correlated but are not expected to be identical.

Overall survival or time to disease progression did not differ between treatment groups in any of the three studies. However, in study 20050244, patients with multiple myeloma had a shorter overall survival than patients with solid tumours. Stratification was done in this study according to tumour type (non-small lung cancer or multiple myeloma or other) but since patients with multiple myeloma constituted only 10% of the study population (93 patients in the zoledronic acid and 87 in the denosumab group) and since the multiple myeloma patients had an imbalance between treatment groups at baseline for several factors that could have prognostic significance, and also due to the fact that an imbalance was seen between treatment arms for the use of other treatment modalities during the study, conclusions on the efficacy in the subgroup multiple myeloma cannot be drawn. The indication for XGEVA can therefore not be granted at present in this subgroup of patients, until new supportive data have been presented.

Healthcare utilisation was lower in the denosumab group than in the zoledronic acid treatment group, probably because fewer patients in this group had skeletal-related events. In all three studies, the % decrease in the bone turnover markers, uNTX/Cr and BSAP, were greater ($p < 0.0001$) following 3 months of denosumab treatment compared with ZOL. The decline in uNTX/Cr was more marked than the decline in BSAP. Standard deviations were large.

No consistent significant differences between treatment groups were found in Quality of Life questionnaires used in all three studies. However, the applicant has presented data on significant differences in some QoL and pain parameters in favour of denosumab. Analgesic use did not significantly differ between treatment groups in any of the three studies.

2.5.4. Conclusions on the clinical efficacy

In 2 of the 3 pivotal studies (advanced breast cancer with skeletal metastasis; advanced prostate cancer with skeletal metastasis) superiority of denosumab 120 mg sc every 4 weeks was shown to the comparator zoledronic acid while in the third study (advanced solid tumours except prostate cancer or prostate cancer; multiple myeloma or lymphoma and skeletal metastasis) noninferiority was shown. The studies were event driven and the primary efficacy parameter was noninferiority for time to first on-study skeletal related event (SRE) (pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression). The secondary endpoint was superiority for time to first SRE. Patient-reported outcomes (pain parameters, QoL and analgesic use) did not significantly differ between treatment groups. Healthcare utilisation was lower in the denosumab group than in the zoledronic acid treatment group.

Overall survival and progression of disease were equal between treatment groups with the exception of the subgroup of patients with multiple myeloma who had worse outcomes for these parameters in the denosumab treated group. Due to limited sample size and due to a number of imbalances between the treatment groups in study IM103244, firm conclusions could not be drawn on efficacy in the subgroup

of multiple myeloma. An indication for the subgroup of patients with multiple myeloma can therefore not be granted at present, until new data in support of this part of the indication are presented. Following the CHMP assessment, the applicant agreed to exclude multiple myeloma patients from the indication, which was reworded as follows:

"Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastates from solid tumours."

2.6. Clinical safety

Patient exposure

Altogether, 3900 patients have been exposed to denosumab in clinical trials for advanced cancer. Only 10 of those were exposed for 3 years or more. The clinical studies with denosumab provided as part of the MAA for Prolia (denosumab 60 mg SC every 6 months) provided a safety database including more than 13.000 subjects who enrolled in 30 denosumab clinical studies and received at least 1 dose of denosumab (n = 7848) or placebo (n = 5199).

Table 33. Number of subjects receiving denosumab and duration of cumulative exposure by study type

	Denosumab					
	≥ 1 Dose	≥ 1 Month	≥ 6 Months	≥ 1 Year	≥ 2 Years	≥ 3 Years
Overall total exposure	3904	3870	2526	1729	540	10
Phase 1 studies[a]	647	645	75	0	0	0
Phase 2 supportive studies[b]	284	279	238	169	0	0
Phase 3 advanced cancer studies[c]	2841	2814	2151	1535	540	10
Phase 2 studies in other indications[d]	132	132	62	25	0	0

Data included in this analysis are the same as that used for the primary analysis CSRs included in this marketing application, with the exception of Studies 20050136 and 20050244, for which data are included up to end of study date or entire blinded treatment cutoff date, whichever occurred first

[a] Includes studies 20010123, 20010124, 20030148, 20030164, 20030180, 20040176, 20040245, 20050227, 20060286, and 20060446

[b] Includes studies 20040113 and 20040114

[c] Includes studies 20050136, 20050244 and 20050103

[d] Includes studies 20050134 and 20040215

The cumulative mean investigational product exposure time in months differed between studies but did not significantly differ between treatment groups within each study. In study 20050103, exposure time was 11.59 ± 8.13 months for ZOL and 12.6359 ± 8.38 ZOL for denosumab groups. In study 20050136, exposure time was 15.23±7.73 months for ZOL and 15.34±7.47 for denosumab groups. In study 20050244, exposure time was 8.91±7.24 months for ZOL and 9.23±7.40 for denosumab groups.

Adverse events

Of the 5677 subjects who received ≥ 1 dose of investigational product and were included in the primary advanced cancer safety analysis set, 96.2% of subjects in the denosumab group and 96.8% of subjects in the ZOL group had ≥ 1 adverse event (AE) while on study. By preferred term, the most common AEs in either treatment group were nausea (30.8% denosumab, 31.6% ZOL), anemia (27.1%, 30.3%), fatigue (27.1%, 27.0%), back pain (25.3%, 26.3%), decreased appetite (23.1%,

24.5%), asthenia (21.4%, 21.9%), constipation (21.2%, 23.6%), dyspnea (20.6%, 17.9%), diarrhea (20.3%, 18.7%), arthralgia (20.1%, 22.3%), bone pain (19.9%, 22.5%), and vomiting (19.9%, 20.1%). The most common AEs were similar across the 3 pivotal studies. By MedDRA system organ class, the most common AEs were: general disorders and administration site conditions (65.4% denosumab, 68.8% ZOL), musculoskeletal and connective tissue disorders (63.1%, 67.4%), and gastrointestinal disorders (60.2%, 59.8%).

Table 34. Summary of subject incidence of AEs, primary advanced cancer safety analysis set

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Adverse events regardless of relationship								
All	985 (97.2)	977 (95.8)	842 (95.9)	841 (95.8)	918 (97.1)	916 (97.1)	2745 (96.8)	2734 (96.2)
Serious	471 (46.5)	453 (44.4)	581 (66.2)	552 (62.9)	568 (60.1)	594 (63.0)	1620 (57.1)	1599 (56.3)
Fatal	215 (21.2)	204 (20.0)	331 (37.7)	329 (37.5)	276 (29.2)	283 (30.0)	822 (29.0)	816 (28.7)
Leading to study discontinuation	71 (7.0)	48 (4.7)	133 (15.1)	131 (14.9)	76 (8.0)	91 (9.7)	280 (9.9)	270 (9.5)
Leading to investigational product discontinuation	125 (12.3)	98 (9.6)	109 (12.4)	91 (10.4)	138 (14.6)	164 (17.4)	372 (13.1)	353 (12.4)
CTCAE Grade 3, 4, or 5	635 (62.7)	609 (59.7)	702 (80.0)	673 (76.7)	672 (71.1)	718 (76.1)	2009 (70.8)	2000 (70.4)
Adverse events related to investigational product[a]								
All	434 (42.8)	329 (32.3)	203 (23.1)	196 (22.3)	303 (32.1)	302 (32.0)	940 (33.1)	827 (29.1)
Serious	36 (3.6)	52 (5.1)	32 (3.6)	36 (4.1)	40 (4.2)	59 (6.3)	108 (3.8)	147 (5.2)
Fatal	4 (0.4)	5 (0.5)	3 (0.3)	6 (0.7)	3 (0.3)	5 (0.5)	10 (0.4)	16 (0.6)
Leading to study discontinuation	15 (1.5)	20 (2.0)	6 (0.7)	10 (1.1)	14 (1.5)	19 (2.0)	35 (1.2)	49 (1.7)
Leading to investigational product discontinuation	32 (3.2)	41 (4.0)	17 (1.9)	19 (2.2)	27 (2.9)	51 (5.4)	76 (2.7)	111 (3.9)
CTCAE Grade 3, 4, or 5	63 (6.2)	62 (6.1)	50 (5.7)	61 (6.9)	62 (6.6)	91 (9.7)	175 (6.2)	214 (7.5)

N = Number of subjects who received ≥ 1 active dose of investigational product
CTCAE version 3.0
Includes only treatment-emergent adverse events
[a] Includes only events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product

Table 35. Adverse Events by Preferred Term in Descending Order of Frequency (≥ 5% Subject Incidence in Either Treatment Group) (Primary Advanced Cancer Safety Analysis Set)

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting adverse events[a]	985 (97.2)	977 (95.8)	842 (95.9)	841 (95.8)	918 (97.1)	916 (97.1)	2745 (96.8)	2734 (96.2)
Nausea	384 (37.9)	356 (34.9)	266 (30.3)	248 (28.2)	245 (25.9)	272 (28.8)	895 (31.6)	876 (30.8)
Anaemia	232 (22.9)	192 (18.8)	286 (32.6)	242 (27.6)	341 (36.1)	337 (35.7)	859 (30.3)	771 (27.1)
Fatigue	324 (32.0)	301 (29.5)	220 (25.1)	211 (24.0)	222 (23.5)	257 (27.3)	766 (27.0)	769 (27.1)
Back pain	264 (26.1)	241 (23.6)	196 (22.3)	173 (19.7)	287 (30.4)	304 (32.2)	747 (26.3)	718 (25.3)
Decreased appetite	192 (19.0)	193 (18.9)	228 (26.0)	196 (22.3)	274 (29.0)	267 (28.3)	694 (24.5)	656 (23.1)
Asthenia	202 (19.9)	196 (19.2)	180 (20.5)	172 (19.6)	239 (25.3)	239 (25.3)	621 (21.9)	607 (21.4)
Constipation	205 (20.2)	176 (17.3)	214 (24.4)	191 (21.8)	251 (26.6)	236 (25.0)	670 (23.6)	603 (21.2)
Dyspnoea	190 (18.8)	222 (21.8)	200 (22.8)	220 (25.1)	117 (12.4)	143 (15.2)	507 (17.9)	585 (20.6)
Diarrhoea	207 (20.4)	231 (22.6)	171 (19.5)	168 (19.1)	152 (16.1)	178 (18.9)	530 (18.7)	577 (20.3)
Arthralgia	291 (28.7)	250 (24.5)	139 (15.8)	126 (14.4)	202 (21.4)	194 (20.6)	632 (22.3)	570 (20.1)
Vomiting	238 (23.5)	212 (20.8)	183 (20.8)	186 (21.2)	149 (15.8)	168 (17.8)	570 (20.1)	566 (19.9)

	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)

Preferred Term	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Bone pain	238 (23.5)	186 (18.2)	156 (17.8)	143 (16.3)	245 (25.9)	235 (24.9)	639 (22.5)	564 (19.9)
Pain in extremity	222 (21.9)	204 (20.0)	132 (15.0)	123 (14.0)	196 (20.7)	197 (20.9)	550 (19.4)	524 (18.4)
Oedema peripheral	150 (14.8)	174 (17.1)	138 (15.7)	106 (12.1)	174 (18.4)	192 (20.4)	462 (16.3)	472 (16.6)
Cough	180 (17.8)	171 (16.8)	156 (17.8)	173 (19.7)	83 (8.8)	93 (9.9)	419 (14.8)	437 (15.4)
Pyrexia	247 (24.4)	170 (16.7)	182 (20.7)	139 (15.8)	133 (14.1)	100 (10.6)	562 (19.8)	409 (14.4)
Headache	214 (21.1)	197 (19.3)	96 (10.9)	101 (11.5)	72 (7.6)	62 (6.6)	382 (13.5)	360 (12.7)
Musculoskeletal pain	148 (14.6)	149 (14.6)	99 (11.3)	97 (11.0)	138 (14.6)	111 (11.8)	385 (13.6)	357 (12.6)
Weight decreased	94 (9.3)	79 (7.7)	106 (12.1)	100 (11.4)	132 (14.0)	151 (16.0)	332 (11.7)	330 (11.6)
Insomnia	136 (13.4)	124 (12.2)	94 (10.7)	89 (10.1)	94 (9.9)	89 (9.4)	324 (11.4)	302 (10.6)
Abdominal pain	119 (11.7)	122 (12.0)	97 (11.0)	96 (10.9)	64 (6.8)	74 (7.8)	280 (9.9)	292 (10.3)
Neutropenia	123 (12.1)	125 (12.3)	109 (12.4)	99 (11.3)	46 (4.9)	53 (5.6)	278 (9.8)	277 (9.8)
Alopecia	142 (14.0)	159 (15.6)	62 (7.1)	48 (5.5)	62 (6.6)	58 (6.2)	266 (9.4)	265 (9.3)
Hypocalcaemia	34 (3.4)	56 (5.5)	49 (5.6)	93 (10.6)	51 (5.4)	116 (12.3)	134 (4.7)	265 (9.3)
Chest pain	84 (8.3)	93 (9.1)	93 (10.6)	97 (11.0)	70 (7.4)	73 (7.7)	247 (8.7)	263 (9.3)
Dizziness	114 (11.3)	106 (10.4)	75 (8.5)	70 (8.0)	65 (6.9)	56 (5.9)	254 (9.0)	232 (8.2)

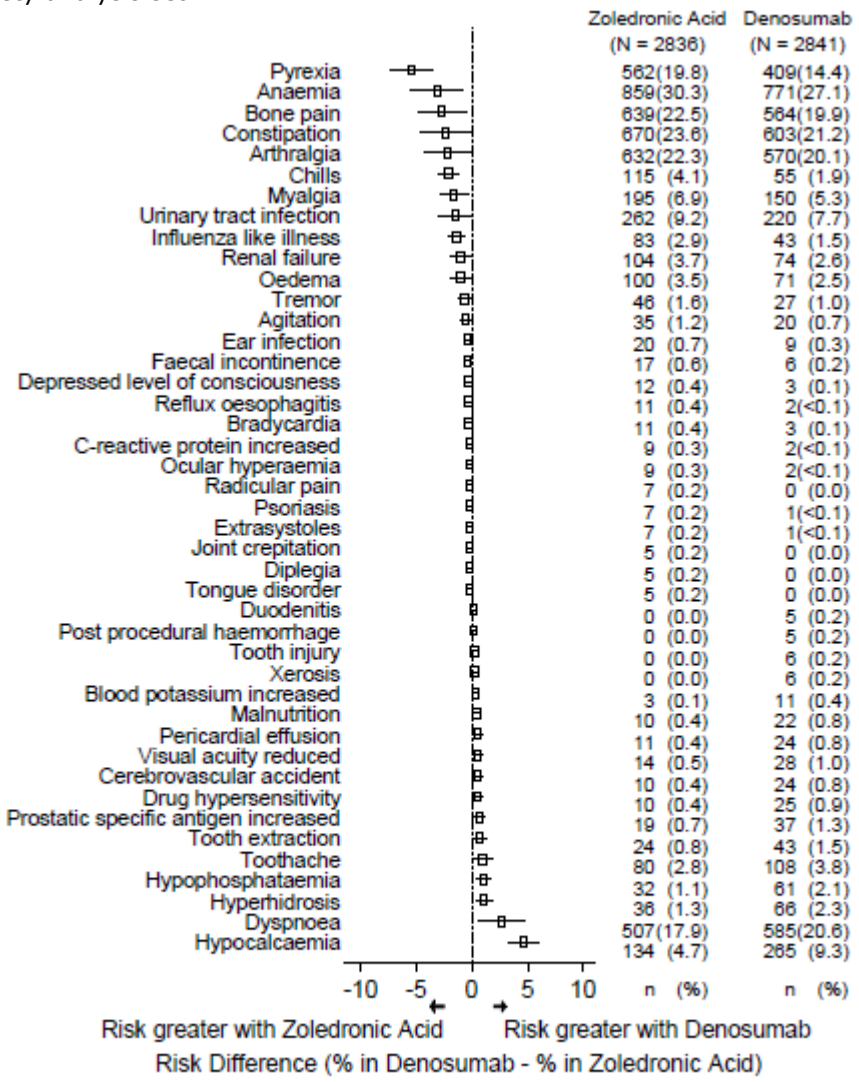
Preferred Term	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Pain	97 (9.6)	72 (7.1)	52 (5.9)	57 (6.5)	94 (9.9)	93 (9.9)	243 (8.6)	222 (7.8)
Urinary tract infection	92 (9.1)	72 (7.1)	46 (5.2)	43 (4.9)	124 (13.1)	105 (11.1)	262 (9.2)	220 (7.7)
Thrombocytopenia	60 (5.9)	68 (6.7)	102 (11.6)	96 (10.9)	37 (3.9)	52 (5.5)	199 (7.0)	216 (7.6)
Anxiety	74 (7.3)	75 (7.4)	58 (6.6)	75 (8.5)	52 (5.5)	46 (4.9)	184 (6.5)	196 (6.9)
Rash	100 (9.9)	97 (9.5)	76 (8.7)	67 (7.6)	25 (2.6)	29 (3.1)	201 (7.1)	193 (6.8)
Musculoskeletal chest pain	81 (8.0)	82 (8.0)	52 (5.9)	54 (6.2)	55 (5.8)	50 (5.3)	188 (6.6)	186 (6.5)
Depression	86 (8.5)	72 (7.1)	56 (6.4)	62 (7.1)	40 (4.2)	52 (5.5)	182 (6.4)	186 (6.5)
Dehydration	42 (4.1)	46 (4.5)	70 (8.0)	68 (7.7)	52 (5.5)	65 (6.9)	164 (5.8)	179 (6.3)
Paraesthesia	73 (7.2)	69 (6.8)	60 (6.8)	46 (5.2)	71 (7.5)	53 (5.6)	204 (7.2)	168 (5.9)
Abdominal pain upper	82 (8.1)	71 (7.0)	39 (4.4)	51 (5.8)	43 (4.6)	45 (4.8)	164 (5.8)	167 (5.9)
Leukopenia	76 (7.5)	81 (7.9)	73 (8.3)	51 (5.8)	28 (3.0)	33 (3.5)	177 (6.2)	165 (5.8)
Rib fracture	93 (9.2)	83 (8.1)	46 (5.2)	40 (4.6)	27 (2.9)	35 (3.7)	166 (5.9)	158 (5.6)
Pleural effusion	62 (6.1)	64 (6.3)	49 (5.6)	52 (5.9)	26 (2.8)	37 (3.9)	137 (4.8)	153 (5.4)
Myalgia	106 (10.5)	82 (8.0)	32 (3.6)	31 (3.5)	57 (6.0)	37 (3.9)	195 (6.9)	150 (5.3)
Nasopharyngitis	94 (9.3)	84 (8.2)	31 (3.5)	25 (2.8)	38 (4.0)	40 (4.2)	163 (5.7)	149 (5.2)

Preferred Term	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Thoracic vertebral fracture	78 (7.7)	64 (6.3)	46 (5.2)	38 (4.3)	30 (3.2)	47 (5.0)	154 (5.4)	149 (5.2)
Hypertension	65 (6.4)	67 (6.6)	43 (4.9)	33 (3.8)	45 (4.8)	48 (5.1)	153 (5.4)	148 (5.2)
Neuropathy peripheral	71 (7.0)	71 (7.0)	42 (4.8)	46 (5.2)	29 (3.1)	30 (3.2)	142 (5.0)	147 (5.2)
Pneumonia	43 (4.2)	32 (3.1)	56 (6.4)	67 (7.6)	31 (3.3)	48 (5.1)	130 (4.6)	147 (5.2)
Stomatitis	71 (7.0)	90 (8.8)	32 (3.6)	33 (3.8)	12 (1.3)	23 (2.4)	115 (4.1)	146 (5.1)
Dyspepsia	74 (7.3)	52 (5.1)	39 (4.4)	38 (4.3)	34 (3.6)	42 (4.5)	147 (5.2)	132 (4.6)
Hypokalaemia	51 (5.0)	40 (3.9)	65 (7.4)	55 (6.3)	40 (4.2)	35 (3.7)	156 (5.5)	130 (4.6)
Neck pain	71 (7.0)	66 (6.5)	38 (4.3)	29 (3.3)	35 (3.7)	30 (3.2)	144 (5.1)	125 (4.4)

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N=1013)	Denosumab 120 mg Q4W (N=1020)	Zoledronic Acid 4 mg Q4W (N=878)	Denosumab 120 mg Q4W (N=878)	Zoledronic Acid 4 mg Q4W (N=945)	Denosumab 120 mg Q4W (N=943)	Zoledronic Acid 4 mg Q4W (N=2836)	Denosumab 120 mg Q4W (N=2841)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 12.1.
[a] Includes all adverse events, not only those occurring with ≥ 5% frequency

Fig 7. Forest plot of AEs with unadjusted p-value < 0.05 by Preferred Term, primary advanced cancer safety analysis set



N = Number of subjects who received >= 1 active dose of investigational product; n = Number of subjects reporting >= 1 event. Unadjusted p-value is calculated from Cochran-Armitage test stratified by study.
Risk difference is based on Mantel-Haenszel method adjusting for the stratification variable of study.

Pyrexia, anemia, bone pain, constipation, arthralgia, and chills were adverse events that were more common in the zoledronic acid treatment group than in the denosumab treatment group. Hypocalcemia and dyspnea were more common in the denosumab group than in the ZOL group. Overall, the incidence of adverse events was similar between treatment groups. Some types of AEs of special interest were selected for additional analyses.

• *Hypocalcemia* is a known risk during denosumab treatment and was more common in the denosumab treatment group than in the ZOL treatment group. Most cases of hypocalcemia reversed spontaneously or after oral calcium supplementation; very few of the hypocalcemia adverse events in

the pivotal studies requested intravenous calcium treatment. Administration of calcium and vitamin D with investigational product was strongly recommended for participants in denosumab phase 3 studies and is also recommended in the SmPC proposal. Hypocalcemic events were more common among patients who did not receive calcium supplementation. Hypocalcemic events were more common among patients treated with denosumab than among patients treated with zoledronic acid and this difference between treatment groups was larger in the small group of patients who did not receive calcium supplementation.

• The incidence of any type of *infection* did not differ between study groups, with the exception that staphylococcal infections were more common in the denosumab group than in the ZOL group (0.5% versus 0.2%). The overall incidence of bacterial infections did not differ between treatment groups.

• *Osteonecrosis of the jaw (ONJ)* was more common in the denosumab treated group of patients than in patients treated with ZOL.

Table 36. Subject incidence of adjudicated positive ONJ adverse events

	Study 20050136		Study 20050244		Study 20050103		Overall	
	Zoledronic Acid 4 mg Q4W (N = 1013) n (%)	Denosumab 120 mg Q4W (N = 1020) n (%)	Zoledronic Acid 4 mg Q4W (N = 878) n (%)	Denosumab 120 mg Q4W (N = 878) n (%)	Zoledronic Acid 4 mg Q4W (N = 945) n (%)	Denosumab 120 mg Q4W (N = 943) n (%)	Zoledronic Acid 4 mg Q4W (N = 2836) n (%)	Denosumab 120 mg Q4W (N = 2841) n (%)
Number of subjects having adjudicated positive ONJ AE	14 (1.4)	20 (2.0)	11 (1.3)	10 (1.1)	12 (1.3)	22 (2.3)	37 (1.3)	52 (1.8)

N = Number of subjects who received ≥ 1 active dose of investigational product
Includes only treatment-emergent adverse events
ONJ = Osteonecrosis of the jaw

The cumulative incidence of ONJ in the denosumab and ZOL groups, respectively, was 0.8% and 0.5% at 1 year, 1.8% and 1.0% at 2 years, and 1.8% and 1.3% at 3 years. By calendar time period, the incidence of ONJ was 22 subjects (0.8%) in the denosumab group and 15 subjects (0.5%) in the ZOL group in the first 12 months on study, 51 subjects (1.8%) and 28 subjects (1.0%), respectively, at 24 months, and 52 subjects (1.8%) and 36 subjects (1.3%), respectively, at 36 months, indicating that most cases of ONJ in the denosumab group occurred within the first 2 years on study.

• No significant differences were observed between the denosumab and ZOL treatment groups in the incidence of *new primary malignancy* (1.0 and 0.6 %, respectively).

• *Hypersensitivity* was not a significant problem in the clinical studies with denosumab. Hypersensitivity reactions reported to be associated with treatment were rare but tended to be more common in the denosumab treated group; the difference between treatment groups was however not significant.

• *Eczema* did not occur more often in denosumab treated patients than in ZOL treated patients in the pivotal studies.

• The subject incidence of *cataract* AEs was similar between treatment groups.

• *Cardiac disorders*: AEs (but not SAEs) of pericardial effusion were more common with denosumab than with ZOL treatment. Study 20050244 had more fatal cardiac AEs among denosumab treated patients than among patients in the comparator arm; this difference was driven by a difference between treatment groups in cardiac arrest due to disease progression. The other two studies did not have this difference in cardiac AEs between treatment groups. Otherwise, cardiac AEs were similar across treatment groups.

• AEs of *vascular disorders*, such as hypertension, hypotension or vascular AEs, did not differ between treatment groups.

• *Renal toxicity*

Table 37. AEs potentially associated with renal toxicity by Preferred Term in descending order of frequency by baseline creatinine clearance (≥ 2% subject incidence in either treatment group)

	≤ 60 mL/min		> 60 mL/min	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=482) n (%)	Denosumab 120 mg Q4W (N=496) n (%)	Zoledronic Acid 4 mg Q4W (N=2326) n (%)	Denosumab 120 mg Q4W (N=2326) n (%)
Number of subjects reporting adverse events potentially associated with renal toxicity[a]	119 (24.7)	84 (16.9)	209 (9.0)	177 (7.6)
Blood creatinine increased	45 (9.3)	30 (6.0)	88 (3.8)	74 (3.2)
Renal failure	39 (8.1)	26 (5.2)	62 (2.7)	48 (2.1)

N = Number of subjects who received ≥ 1 active dose of investigational product and had a non-missing baseline creatinine clearance
n = Number of subjects reporting ≥ 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 12.1.
[a] Includes all adverse events, not only those occurring with ≥ 2% frequency

Serious adverse event/deaths/other significant events

Fatal AEs were common but did not differ between treatment groups. In study 20050244, fatal events due to malignant neoplasm progression were more common in the denosumab group than in the ZOL group. It is not clear if this relates to type of tumour or not. The applicant presented how the fatal AEs in study 20050244 were distributed with respect to type of tumour. Since there was an imbalance between treatment groups at baseline with respect to tumour type, no firm conclusions could be drawn on these data. More SAEs of prostate cancer were seen in the ZOL treatment group while more SAEs of osteonecrosis, hypocalcemia and fatigue were seen in the denosumab treatment group.

The all over incidence of serious adverse events (SAEs) was 56.3% in the denosumab group and 57.1% in the ZOL group.

Table 38. SAEs reported for ≥ 1% of subjects in either treatment group by preferred term in descending
order of frequency, primary advanced cancer safety analysis set

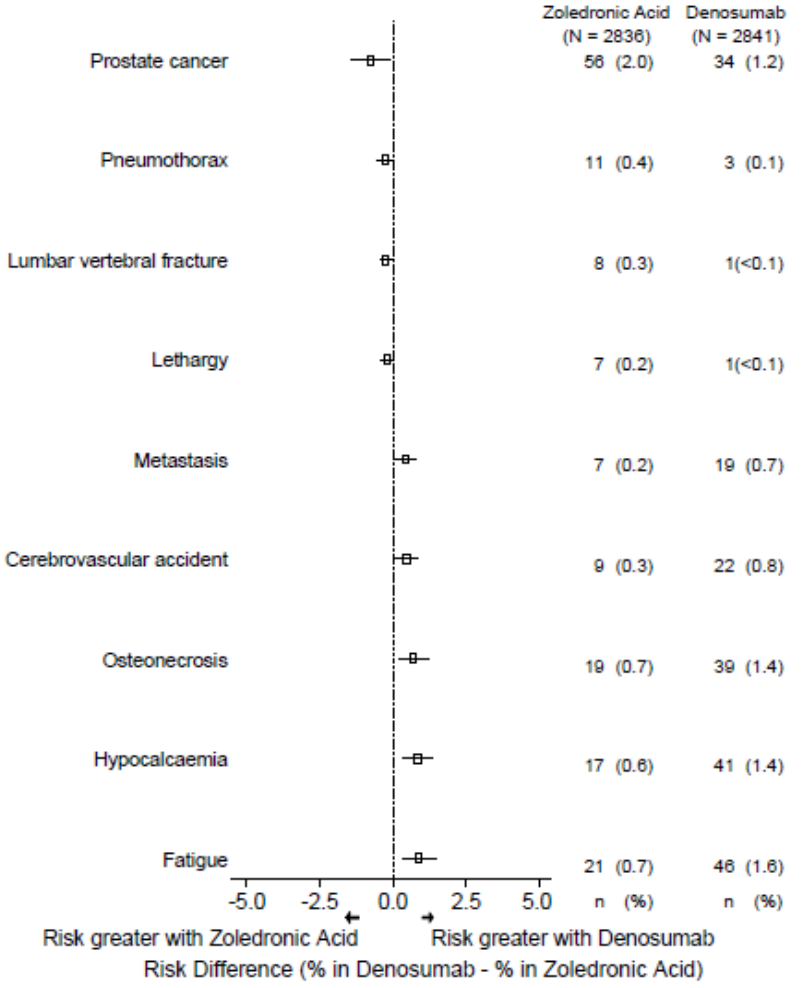
	Study 20050136		Study 20050244		Study 20050103		Overall	
Preferred Term	Zoledronic Acid 4 mg Q4W (N=1013) n (%)	Denosumab 120 mg Q4W (N=1020) n (%)	Zoledronic Acid 4 mg Q4W (N=878) n (%)	Denosumab 120 mg Q4W (N=878) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting serious adverse events	471 (46.5)	453 (44.4)	581 (66.2)	552 (62.9)	568 (60.1)	594 (63.0)	1620 (57.1)	1599 (56.3)
Anaemia	32 (3.2)	27 (2.6)	49 (5.6)	25 (2.8)	82 (8.7)	108 (11.5)	163 (5.7)	160 (5.6)
Dyspnoea	38 (3.8)	53 (5.2)	54 (6.2)	55 (6.3)	28 (3.0)	36 (3.8)	120 (4.2)	144 (5.1)
Pneumonia	25 (2.5)	20 (2.0)	44 (5.0)	52 (5.9)	24 (2.5)	40 (4.2)	93 (3.3)	112 (3.9)
Malignant neoplasm progression	7 (0.7)	6 (0.6)	100 (11.4)	103 (11.7)	3 (0.3)	2 (0.2)	110 (3.9)	111 (3.9)
Metastases to central nervous system	46 (4.5)	47 (4.6)	44 (5.0)	43 (4.9)	6 (0.6)	14 (1.5)	96 (3.4)	104 (3.7)
Respiratory failure	20 (2.0)	20 (2.0)	40 (4.6)	45 (5.1)	14 (1.5)	24 (2.5)	74 (2.6)	89 (3.1)
Dehydration	24 (2.4)	13 (1.3)	34 (3.9)	35 (4.0)	19 (2.0)	36 (3.8)	77 (2.7)	84 (3.0)
Vomiting	31 (3.1)	31 (3.0)	24 (2.7)	21 (2.4)	22 (2.3)	24 (2.5)	77 (2.7)	76 (2.7)
General physical health deterioration	15 (1.5)	20 (2.0)	38 (4.3)	26 (3.0)	28 (3.0)	29 (3.1)	81 (2.9)	75 (2.6)
Asthenia	14 (1.4)	12 (1.2)	16 (1.8)	21 (2.4)	29 (3.1)	37 (3.9)	59 (2.1)	70 (2.5)
Pyrexia	26 (2.6)	21 (2.1)	21 (2.4)	26 (3.0)	18 (1.9)	19 (2.0)	65 (2.3)	66 (2.3)
Pleural effusion	25 (2.5)	24 (2.4)	27 (3.1)	23 (2.6)	9 (1.0)	12 (1.3)	61 (2.2)	59 (2.1)
Spinal cord compression	8 (0.8)	6 (0.6)	26 (3.0)	27 (3.1)	33 (3.5)	24 (2.5)	67 (2.4)	57 (2.0)
Back pain	14 (1.4)	8 (0.8)	19 (2.2)	15 (1.7)	36 (3.8)	29 (3.1)	69 (2.4)	52 (1.8)
Pulmonary embolism	18 (1.8)	11 (1.1)	18 (2.1)	19 (2.2)	16 (1.7)	20 (2.1)	52 (1.8)	50 (1.8)
Metastases to liver	28 (2.8)	20 (2.0)	13 (1.5)	16 (1.8)	5 (0.5)	13 (1.4)	46 (1.6)	49 (1.7)
Febrile neutropenia	22 (2.2)	17 (1.7)	31 (3.5)	21 (2.4)	8 (0.8)	8 (0.8)	61 (2.2)	46 (1.6)
Fatigue	5 (0.5)	15 (1.5)	6 (0.7)	11 (1.3)	10 (1.1)	20 (2.1)	21 (0.7)	46 (1.6)
Bone pain	13 (1.3)	10 (1.0)	15 (1.7)	11 (1.3)	34 (3.6)	24 (2.5)	62 (2.2)	45 (1.6)
Diarrhoea	16 (1.6)	19 (1.9)	13 (1.5)	14 (1.6)	13 (1.4)	12 (1.3)	42 (1.5)	45 (1.6)
Urinary tract infection	9 (0.9)	7 (0.7)	9 (1.0)	9 (1.0)	30 (3.2)	28 (3.0)	48 (1.7)	44 (1.5)
Nausea	23 (2.3)	21 (2.1)	16 (1.8)	14 (1.6)	14 (1.5)	8 (0.8)	53 (1.9)	43 (1.5)
Abdominal pain	14 (1.4)	15 (1.5)	17 (1.9)	18 (2.1)	12 (1.3)	8 (0.8)	43 (1.5)	41 (1.4)
Hypocalcaemia	2 (0.2)	5 (0.5)	8 (0.9)	12 (1.4)	7 (0.7)	24 (2.5)	17 (0.6)	41 (1.4)
Neutropenia	14 (1.4)	16 (1.6)	11 (1.3)	14 (1.6)	4 (0.4)	10 (1.1)	29 (1.0)	40 (1.4)
Thrombocytopenia	11 (1.1)	12 (1.2)	23 (2.6)	17 (1.9)	5 (0.5)	10 (1.1)	39 (1.4)	39 (1.4)
Osteonecrosis	11 (1.1)	18 (1.8)	4 (0.5)	7 (0.8)	4 (0.4)	14 (1.5)	19 (0.7)	39 (1.4)
Renal failure	9 (0.9)	1 (<0.1)	13 (1.5)	10 (1.1)	28 (3.0)	26 (2.8)	50 (1.8)	37 (1.3)

Table 38, ctd

Spinal cord compression	8 (0.8)	6 (0.6)	26 (3.0)	27 (3.1)	33 (3.5)	24 (2.5)	67 (2.4)	57 (2.0)
Back pain	14 (1.4)	8 (0.8)	19 (2.2)	15 (1.7)	36 (3.8)	29 (3.1)	69 (2.4)	52 (1.8)
Pulmonary embolism	18 (1.8)	11 (1.1)	18 (2.1)	19 (2.2)	16 (1.7)	20 (2.1)	52 (1.8)	50 (1.8)
Metastases to liver	28 (2.8)	20 (2.0)	13 (1.5)	16 (1.8)	5 (0.5)	13 (1.4)	46 (1.6)	49 (1.7)
Febrile neutropenia	22 (2.2)	17 (1.7)	31 (3.5)	21 (2.4)	8 (0.8)	8 (0.8)	61 (2.2)	46 (1.6)
Fatigue	5 (0.5)	15 (1.5)	6 (0.7)	11 (1.3)	10 (1.1)	20 (2.1)	21 (0.7)	46 (1.6)
Bone pain	13 (1.3)	10 (1.0)	15 (1.7)	11 (1.3)	34 (3.6)	24 (2.5)	62 (2.2)	45 (1.6)
Diarrhoea	16 (1.6)	19 (1.9)	13 (1.5)	14 (1.6)	13 (1.4)	12 (1.3)	42 (1.5)	45 (1.6)
Urinary tract infection	9 (0.9)	7 (0.7)	9 (1.0)	9 (1.0)	30 (3.2)	28 (3.0)	48 (1.7)	44 (1.5)
Nausea	23 (2.3)	21 (2.1)	16 (1.8)	14 (1.6)	14 (1.5)	8 (0.8)	53 (1.9)	43 (1.5)
Abdominal pain	14 (1.4)	15 (1.5)	17 (1.9)	18 (2.1)	12 (1.3)	8 (0.8)	43 (1.5)	41 (1.4)
Hypocalcaemia	2 (0.2)	5 (0.5)	8 (0.9)	12 (1.4)	7 (0.7)	24 (2.5)	17 (0.6)	41 (1.4)
Neutropenia	14 (1.4)	16 (1.6)	11 (1.3)	14 (1.6)	4 (0.4)	10 (1.1)	29 (1.0)	40 (1.4)
Thrombocytopenia	11 (1.1)	12 (1.2)	23 (2.6)	17 (1.9)	5 (0.5)	10 (1.1)	39 (1.4)	39 (1.4)
Osteonecrosis	11 (1.1)	18 (1.8)	4 (0.5)	7 (0.8)	4 (0.4)	14 (1.5)	19 (0.7)	39 (1.4)
Renal failure	9 (0.9)	1 (<0.1)	13 (1.5)	10 (1.1)	28 (3.0)	26 (2.8)	50 (1.8)	37 (1.3)
Cardiac failure	7 (0.7)	6 (0.6)	5 (0.6)	10 (1.1)	23 (2.4)	21 (2.2)	35 (1.2)	37 (1.3)
Multi-organ failure	9 (0.9)	9 (0.9)	8 (0.9)	10 (1.1)	18 (1.9)	18 (1.9)	35 (1.2)	37 (1.3)
Urinary retention	0 (0.0)	1 (<0.1)	9 (1.0)	3 (0.3)	35 (3.7)	32 (3.4)	44 (1.6)	36 (1.3)
Hepatic failure	16 (1.6)	24 (2.4)	4 (0.5)	2 (0.2)	6 (0.6)	10 (1.1)	26 (0.9)	36 (1.3)
Prostate cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	56 (5.9)	34 (3.6)	56 (2.0)	34 (1.2)
Pain	8 (0.8)	4 (0.4)	6 (0.7)	12 (1.4)	12 (1.3)	16 (1.7)	26 (0.9)	32 (1.1)
Haematuria	0 (0.0)	0 (0.0)	2 (0.2)	8 (0.9)	37 (3.9)	23 (2.4)	39 (1.4)	31 (1.1)
Decreased appetite	8 (0.8)	10 (1.0)	7 (0.8)	7 (0.8)	13 (1.4)	13 (1.4)	28 (1.0)	30 (1.1)
Sepsis	4 (0.4)	2 (0.2)	11 (1.3)	16 (1.8)	11 (1.2)	12 (1.3)	26 (0.9)	30 (1.1)
Renal failure acute	6 (0.6)	0 (0.0)	15 (1.7)	10 (1.1)	16 (1.7)	18 (1.9)	37 (1.3)	28 (1.0)
Chest pain	9 (0.9)	5 (0.5)	10 (1.1)	14 (1.6)	13 (1.4)	9 (1.0)	32 (1.1)	28 (1.0)
Deep vein thrombosis	8 (0.8)	4 (0.4)	13 (1.5)	15 (1.7)	8 (0.8)	8 (0.8)	29 (1.0)	27 (1.0)
Cachexia	7 (0.7)	6 (0.6)	10 (1.1)	4 (0.5)	12 (1.3)	14 (1.5)	29 (1.0)	24 (0.8)
Pain in extremity	3 (0.3)	8 (0.8)	7 (0.8)	5 (0.6)	20 (2.1)	10 (1.1)	30 (1.1)	23 (0.8)
Disease progression	12 (1.2)	11 (1.1)	13 (1.5)	8 (0.9)	2 (0.2)	0 (0.0)	27 (1.0)	19 (0.7)

N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 12.1.

Fig 8. Forest plot of SAEs with unadjusted P-value < 0.05 by Preferred Term, Primary advanced cancer safety analysis set



N = Number of subjects who received >= 1 active dose of investigational product; n = Number of subjects reporting >= 1 event.
Unadjusted p-value is calculated from Cochran-Armitage test stratified by study.
Risk difference is based on Mantel-Haenszel method adjusting for the stratification variable of study.

Laboratory findings

Low calcium values were more common in the denosumab treatment group but were seldom very low.

Increased creatinine levels occurred in both treatment groups but were more common in the ZOL treatment group.

Safety in special populations

Overall, the AEs and SAEs did not significantly differ between groups analysed in subgroup analyses.

Immunological events

Overall, 0.4% of the 3508 denosumab-treated subjects who were tested for antibodies in the studies included in this application were positive for binding antibodies. In most of these subjects, the antibodies were transiently detected. No neutralising antibodies have been observed to date in the denosumab clinical development program.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with denosumab. In clinical studies, denosumab was given together with standard therapies for cancer. Concomitant cancer therapy, chemotherapy or hormone therapy in patients with breast cancer did not affect denosumab pharmacokinetics or pharmacodynamics. The absence of specified interaction studies is acceptable, as denosumab has a low potential to interfere with the expression or activity of the CYP enzyme system in the liver.

Discontinuation due to adverse events

Investigational product withdrawal due to AEs was reported for 12.4% of subjects in the denosumab group and for 13.1% of subjects in the ZOL group. Osteonecrosis of the jaw was the most common adverse event that led to study withdrawal, followed by hypocalcemia. Both these adverse events were more common as the cause for study withdrawal in the denosumab treatment group. All except 3 cases of osteonecrosis were in the jaw. In the remaining 3 cases, the osteonecrosis was localised in the hip. These 3 events were all confounded by bone metastases in the hip.

Post marketing experience

At the time of the submission of this application, XGEVA (denosumab) has not yet been marketed.

2.6.1. Discussion on clinical safety

The safety database for denosumab-Amgen is appropriate for this application, and is in accordance with current guidelines. It is noted that only 10 patients have received the drug for 3 years or more. Pyrexia, anemia, bone pain, constipation, arthralgia, and chills were adverse events that were more common in the zoledronic acid treatment group than in the denosumab treatment group. Hypocalcemia and dyspnea were more common in the denosumab group than in the zoledronic acid group. All over, the incidence of adverse events was similar between treatment groups. Some types of adverse advents of special interest were selected for additional analyses. *Hypocalcemia* was more common in the denosumab treatment group than in the zoledronic acid group. Most cases of hypocalcemia reversed spontaneously or after oral calcium supplementation; very few of the hypocalcemia adverse events in the pivotal studies requested intravenous calcium treatment.

The incidence of any type of infection did not differ between study groups, with the exception that staphylococcal infections were more common in the denosumab group than in the zoledronic acid group (0.5% versus 0.2%). The all over incidence of bacterial infections did not differ between treatment groups. No significant differences were observed between the denosumab and ZOL treatment groups in the incidence of new primary malignancy. Hypersensitivity reactions reported to be associated with treatment were rare but tended to be more common in the denosumab treated group; the difference between treatment groups was however not significant. The subject incidences of cataract and eczema were similar between treatment groups in the pivotal studies.

Adverse events - but not severe adverse events - of pericardial effusion were more common with denosumab than with zoledronic acid treatment. Study 20050244 had more fatal cardiac AEs among denosumab treated patients than among patients in the comparator arm; this difference was driven by a difference between treatment groups in cardiac arrest due to disease progression. The other two studies did not have this difference in cardiac adverse events between treatment groups. Otherwise, cardiac AEs were similar across treatment groups. Adverse events of vascular disorders, such as hypertension, hypotension or vascular adverse events, did not differ between treatment groups.

Deterioration of renal function was more common in the zoledronic acid treatment group than in the denosumab treatment group, but was not uncommon in the denosumab group either. The pharmacokinetic study 20040245 in patients with renal impairment indicated that renal impairment does not impact the pharmacokinetics of denosumab. It should however be noted that patients with a calculated baseline GFR below 30 mL/min were excluded from the phase 3 studies. The experience of denosumab treatment in patients with GFR below 30 mL/min is therefore limited, which is reflected in section 4.2 of the product information.

Osteonecrosis of the jaw, ONJ: The denosumab pivotal studies excluded from participation patients with history or current evidence of ONJ, active dental or jaw condition which required oral surgery, nonhealed dental/oral surgery or planned invasive dental procedure for the course of the study. Still after exclusion of patients with all these known ONJ risk factors from study participation, the ONJ incidence for the denosumab patients in these three pivotal studies was high, higher than for the comparator. The highest incidence of ONJ in a denosumab treatment arms was 2.3 % in study 2005103 (comparator 1.3 %). In the pooled data set from all 3 studies, ONJ incidence for denosumab was 1.8 % and for the comparator zoledronic acid 1.3 %. However, the frequencies of severe ONJ (CTCAE grade ≥ 3) were the same for denosumab and zoledronic acid. In the patients who developed ONJ there was no discernible impact on pain (as measured by pain scores) or quality-of-life. Furthermore, the condition resolved in 40% of denosumab-treated patients (30% for zoledronic acid).

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

2.6.2. Conclusions on the clinical safety

The safety database for XGEVA (denosumab) is appropriate. The incidence of adverse events was similar between treatment groups and the adverse events and serious adverse events did not significantly differ between groups analysed in subgroup analyses. Osteonecrosis of the jaw was the most common adverse event that led to study withdrawal, followed by hypocalcemia. Less renal impairment was reported for denosumab than for zoledronic acid. Pyrexia was more common in the zoledronic acid treatment group, hypocalcemia (mostly non serious) and osteonecrosis was more common in the denosumab treatment group. In particular, the incidence of osteonecrosis of the jaw (ONJ) was higher in the denosumab group (1.8%) than in the zoldedronic acid group (1.3%) which is a matter of concern. However, the frequencies of severe ONJ (CTCAE grade ≥ 3) were the same for denosumab and zoledronic acid. In patients who developed ONJ there was no discernible impact on pain (as measured by pain scores) or quality-of-life. Furthermore, the condition resolved in 40% of denosumab-treated patients (30% for zoledronic acid). Preventive measures against ONJ are included in the Risk Management Plan for this product.

2.7. 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 applicant submitted a risk management plan (version 1.3), which included a risk minimisation plan.

Safety specification

The safety concerns specified by the applicant are now considered acceptable and include 3 identified risks; hypocalcemia, osteonecrosis of the jaw (ONJ) and skin infections leading to hospitalisation and 7 potential risks; infections, hypersensitivitity reactions, cardiovascular events, malignancy, osteonecrosis outside the jaw, immunogenicity and cataracts in men with prostate cancer receiving androgen deprivation therapy (ADT). Use in pregnant and lactating women, children, adult/pediatric off-label use, use in patients with renal/hepatic impairment, use in patients with multiple myeloma and use in patient with previous iv bisphosphonate treatment are addressed as missing information.

Table 39. Summary of the risk management plan

	Agreed Pharmacovigilance Activities	**Agreed Risk Minimization Activities**
Identified Risks		
Hypocalcaemia	Routine PV activities, including: • Cumulative reporting in periodic reports and assessment of events from ongoing clinical studies and spontaneous reports • Targeted follow-up of postmarketing reports using a focused questionnaire • Cumulative analysis of reports of hypocalcemia in PSURs Proactive surveillance: • Study to examine changes in serum calcium levels in patients with severe renal impairment or receiving dialysis administered a 120-mg dose of denosumab	4.3 Contraindications Severe, untreated hypocalcaemia 4.4 Special Warnings and Precautions for Use *Hypocalcaemia* Pre-existing hypocalcaemia must be corrected prior to initiating therapy with XGEVA. Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Monitoring of calcium levels in these patients is recommended. If hypocalcaemia occurs while receiving XGEVA, additional short-term calcium supplementation may be necessary. 4.8 Undesirable Effects *Tabulated List of Adverse Reactions* Hypocalcemia is listed under metabolism and nutrition disorders as common. *Description of Selected Adverse Reactions* Hypocalcaemia In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, hypocalcaemia was reported in 9.6% of patients treated with XGEVA and 5.0% of patients treated with zoledronic acid. A grade 3 decrease in serum calcium levels was experienced in 2.5% of patients treated with XGEVA and 1.2% of patients treated with zoledronic acid. A grade 4 decrease in serum calcium levels was experienced in 0.6% of patients treated with XGEVA and 0.2% of patients treated with zoledronic acid.

Hypocalcaemia (continued)		4.8 Undesirable Effects *Other Special Populations* In a clinical study of patients without advanced cancer with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis, there was a greater risk of developing hypocalcaemia in the absence of calcium supplementation.
ONJ	Routine PV activities, including: • Assessment of events reported from ongoing clinical studies and spontaneous reports • Targeted follow-up of postmarketing reports using a focused questionnaire • Cumulative analysis in PSURs of ONJ events reported through clinical study and postmarketing surveillance Proactive surveillance: • Ongoing medical reviews and expedited reporting to regulatory agencies of all reported cases of ONJ • Proposed EU- and North America-based case registry to monitor ONJ in the postmarketing setting • EU-based observational cohort study to evaluate the incidence of ONJ in the postmarketing setting • Ongoing adjudication in clinical studies • Survey to evaluate European-based treating physicians' knowledge of prescribing information related to ONJ	4.4 Special Warnings and Precautions for Use *Osteonecrosis of the Jaw* Osteonecrosis of the jaw (ONJ) was reported in patients treated with denosumab, predominantly in patients with advanced malignancies involving bone. Patients who developed ONJ in clinical studies generally had known risk factors for ONJ, including invasive dental procedures (eg, tooth extraction, dental implants, oral surgery), poor oral hygiene or other pre-existing dental disease, advanced malignancies, infections, or concomitant therapies (eg, chemotherapy, corticosteroids, angiogenesis inhibitors, radiotherapy to the head and neck). A dental examination with appropriate preventive dentistry should be considered prior to treatment with XGEVA in patients with active dental and jaw conditions (as listed above). While on treatment, patients should avoid invasive dental procedures if possible. Good oral hygiene practices should be maintained during treatment with XGEVA. Patients who are suspected of having or who develop ONJ while on XGEVA therapy should receive care by a dentist or oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

ONJ (continued)		An individual risk/benefit evaluation should be done for each patient before prescribing XGEVA in patients with unavoidable risk factors for ONJ; and in patients who have developed ONJ during treatment with XGEVA. 4.8 Undesirable Effects *Tabulated List of Adverse Reactions* Osteonecrosis of the jaw is listed under musculoskeletal and connective tissue disorders as common. *Description of Selected Adverse Reactions* Osteonecrosis of the Jaw (ONJ) In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, ONJ was confirmed in 1.8% of patients treated with XGEVA and 1.3% of patients treated with zoledronic acid. Clinical characteristics of these cases were similar between treatment groups. Among subjects with confirmed ONJ, most (81% in both treatment groups) had a history of tooth extraction, poor oral hygiene, and/or use of a dental appliance. In addition most subjects were receiving or had received chemotherapy. Patients with certain identified risk factors for ONJ were excluded from participation in the pivotal studies. 5.1 Pharmacodynamic Properties *Clinical Efficacy in Patients with Bone Metastases from Solid Tumors* Patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure, were not eligible for inclusion in these studies.

Skin Infections Leading to Hospitalization	Routine PV activities, including: • Assessment of events reported from ongoing clinical studies and spontaneous reports • Targeted follow-up of postmarketing reports using a focused questionnaire • Cumulative analysis in PSURs	4.4 Special Warnings and Precautions for Use *Skin Infections Leading to Hospitalisation (predominantly cellulitis)* In clinical trials in patients with advanced malignancies involving bone, skin infections leading to hospitalisation (predominantly cellulitis) were reported. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis. 4.8 Undesirable Effects *Tabulated List of Adverse Reactions* Cellulitis is listed under infections and infestations as uncommon. *Description of Selected Adverse Reactions* Skin infections (predominantly cellulitis) leading to hospitalisation In three phase 3 active-controlled clinical trials in patients with advanced malignancies involving bone, skin infections leading to hospitalisation (predominantly cellulitis) were reported more frequently in patients receiving XGEVA (0.9%) compared with zoledronic acid (0.7%). In postmenopausal women with osteoporosis, skin infections leading to hospitalisation were reported for 0.4% women receiving Prolia (denosumab 60 mg every 6 months) and for 0.1% women receiving placebo.

Potential Risks		
Infection	Routine PV activities, including: • Assessment of adverse events and serious adverse events of infection from ongoing clinical studies and spontaneous reports • Targeted follow-up of postmarketing reports using a focused questionnaire • Cumulative analysis of serious adverse events of infection in PSURs Proactive Surveillance: EU-based observational cohort study to evaluate infection leading to hospitalization in the postmarketing setting	None
Hypersensitivity Reactions	Routine PV activities, including: • Assessment of events reported from ongoing clinical studies and spontaneous reports • Cumulative analysis in PSURs Proactive surveillance: • Evaluation of adverse event profiles (including hypersensitivity adverse events) in subjects who test positive for antidenosumab antibodies in clinical studies	4.3 Contraindications Hypersensitivity to the active substance or any of the excipients. 4.8 Undesirable Effects *Tabulated List of Adverse Reactions* Drug hypersensitivity is listed under immune system disorders as uncommon.
Cardiovascular Events	Routine PV activities, including: • Assessment of events reported from ongoing clinical studies and spontaneous reports • Cumulative analysis in PSURs	None

Malignancy	Routine PV activities, including: • Assessment of events reported from ongoing clinical studies and spontaneous reports • Cumulative analysis in PSURs	None
Osteonecrosis outside the jaw (avascular necrosis)	Routine PV activities, including: • Assessment of events reported from ongoing clinical studies and spontaneous reports • Cumulative analysis in PSURs	None
Immunogenicity	Proactive surveillance: • Testing for antidenosumab antibodies in all ongoing clinical studies • Evaluation of adverse event profiles in subjects who test positive for antidenosumab antibodies in clinical studies • During the postmarketing period, testing for antidenosumab antibodies will be available for any patient on denosumab at the request of the treating physician	5.1 Pharmacodynamic Properties *Immunogenicity* In clinical studies, neutralising antibodies have not been observed for XGEVA. Using a sensitive immunoassay < 1% of patients treated with denosumab for up to 3 years tested positive for non neutralising binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.
Cataracts in Men With Prostate Cancer Undergoing ADT	Routine PV activities, including: • Assessment of events reported from ongoing clinical studies and spontaneous reports Proactive surveillance: • 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	None

Important Missing (or Limited) Information		
Pregnant Women	Routine PV activities and proactive surveillance, including: • 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 and will be asked to provide medical records of infants through 12 months of age.	4.6 Fertility, Pregnancy and Lactation *Pregnancy* There are no adequate data from the use of XGEVA in pregnant women. Animal studies are insufficient with respect to reproductive toxicity). In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL (the target of denosumab) could interfere with the development of lymph nodes in the foetus and could lead to postnatal impairment of dentition and bone growth. XGEVA is not recommended for use in pregnant women and women of childbearing potential not using contraception. 5.3 Preclinical Safety Data In preclinical studies knockout mice lacking RANK or RANKL had an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) and exhibited impairment of lymph node formation.
Lactating Women	Routine activities will include providing access for all applicable patients to a global Lactation Surveillance Program to follow children of participating mothers through up to 1 year of age.	4.6 Fertility, Pregnancy and Lactation *Breast-feeding* It is unknown whether denosumab is excreted in human milk. Knockout mouse studies suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum. A decision on whether to abstain from breast-feeding or to abstain from therapy with XGEVA should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of XGEVA therapy to the woman.

Children, Including Off-label Pediatric Use	Routine PV activities, including cumulative reports in PSURs Proactive surveillance: • Monitoring for off-label use in children through postmarketing surveillance • Study to collect data on pediatric off-label use • Clinical study activities as described in the PIP	4.2 Posology and Method of Administration *Pediatric Population* XGEVA is not recommended in paediatric patients (age < 18) as the safety and efficacy of XGEVA in these patients have not been established. Inhibition of RANK/RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption, and these changes were partially reversible upon cessation of RANKL inhibition. 5.3 Preclinical Safety Data In preclinical studies knockout mice lacking RANK or RANKL had an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) and exhibited impairment of lymph node formation. Neonatal RANK/RANKL knockout mice exhibited decreased body weight, reduced bone growth, altered growth plates and lack of tooth eruption. Reduced bone growth, altered growth plates and impaired tooth eruption were also seen in studies of neonatal rats administered RANKL inhibitors, and these changes were partially reversible when dosing of RANKL inhibitor was discontinued. Adolescent primates dosed with denosumab at 2.7 and 15 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.
Potential Adult Off-label Use	Routine PV activities, including cumulative reports in PSURs Proactive surveillance: • Monitoring for off-label use through postmarketing surveillance • Study to collect data on off-label use	4.1 Therapeutic Indications Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

Patients with Multiple Myeloma	Proactive surveillance: • A Phase 3b study to evaluate the safety and efficacy of denosumab compared with an active comparator in subjects with newly diagnosed multiple myeloma	5.1 Pharmacodynamic Properties *Disease Progression and Overall Survival* A post-hoc analysis in study 2 (patients with other solid tumours or multiple myeloma) examined overall survival for the 3 tumour types used for stratification (non-small cell lung cancer, multiple myeloma, and other). Overall survival was longer for XGEVA in non-small cell lung cancer (hazard ratio [95% CI] of 0.79 [0.65, 0.95]; n = 702) and longer for zoledronic acid in multiple myeloma (hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n = 180) and similar between XGEVA and zoledronic acid in other tumour types (hazard ratio [95% CI] of 1.08 (0.90, 1.30); n = 894).
Use in Patients with Renal Impairment	Proactive surveillance: • Study to examine safety in patients with severe renal impairment or receiving dialysis administered a 120-mg dose of denosumab	4.2 Posology and Method of Administration *Patients with Renal Impairment* No dose adjustment is required in patients with renal impairment. Experience in patients on dialysis or with severe renal impairment (creatinine clearance < 30 mL/min) is limited. 4.4 Special Warnings and Precautions for Use *Hypocalcemia* Pre-existing hypocalcaemia must be corrected prior to initiating therapy with XGEVA. Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Monitoring of calcium levels in these patients is recommended. If hypocalcaemia occurs while receiving XGEVA, additional short-term calcium supplementation may be necessary

Use in Patients with Renal Impairment (continued)		4.8 Undesirable Effects *Other Special Populations* In a clinical study of patients without advanced cancer with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis, there was a greater risk of developing hypocalcaemia in the absence of calcium supplementation. 5.2 Pharmacokinetics Properties *Special Populations* In a study of 55 patients without advanced cancer but with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab. There is no need for renal monitoring when receiving XGEVA.
Use in Patients with Hepatic Impairment	Routine PV activities, including evaluation in the PSUR of hepatic adverse events under the hepatobiliary system organ class	4.2 Posology and Method of *Patients with Hepatic Impairment* The safety and efficacy of denosumab have not been studied in patients with hepatic impairment. 5.2 Pharmacokinetic Properties Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids. *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.

Patients with Previous IV Treatment with Bisphosphonate	The incidence of ONJ will be examined in subjects previously exposed to bisphosphonates using data from the following sources: • Continued collection of safety information in the open-label extension phases of pivotal studies • Collection of information on prior bisphosphonate exposure in all ongoing clinical studies. • Collection of information on prior IV bisphosphonate use among denosumab-treated subjects in the planned ONJ registry program • Collection of information on the incidence of ONJ in the postmarketing setting in the observational cohort study in patients with advanced cancer • Request for information on prior or current bisphosphonate use in the ONJ questionnaire planned for postmarketing surveillance.	<u>4.5 Interaction with Other Medicinal Products and Other Forms of Interaction</u> In clinical trials, XGEVA has been administered in combination with standard anti-cancer treatment and in subjects previously receiving bisphosphonates. There were no clinically-relevant alterations in trough serum concentration and pharmacodynamics of denosumab (creatinine adjusted urinary N-telopeptide, uNTx/Cr) by concomitant chemotherapy and/or hormone therapy or by previous intravenous bisphosphonate exposure. <u>5.1 Pharmacodynamic Properties</u> *Clinical Efficacy in Patients with Bone Metastases from Solid Tumours* Efficacy and safety of 120 mg XGEVA SC every 4 weeks or 4 mg zoledronic acid (dose-adjusted for reduced renal function) IV every 4 weeks were compared in three randomised, double-blind, active-controlled studies, in IV-bisphosphonate naïve patients with advanced malignancies involving bone: adults with breast cancer (study 1), other solid tumours or multiple myeloma (study 2), and castrate-resistant prostate cancer (study 3).

<u>Pharmacovigilance activities</u>

The below pharmacovigilance activities, in addition to the routine pharmacovigilance, are needed to investigate further some of the safety concerns:

1) Study 20101102; ONJ patients identified from selected sentinel sites within EU and US will be followed for a total duration of 5 years. The natural history of positively-adjudicated ONJ in subjects with cancer will be described.

2) Clinical trials including the following studies;

   - A prospective, randomized, placebo-controlled trial is being conducted to further evaluate the incidence of cataracts in men receiving denosumab concurrently with ADT for prostate cancer (Study 20080560).
   - An open-label, multi-center, phase 2 study of denosumab in subjects with giant cell tumour of bone (Study 20062004) in which children aged 12-17 years will be investigated.
   - Clinical studies monitoring malignancy including 3 randomized, phase 3 clinical studies in cancer populations (ie, Studies 20050147, 20050209, 20060359) with predefined cancer-specific safety outcomes comparing effects of denosumab relative to placebo.
   - Study 20101361 to examine changes in serum calcium levels and safety in patients with severe renal impairment or receiving dialysis administered a 120 mg dose of denosumab.
   - A Phase 3b Study 20090482 will evaluate the safety and efficacy of denosumab compared with an active comparator in subjects with newly diagnosed multiple myeloma.

- Study 20101361 to examine safety in patients with severe renal impairment or receiving dialysis administered a 120 mg dose of denosumab.
- Continued collection of safety information in the open-label extension phases of Studies 20050136 and 20050103. From both studies, safety information will be available from 948 subjects, including 472 subjects who previously received treatment with zoledronic acid before receiving denosumab.

3) Pregnancy and lactation surveillance programs.

4) Study 20101335 collecting data on off-label use in Europe.

5) Observational cohort study using health registries in Norway, Sweden/Denmark (Study 20101363). In the observational cohort study approximately 1000 naïve XGEVA patients, approximately 1000 XGEVA patients with previous iv bisphosphonate treatment and approximately 2000 naïve Zometa patients will be included. A descriptive analysis of the incidence of ONJ and infections in the 3 treatment groups will be provided. The incidence of ONJ and infections leading to hospitalisation will be compared in these 3 groups. The patients will be followed for up to 5 years after treatment initiation. The study will include Denmark, Norway, and Sweden and the applicant will also consider including the PHARMO data system in the Netherlands. Annual reporting will start in 2013 and final results for the 1-, 2-, 3-, 4- and 5-year cumulative incidence analyses are anticipated to be available in Q1 2016, Q1 2017, Q1 2018, Q1 2019 and Q1 2020 (final report). The presented outline is accepted, and the final study protocol will be submitted for CHMP review as a post-approval commitment.

Risk minimisation activities

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.

In order to assess the effectiveness of the risk minimisation the applicant proposes to perform a survey to evaluate treating physicians' awareness and understanding of recommendations provided in the proposed denosumab prescribing information related to ONJ (Study 20110102), which is acceptable.

Proposals for Pharmacovigilance and Risk minimisation activities presented by the applicant are summarized in the table 39. For the wording of the specific SmPC sections mentioned in the table please refer to the XGEVA product information.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

In conclusion, the user test is considered acceptable.

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

In the integrated pivotal trial, based on 3 separate pivotal trials of advanced cancer metastasised to bone with approximately 5700 subjects, superiority of denosumab over zoledronic acid was shown. The hazard ratio (HR) of denosumab vs. zoledronic acid was 0.83 (95% CI 0.76; 0.90); p < 0.0001, for the primary endpoint, Time-to-first Skeletal Related Event (SRE), defined as one or more of the following local, irreversible events: pathologic fracture, radiation therapy of bone, bone surgery, or spinal cord compression. Internal consistency was shown by the similar results of the secondary endpoint Time-to-first *and subsequent* SRE, rate ratio 0.82 (95% CI: 0.75, 0.89); p < 0.0001. Median time to first SRE in the breast cancer study 20050136 was not reached for denosumab and was 26.4 months for zoledronic acid, was in prostate cancer study 2005103 = 20.7 months for denosumab and 17.1 months for zoledronic acid, while in study 2050244 it was 20.6 months for denosumab and 16.3 months for zoledronic acid. For each of the three included trials efficacy results very similar to the integrated analysis were observed. Thus, HRs for Time-to-first SRE were 0.82 (95% CI:71; 0.95) p= 0.01 in Study 20050136 in breast cancer patients; 0.82 (95% CI: 0.71; 0.95), p= 0.0085 in Study 20050103 in prostate cancer patients; and 0.84 (95% CI: 0.71; 0.98), p= 0.03 in Study 20050244 in patients with solid tumours excluding breast and prostate cancer, but including multiple myeloma and lymphoma. Superiority of denosumab was shown for the former in two trials and non-inferiority for the latter.

The median time to first on-study SRE was prolonged by 3 months or more in the denosumab treatment arm compared to the zoledronic treatment arm, in all 3 pivotal studies.

The effects seen were independent of subgroup in a number of subgroup analyses. The effects demonstrated in the pivotal studies for denosumab thus appear superior with regard to SREs as defined than those demonstrated up to now for any of the bisphosphonates for a similar indication. The individual components of the *Skeletal related events* primary efficacy parameter were further characterised, showing that the frequencies of each component were consistently in favour of denosumab vs. zoledronic acid. The differences between treatment arms with regard to frequency of the SRE component were thus 0.3 % for spinal cord compression, 0.3% for surgery to bone, 2,7% for fracture (p=0.009), and 4.0% for radiation of bone, (p<0.0001).

Overall survival appeared identical across treatment groups in all three studies, with the exception of the subgroup of patients with multiple myeloma in Study 20050244 that had a shorter overall survival than patients with solid tumours. Time to first overall disease progression and time to first disease progression in bone did not differ between treatment groups in any of the 3 pivotal studies, with the exception of the multiple myeloma group, see Risks below.

In all three studies, the % decrease in the bone turnover markers, uNTX/Cr and BSAP, were greater (p< 0.0001) following 3 months of denosumab treatment compared with ZOL. The decline in uNTX/Cr was more marked than the decline in BSAP, as a sign of potent bone turnover suppression.

Healthcare utilisation was lower in the denosumab group than in the zoledronic acid treatment group, probably because fewer patients in this group had skeletal-related events.

Denosumab is administered as a subcutaneous injection in a fixed dose. No intravenous line and no highly specialised health care personnel is therefore needed for administration of the drug, which is an advantage over the comparator.

The results of the pharmacokinetic Study 20040245 indicate that renal impairment does not impact the pharmacokinetics of denosumab and there is no need for dose adjustments in renally impaired patients. There is no reason to believe that hepatic impairment has any influence on the pharmacokinetics of denosumab as monoclonal antibodies are eliminated by catabolism and/or receptor-mediated processes and not by hepatic metabolic clearance.

The acute phase reactions (e. g. fever, muscle pain and bone pain, and arthralgia), frequently seen after administration of potent bisphosponates, at least at the initial administration, very rarely occurred after denosumab administration, constituting another advantage over the alternative treatment.

- Uncertainty in the knowledge about the beneficial effects.

Some tumour types were very rare in study 20050244 and firm conclusions can therefore not be drawn on the treatment effect for each of these individual tumour types.

Denosumab has not, in healthy volunteers or in patients with non-malignant disease and renal impairment, demonstrated any nephrotoxicity. Up to now, the drug has however not been administered to patients with severely impaired renal function *and* advanced malignancy, many of whom are undergoing simultaneous treatment with a number of nephrotoxic drugs.

The time to pain improvement (i.e. $\geq$ 2 point decrease from baseline in BPI-SF worst pain score) was similar for denosumab and zoledronic acid in each study and the integrated analyses. In a post-hoc analysis of the combined dataset, the median time to worsening pain (> 4-point worst pain score) in patients with mild or no pain at baseline was delayed for denosumab compared to zoledronic acid (198 versus 143 days) ($p = 0.0002$). Analgesic use did not significantly differ between treatment groups in any of the three studies.

Risks

- Unfavourable effects

In Study 20050244, a shorter overall survival was seen in the sub-group of patients with multiple myeloma and disease progression seemed to be enhanced in this small subgroup of patients, consistent with the worse outcome in this subgroup. Differences in baseline disease characteristics, the proportion of patients going on to receive stem-cell transplantation as well as statistical factors due to the small sample size may have affected this result to an uncertain degree. The gravity of the results will however preclude a positive B/R balance for this subgroup. Following the CHMP assessment, the applicant agreed to exclude multiple myeloma patients from the indication.

Osteonecrosis of the jaw (ONJ) is a condition previously associated with bisphosphonate treatment, with increasing frequencies reported for the newer, more potent, generations of bisphosphonates compared with first generation of this drug class. This has led to increasing concern regarding this adverse reaction, which may be very painful and debilitating in severe cases. Zoledronic acid, the comparator in all three pivotal studies, is to date the most potent approved bisphosphonate. Known risk factors for the development of ONJ are malignant disease, poor oral hygiene, history of tooth extraction, use of a dental appliance, use of antiangiogenic drugs, chemotherapy, and previous bisphosphonate therapy. The denosumab pivotal studies excluded from participation patients with a history or current evidence of ONJ, active dental or jaw condition which required oral surgery, nonhealed dental/oral surgery or planned invasive dental procedure for the course of the study. Subject incidence of ONJ in the denosumab treatment arms were 2.0 % in Study 20050136 (comparator 1.4 %), 1.1 % in Study 20050244 (comparator 1.3 %), and 2.3 % in Study 2005103 (comparator 1.3 %). In the pooled data set from all three studies, ONJ incidence for denosumab was

1.8 % and for the comparator zoledronic acid 1.3%. This overall frequency of ONJ is comparable with frequencies seen in other studies of bisphosphonates in this category of patients, where frequencies typically range between 0.5 and 4%, with a 2% average. Considerably higher frequencies have also been repeatedly reported, however results might not be entirely directly translatable - due to differences in ONJ definitions used, patient populations, and preventive measures. Upon further characterisation of the ONJ cases it has been shown that ONJ in many of the cases related to denosumab is not a severely debilitating or permanent condition: In the denosumab arm, 75% of cases were mild or moderate, where mild = asymptomatic (CTCAE grade 1). The absolute frequencies of severe ONJ (CTCAE grade ≥ 3) were the same for denosumab and zoledronic acid (0.4%). In patients who developed ONJ there was no discernible impact on pain (as measured by pain scores before and after ONJ event) or quality-of-life. Furthermore, the condition resolved in 40% of denosumab-treated patients (30% for zoledronic acid). Since the antiresorptive effect of denosumab is more rapidly reversible, this could theoretically offer an advantage compared with zoledronic acid in cases of ONJ.

Hypocalcemia was more commonly seen after denosumab treatment than after treatment with zoledronic acid. The hypocalcemia was however still not very common and was mostly mild and resolved spontaneously or after oral calcium medication and very rarely required IV calcium therapy.

Adverse events of hypocalcemia and dyspnea were more common in the denosumab group than in the zoledronic acid group in the pivotal studies but overall, the incidence of adverse events was similar between treatment groups.

The only cardiovascular adverse event that differed in incidence between treatment groups in the pivotal studies was the adverse event of pericardial effusion, and in study 20050244 denosumab treated patients had more fatal cardiac adverse event than zoledronic acid treated patients. These differences can however be accounted for by a difference in disease progression between treatment arms.

- Uncertainty in the knowledge about the unfavourable effects.

There is no clear indication of increasing incidence of ONJ with increasing duration of denosumab treatment. The risk factors identified for ONJ associated with denosumab therapy, such as poor oral hygiene, use of dental appliance, and tooth extraction are well known also for bisphosphonates. However, the question as to whether the total dose is considered an important additional risk factor for ONJ remains. Therefore the applicant is recommended to gain additional information on dosing and its relationship with the frequency of ONJ post-approval, and to consider a further dose-response study in this regard.

Pharmacovigilance activities proposed by the applicant in the Risk Management Plan are endorsed. The outlines of the proposed Observational Cohort Study on ONJ are considered acceptable. The applicant will provide a detailed protocol for review by the CHMP as a post-approval commitment.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects.

There is a need for new effective treatment of metastatic bone disease in advanced cancer, in particular in the category of patients with impaired renal function, as the currently best therapy, bisphosphonates, can be nephrotoxic and associated with cytokine release symptoms such as fever and influenza-like symptoms. The reduction of SREs demonstrated in the pivotal studies for denosumab are better than those demonstrated up to now for any of the bisphosphonates for a similar indication. A 17%-risk reduction in Time-to-first SRE and a prolonged median Time-to-first on-study

SRE of over 8 months experienced by denosumab treated patients compared to zoledronic acid treated patients in the integrated pivotal study is of clear clinical relevance and benefit to patients. It should be noted that the 4 components of the composite SRE endpoint are all of clinical importance in the management of cancer patients.

The decrease in overall survival and time to disease progression for denosumab vs. zoledronic acid treated patients seen in the subgroup of patients with multiple myeloma is a serious concern. Study baseline data and additional treatments during study were not balanced between study groups, and B/R therefore not assessable for this subgroup. Denosumab is therefore at present not considered approvable for this category of patients.

The adverse event osteonecrosis of the jaw in patients treated with denosumab is an important concern, although not of significantly of higher frequency than for the comparator. The applicant has however extensively discussed this finding and demonstrated that ONJ in many of the cases related to denosumab is not a severely debilitating or permanent condition, diminishing the importance of the condition in this category of terminally ill patients with advanced cancer with skeletal metastases. It is not known how the reversibility of ONJ relates to the severity of the condition in patients treated with denosumab.

- Benefit-risk balance

The overall benefit of denosumab in the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours in patients with advanced malignant disease involving bone has been convincingly demonstrated. The increased incidence of osteonecrosis of the jaw of 0.5% for densoumab compared with the comparator in the integrated pivotal study is considered to be outweighed by the superiority of denosumab to zoledronic acid to prevent skeletal related events in patients with advanced solid tumours and skeletal metastases.

The RMP provided is considered acceptable and all safety issues identified have been appropriately addressed in the product information. In addition, the CHMP requested a Scientific Advisory Group (SAG) to provide further clinical insights on the Benefit-Risk balance in patients with advanced malignancy and skeletal metastases, and to discuss ONJ in the malignant setting as compared to ONJ in the non-malignant setting, and further to discuss how post-approval denosumab studies in the malignant population should be best designed to identify and monitor risk factors for ONJ.

As per CHMP request, an oncology SAG meeting reinforced with additional experts on ONJ was convened on 3 May 2011 to provide advice on the list of questions adopted by the CHMP at its March 2011 meeting. The SAG provided the following answers to the questions raised by the Committee:

1. The SAG is asked to discuss the clinical relevance of the demonstrated effect, both in absolute terms and in relation to zoledronic acid.

The observed effect in terms of skeletal-related events (SRE) is considered clinically relevant. The minimum effect in terms of median time to first on-study SRE to be considered clinically relevant is judged to be about 3 months. This is in the range of the advantage observed in terms of this endpoint compared to zoledronic acid. Thus, concerning this endpoint, denosumab has shown a superior effect compared to zoledronic acid based on two of the three studies, i.e. in advanced breast with bone metastases and prostate cancer with bone metastases, but not in the study including a range of different tumor types with bone metastases (but not breast and prostate cancer) including myeloma. However, the absolute and relative overall efficacy for denosumab need to also take into account other important clinical endpoints, including long-term efficacy and safety outcomes. There are no data available to conclude on the overall efficacy and safety of denosumab beyond the median duration of follow-up of the pivotal studies, which was

about 2 years. Thus, it can be reasonably assumed that the overall efficacy is probably not inferior although data are missing to rule out any long-term detrimental effects or to establish a claim of superior overall efficacy (PFS, OS) compared to zoledronic acid.

The analysis of the efficacy data provided raised some methodological concerns as to how patients were handled in the analysis of the primary endpoint in case of competing risks (e.g. death, progression), which might introduce informative censoring. In addition, standard methods (Kaplan-Meier, logrank test, Cox model) do not take into consideration competing risks. Further analyses using classical competing risks methods (e.g. cumulative incidence curves, Gray test) and analyses of the corresponding composite endpoints, such as SRE and progression free survival (risks: SRE, progression and death) or SRE-free survival (risks: SRE and death; provided that SRE was foreseen to be assessed after progression as well), should be requested.

2. The significance of the observed ONJ in patients with advanced cancer and skeletal metastases should be discussed. The importance of ONJ should be discussed in relation to the response to Question 1.

In this patient population, the observed incidence, duration and severity of ONJ was not considered to be a major issue compared to many other more frequent, severe and long-lasting side-effects of concomitant treatments often only with palliative intent. Thus, compared to the clinically relevant effect observed in terms of SREs, the observed cases of ONJ were considered acceptable and comparable to what is expected from zoledronic acid, but longer follow-up is needed for more definitive conclusions.

However, it should be noted that no comprehensive safety (or efficacy) data are available beyond the duration of follow-up in the clinical trials (about 2 years median follow-up). Beyond the observation period, it is possible (or even likely in view of the potent mechanism of action) that new cases will be observed increasing the overall incidence.

Furthermore, there is a risk that unless adequate risk minimisation measures are in place, the preventive measures will be generally less stringent in clinical practice compared to the clinical trials.

3. How can post approval denosumab studies in this population best be designed to identify and monitor risk factors for ONJ (e. g treatment with angiogenesis inhibitors, corticosteroids, or earlier bisphosphonate therapy)?

Observational and registry studies (of adequate size and analysed using adequate statistical methodology including analysis of competing-risks) should be designed with the aim to identify additional intrinsic or extrinsic risk factors, including smoking and co-medications (e.g., TKIs), and allow optimising preventive measures. The studies should include long-term follow-up particularly in indications such as prostate or breast cancer where longer survival times can be expected. Registry studies including cases of ONJ should equally include life-long follow-up to study long-term management and outcome.

4. In the clinical studies, the event rate of ONJ was relatively low. Are there additional measures to undertake in order to help clinicians to adhere to the recommendations in the SmPC with respect to risk factors for ONJ? How can measure of effectiveness of risk minimisation proposed for ONJ post approval in this population best be designed?

Risk minimisation measures should aim to train physicians and patients about the recommended preventive measures to minimise the risk of ONJ. Measures to increase the awareness of dental practitioners about the risk factors for ONJ should be explored. Measures to increase awareness about current guidelines about ONJ management should be explored.

The CHMP considered the data submitted by the applicant and the argumentation put forward by the applicant and the SAG experts. The CHMP considered that the currently available data on quality, safety and efficacy are sufficient to conclude on a positive benefit-risk balance for XGEVA (denosumab).

2.8.1. Discussion on the benefit-risk balance

Following the assessment of all data on quality, safety and efficacy provided as part of the present MAA, the CHMP concluded that the benefit/risk balance for XGEVA (denosumab) is positive for the following indication:

"Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours."

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.

Further, the CHMP reviewed the data and justifications submitted by the applicant taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and taking into account the provisions of the "*Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)*", and considered that as the new therapeutic indication brings significant clinical benefit in comparison with existing therapies for this indication in terms of prolonged time to first skeletal event, less nephrotoxicity and a simpler mode of administration, the applicant´s request for the extension by 1 year of the marketing protection for denosumab is recommended for approval.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of XGEVA in the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours was favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP reviewed the data submitted by the Applicant taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considered by consensus the indication to be new for denosumab and that it would bring a significant clinical benefit in comparison with existing therapies for this indication.