13 October 2016
EMA/CHMP/52035/2017
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

XGEVA

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/002173/II/0045

Note

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

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List of abbreviations

Abbreviation or Term	Definition/Explanation
CTCAE	common terminology criteria for adverse events
CSC	corrected serum calcium
CSR	clinical study report
HCM	hypercalcemia of malignancy
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PTHrP	parathyroid hormone related protein
Q4W	every 4 weeks
RANKL	RANK ligand
SC	Subcutaneous
sCTX	serum C telopeptide
uCa/uCr	urinary calcium adjusted for urinary creatinine
uNTx/uCr	urinary N telopeptide adjusted for urinary creatinine

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 29 June 2016 an application for a variation.

The following variation was requested:

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

Extension of Indication to include treatment of hypercalcemia of malignancy refractory to intravenous bisphosphonate for XGEVA; as a consequence, sections 4.2, 4.3, 4.8, 5.1 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0125/2016 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

2. Scientific discussion

2.1. Introduction

Hypercalcemia of malignancy (HCM)

Hypercalcemia of malignancy (HCM) is a serious cancer complication that generally affects cancer patients towards the end stages of their disease. The most common types of HCM are skeletal or osteolytic hypercalcemia, which results from increased osteolytic bone resorption in areas surrounding malignant cells, and humoral hypercalcemia, which results from parathyroid hormone related protein (PTHrP) secretion by malignant cells.

Humoral HCM accounts for approximately 80% of HCM and occurs most often in patients with squamous-cell malignancies of the lung, head, and neck and in patients with renal cell carcinoma (Grill and Martin, 2000). Among patients with skeletal involvement, HCM occurs most frequently in patients with multiple myeloma (Berenson et al, 1996) and breast cancer (Mundy, 1999; Vassilopoulou-Sellin et al, 1993; Mundy et al, 1984). Among adult patients with cancer in the United Kingdom between 2003 and 2012, the annual prevalence of grade 1 or higher HCM ranged from 0.20% to 0.67%; grade 2 or higher from 0.07% to 0.26%; grade 3 or higher from 0.02% to 0.09%; and grade 4, 0.02 to 0.06%; and patients with lung cancer or multiple myeloma experienced the highest proportions of HCM (grade 1 or higher; approximately 2% in each) in 2012 (Jick et al, 2015).

As described above, the primary etiology of both skeletal and humoral HCM is increased bone resorption, which leads to elevated calcium concentrations in the extracellular fluid. The increase in bone resorption is initiated by the release of signaling molecules such as PTHrP, prostaglandins, and cytokine by malignant and stromal cells (Mundy, 1999; Roodman, 2001). These molecules stimulate osteoblasts and other stromal cells to express RANK ligand (RANKL), which upon binding its receptor RANK upregulates osteoclast recruitment and differentiation and thus bone resorption, with a resultant increase in calcium concentrations of the extracellular fluid and serum (Fuller et al, 1998; Lacey et al, 2000; Lacey et al, 1998).

The prognosis for patients with HCM is generally poor. Approximately 50% of patients with a diagnosis of HCM die within 30 days (Ralston et al, 1990). Therefore, treatment of HCM often concentrates on palliative treatment of symptoms. These may include fatigue, muscle weakness, mental impairment, renal failure, nausea, vomiting, dehydration, depression, anxiety, cardiac arrhythmias, and coma (Clines, 2011). These symptoms and consequences of HCM are related to both the calcium level and the rate of rise of calcium (Grill and Martin, 2000).

Initial treatment of HCM is generally administration of intravenous (IV) 0.9% saline (Heller and Hosking, 1986; Hasling et al, 1986; Stewart, 2005), followed by forced calciuresis with a loop diuretic in order to correct volume depletion due to hypercalcemia-induced urinary salt wasting and to lower serum calcium by inhibiting renal reabsorption of calcium. Intravenous bisphosphonates inhibit bone resorption and are the first-line treatment for HCM nonresponsive to hydration and diuresis. Treatment with bisphosphonates can be repeated. Other agents that have been approved for the treatment of HCM in some regions of EU are gallium nitrate [Ga(NO3)3] and calcitonin.

Rapporteurs comment: The Applicant states primary etiology of both skeletal and humoral HCM is increased bone resorption. Both bisphosphonates and denosumab are potent inhibitors of bone resorption. The Applicant should elaborate the rationale and present available data on why denosumab would be expected to be effective especially in patients who are refractory to intravenous bisphosphonate.

Denosumab

Denosumab is a fully human monoclonal IgG2 antibody to RANKL that binds with high affinity (dissociation equilibrium constant [Kd] 3 x 10-12 M) and specificity to the soluble and transmembrane forms of human RANKL (Kostenuik et al, 2009). This binding of denosumab to RANKL prevents RANK activation and inhibits the formation, activation, and survival of osteoclasts (Kostenuik et al, 2009). Denosumab is approved under the proprietary name XGEVA (120 mg administered subcutaneously [SC] every 4 weeks [Q4W]) for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors and for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone (GCTB). Denosumab administered 60 mg SC every 6 months (Q6M) is approved for indications related to bone loss under the proprietary name of Prolia. Hypocalcaemia is a common identified risk of denosumab in the approved indications.

Current Application

There are no regulatory guidelines for evaluation of therapies in the proposed indication.

The submission includes data from an open-label, single-arm, phase 2 clinical study, Study 20070315 (N=33). Study 20070315 enrolled adult subjects with HCM that did not respond to recent IV bisphosphonate therapy. In addition, the application provides pooled safety data from the 3 registrational SRE studies.

The risk management plan (RMP) has also been updated. No additional risk minimization activities have been proposed. There are several changes to the SmPC and package leaflet. All are either consequential to the analysis of the pivotal study or are corrections of typographical errors in previous versions of the SmPC.

Rapporteurs comment: The Applicant had originally planned to perform a phase 3 clinical study in order to support a full indication: Treatment of hypercalcemia of malignancy (HCM). The Applicant is asked to clarify in they are planning to perform this study. If not, the Applicant should clarify if the decision was due to any efficacy/safety issues. **(OC)**

2.2. Non-clinical aspects

No new non-clinical data or summary documents were included in the submission. According to the Applicant, no safety concerns were identified that would necessitate further non-clinical evaluation to support the use of denosumab in hypercalcaemia of malignancy patients.

Rapporteur's comment: The proposed posology for the new indication is similar to that for the approved indication 'Giant cell tumour of bone'. In previously conducted repeat-dose toxicity studies in monkeys (the only pharmacologically relevant species), subcutaneous doses up to 10 mg/kg/week and 50 mg/kg/month, given up to 12 months, did not result in any significant toxicity. The exposure in terms of AUC was considerably above the exposure at a clinical therapeutic dose of 120 mg. However, the development of neutralizing anti-drug antibodies that affected the exposure in some animals was a confounding factor. Further non-clinical repeat-dose toxicity studies to support the presently sought indication are not likely to add any value and are thus not considered necessary.

The Applicant has proposed the following addition to section 5.3 of the SmPC:

The role of osteoclast-mediated hypercalcaemia was evaluated in 2 murine models of humoral hypercalcaemia of malignancy through the use of osteoprotegerin (OPG), an endogenous decoy receptor that binds and neutralises RANKL. In one model, mice were inoculated with syngeneic colon

adenocarcinoma cells, and in the other mice were injected with high-dose parathyroid hormone-related protein (PTHrP) (0.5 mg/kg, SC, twice per day). In both models, a single injection of OPG caused more rapid reversal of established hypercalcaemia and longer lasting suppression of hypercalcaemia than high-dose bisphosphonates.

Rapporteur's comment: It is not clear if the proposed text refers to studies submitted in the original MAA, or if these are new studies. The Applicant is asked to clarify. If these studies have not been previously submitted, they should be submitted for assessment (**OC)**.

2.2.1. Pharmacology

No new pharmacokinetic or pharmacodynamic data was included in the submission. The proposed dosing regimen for denosumab in treatment of HCM are intended to facilitate a rapid attainment of steady-state concentrations of denosumab, while remaining within the range of exposures tested in phase 2 and 3 clinical studies. This same dosing regimen, with the additional 120-mg doses on days 8 and 15 of treatment, is the same as that approved for the treatment of GCTB.

2.2.2. Ecotoxicity / environmental risk assessment

The Applicant's justification for not providing an updated environmental risk assessment (ERA) is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

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.

2.3.2. Pharmacokinetics and pharmacodynamics

No new pharmacokinetic or pharmacodynamic data was included in the submission. The proposed dosing regimen for denosumab in treatment of HCM are intended to facilitate a rapid attainment of steady-state concentrations of denosumab, while remaining within the range of exposures tested in phase 2 and 3 clinical studies. This same dosing regimen, with the additional 120-mg doses on days 8 and 15 of treatment, is the same as that approved for the treatment of GCTB.

Rapporteur's comment:

The clinical pharmacology information refers solely to data submitted in previous indications. The Applicant considers it appropriate to target the same steady-state serum denosumab concentrations in HCM patients as in patients with bone metastases from solid tumors, and to facilitate a rapid attainment of steady-state concentrations with the additional doses on days 8 and 15 of treatment, as used in the treatment of GCTB. The goal is to achieve maximal binding and inhibition of RANKL over the entire dosing

interval. It would have been informative to compare denosumab concentrations in previous patient populations with the HCM patient population to verify the targeted denosumab exposure levels in the new patient population. The Applicant is asked justify the lack of pharmacokinetic and pharmacodynamic data in HCM patients and to further discuss the hypothesized PK/PD relationship in HCM patients in comparison to the previously studied patient populations (OC).

2.4. Clinical efficacy

2.4.1. Main study

Study 20070315

Methods

Study 20070315 was a single-arm, multicenter, proof-of-concept study to evaluate the treatment effect of denosumab in the treatment of HCM in subjects with cancer and a CSC > 12.5 mg/dL (3.1 mmol/L) despite IV bisphosphonates administered ≥ 7 days and ≤ 30 days prior to the screening CSC.

Study participants

This definition of HCM included the following subsets:

• Refractory HCM – Previous IV bisphosphonate treatment did not lower CSC to ≤ 11.5 mg/dL (2.9 mmol/L)

• Relapse HCM – **All subjects that did not meet the definition of refractory**

Eligible subjects received denosumab at a dose of 120 mg SC Q4W with a loading dose of 120 mg SC on study days 8 and 15. If CSC > 12.5 mg/dL (3.1 mmol/L) after 4 doses of denosumab or by study day 57, then denosumab was to be discontinued. In other cases, denosumab treatment continued.

The study was planned to enroll a total of 33 subjects assuming a 10% dropout rate.

Main Inclusion Criteria

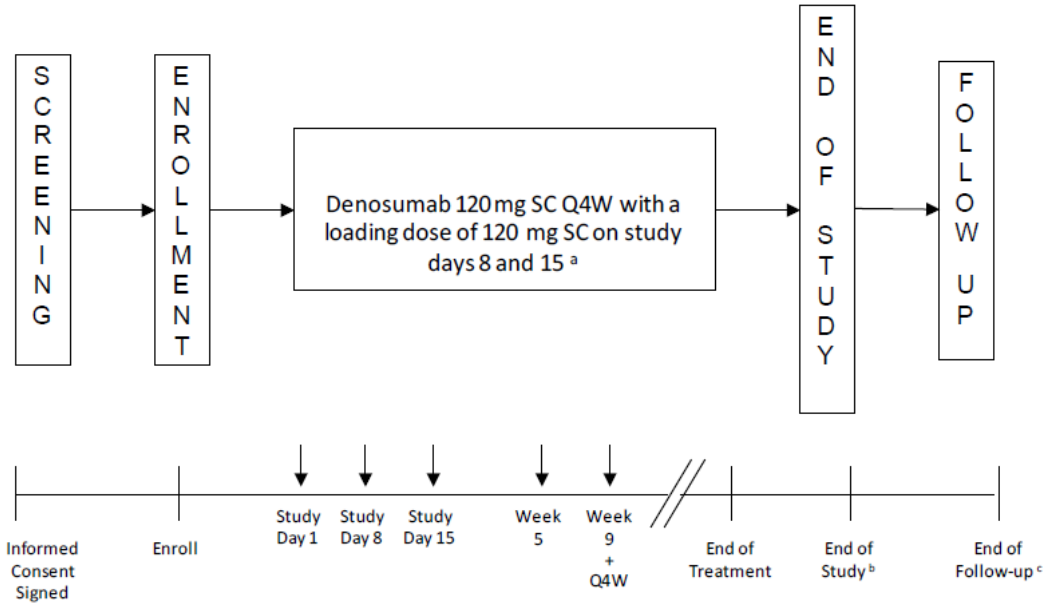
- hypercalcemia of malignancy as defined as documented histologically or
- cytologically confirmed cancer and a CSC > 12.5 mg/dL (3.1 mmol/L) at screening by local laboratory
- last IV bisphosphonate treatment ≥ 7 days and ≤30 days before the screening CSC
- age >18 years
- adequate organ function as defined by the following criteria:
- serum aspartate aminotransferase (AST) ≤ 5 x upper limit of normal (ULN)
- serum alanine aminotransferase (ALT) ≤ 5 x ULN
- serum total bilirubin ≤ 2 x ULN

Main Exclusion Criteria

- evidence of benign hyperparathyroidism, hyperthyroidism, adrenal insufficiency, vitamin D intoxication, milk alkali syndrome, sarcoidosis, or other granulomatous disease
- receiving dialysis for renal failure
- treatment with thiazides, calcitonin, mithramycin, or gallium nitrate within their window of expected therapeutic effect (as determined by the physician) prior to the date of the screening CSC

- treatment with cinacalcet within 4 weeks prior to the date of the screening CSC

Treatments



[a] Eligible subjects will receive denosumab at a dose of 120 mg subcutaneously (SC) every 4 weeks (Q4W with a loading dose of 120 mg SC on study days 8 and 15. If CSC > 12.5 mg/dL (3.1 mmol/L) after 4 doses of denosumab or by study day 57, then denosumab will be discontinued.
[b] The end of study will occur 4 weeks after the last dose of investigational product.
[c] Subjects will be followed for up to 12 months after the end of study.

Study visits during the treatment period occurred on study days 1, 2, 4, 8, 10, 15, 29, 23, 29, weekly up to study day 57, and every month until end of study. The end of study occurred 4 weeks after the last dose of denosumab. Following the end of study visit, subjects were followed for up to 6 months for serious adverse events and for up to 12 months for survival.

Rationale for Selection of Dosages in the Study

The dosing regimen used in Study 20070315 was 120 mg denosumab administered SCQ4W, with additional 120-mg doses on days 8 and 15 of treatment. The 120 mg Q4W dose is the same as that approved for denosumab for the prevention of SREs in patients with bone metastases from solid tumors. Amgen considers it appropriate to target the same steady-state serum denosumab concentrations in patients with HCM and in patients with bone metastases from solid tumors. In both patient populations, the goal is to achieve maximal binding and inhibition of RANKL over the entire dosing interval in a large majority (> 95%) of treated patients. For HCM, the dose and dose regimen are intended to facilitate a rapid attainment of steady-state concentrations of denosumab, while remaining within the range of exposures tested in phase 2 and 3 clinical studies. This same dosing regimen, with the additional 120-mg doses on days 8 and 15 of treatment, is the same as that approved in some regions for the treatment of giant cell tumor of bone (GCTB).

An important distinction from the advanced cancer patient population is that for patients with HCM, the treatment is intended to have a rapid effect on CSC, as opposed to an effect on the bone complications associated with metastatic disease. In the GCTB program, the additional doses on days 8 and 15 of treatment in Study 20040215 met this goal, resulting in median trough serum denosumab concentrations on days 15 and 29 that were comparable (< 16% to 35% difference, respectively) to those at steady state from weeks 9 to 49 of treatment. This is in contrast to patients with bone metastases from solid tumors, in whom steady-state denosumab levels are reached in approximately 4 to 6 months with 120

mg Q4W dosing. Amgen therefore considers the 120 mg Q4W dose regimen, with additional 120-mg doses on days 8 and 15 of treatment, to be the appropriate dosing regimen for patients with HCM.

Rapporteurs comment:

The rationale of choosing the proposed loading dose regimen needs further justification regarding the association of serum denosumab concentrations and serum Ca-concentrations.

Already single dose of 60 mg denosumab are known to be associated with hypocalcemia. The Applicant is asked to present any data with Ca-measurements supporting that current proposed dosing regimen 120 mg X 3 would be more beneficial in hypercalcemia during the first month of treatment compared to a single dose of 120 mg. **(OC)**

With the proposed loading dose regimen, an increase in dose dependent side-effects cannot be excluded compared to the common approved once-a-month regimen.

The Applicant states that denosumab has been evaluated across a wide variety of doses and administration schedules in clinical studies: In subjects with advanced cancer, SC doses of up to 180 mg Q4W have been evaluated. In bone loss studies, repeated SC doses of up to 210 mg have been studied. The applicant is asked to present data from these individual studies: with focus on comparisons of effect on the calcium levels and occurrence adverse events between placebo and different denosumab doses. **(OC)**

Standardization of Laboratory Procedures

A central laboratory, Covance Central Laboratories Services, Inc, was used to analyse the blood samples for baseline and on-study CSC. Blood samples for sCTx, PTHrP, and biomarker development and urine samples for uCa/uCr, uNTx/uCr, and biomarker development were also collected and analysed centrally at various times throughout the study. Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors.

Rapporteurs comment: Six subjects had missing central baseline S-Calcium values. The study subject numbers for these individuals could not be easily found in the documentation. The Applicant is asked to provide the subject numbers for these individuals and comment if using the local values might have had an impact on the main results **(OC)**.

Outcomes/endpoints

Primary Endpoint

Proportion of subjects with a response, defined as CSC ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after the first dose of denosumab

Secondary endpoints:

- Proportion of subjects with a response (ie, CSC ≤11.5 mg/dL [2.9 mmol/L]) by visit
- Proportion of subjects with a complete response (CR) (ie, CSC ≤10.8 mg/dL [2.7 mmol/L]) by visit
- Time to response
- Time to CR

• Duration of response defined as the number of days from the first day of CSC ≤ 11.5 mg/dL (2.9 mmol/L) to the last day of CSC ≤11.5 mg/dL (2.9 mmol/L)

• Duration of CR defined as the number of days from the first day of CSC ≤ 10.8 mg/dL (2.7 mmol/L) to the last day of CSC ≤10.8 mg/dL (2.7 mmol/L)

• Time to relapse/nonresponse of HCM

• Changes in CSC from baseline

Safety endpoints:

• Type, frequency, and severity of adverse events

• Changes in laboratory values

Exploratory Endpoints:

• Changes in CSC in relationship to uCa/uCr, PTHrP, sCTx, and uNTx/uCr

• Calcium toxicity grade shift from baseline

• Overall survival

These endpoints were determined based on precedent with the HCM studies that were the basis for approval of zoledronic acid: complete response was defined as improvement of CSC to ≤ 10.8 mg/dL (2.7 mmol/L) and relapse or end of response was defined as CSC ≥ 11.6 mg/dL (2.9 mmol/L; < 11.6 mg/dL is equivalent to ≤ 11.5 mg/dL). In addition, the zoledronic acid studies used the time point of study day 10 in the primary endpoint definition (Major et al, 2001).

Rapporteurs comment:

In zoledronic acid studies, the primary endpoint, CSC value by the day 10, was defined as improvement of CSC to ≤ 10.8 mg/dL (2.7 mmol/L).

The primary endpoint in the current study is less conservative: proportion of subjects with a response (defined as CSC ≤ 11.5 mg/dL [CTCAE grade 1 or lower]) within 10 days after the first dose of denosumab.

The secondary endpoint CSC limit, proportion of subjects with a complete response is comparable to zoledronic acid studies and may be considered more clinically relevant.

Endpoints that were not pre-defined in the protocol:

• Subject incidence for HCM symptom improvement from baseline up to study day 10 by visit

• Incidence and proportion of subjects whose baseline HCM symptom(s) resolved by study day 10

Sample size

The study was planned to enroll a total of 33 subjects assuming a 10% dropout rate. This sample size was chosen to provide assessment/estimation of proportion of subjects achieving normalizing CSC level (i.e., CSC ≤ 11.5 mg/dL [2.9 mmol/ L]) by study day 10 when treated with denosumab.

Based on approximately 30 evaluable subjects, 95% exact confidence intervals for selected observed response rates were estimated. If all subjects responded to the treatment then a true response rate of lower than 88% was unlikely.

Randomisation

N/A

Blinding (masking)

N/A

Statistical methods

The statistical analyses in this open-label study were descriptive in nature and no hypothesis testing was performed. Categorical data are presented by number and percentage. Continuous data are provided as descriptive statistics (n, mean, standard deviation [SD], median, 25th percentile, 75th percentile, minimum, and maximum). For the time-to-event variables, Kaplan-Meier (KM) point estimates and 95% CI of the 25th percentile, median, and 75th percentile are provided when possible.

The proportion of subjects who achieved a response, ie, CSC ≤ 11.5 mg/dL, by study day 10 was provided, along with 95% CI using an exact method.

One interim analysis was planned and took place when the first 10 subjects had received at least 2 doses of denosumab and completed day 10 assessments. The safety profile and primary and secondary efficacy endpoints were evaluated where appropriate. An overall assessment of efficacy based on the preliminary data was made and the study could be terminated if no response was observed. Otherwise, the study was not expected to stop early unless an important safety signal was detected.

The primary analysis was pre-specified and performed when all subjects had the opportunity to complete day 57 assessments. Safety data were collected throughout the study until end of study, 4 weeks after the last dose of denosumab. After the end-of-study visit, subjects were followed for up to 6 months for serious adverse events and up to 12 months for survival.

Rapporteurs comment:
Deciding on a sample size feasible to e.g. enroll within a reasonable time frame and calculate estimate precision based on a range of potential outcomes is acceptable in the planning stage of a proof-of-concept study. Also, given that Study 20070315 was an uncontrolled proof-of-concept study, descriptive analyses without formal hypotheses testing is acceptable.

Results

Participant flow

Reasons for Study Discontinuation (Full Analysis Set)

	Denosumab 120 mg Q4W n (%)
Enrolled	33
Discontinued study	33 (100.0)
Death	10 (30.3)
Adverse event	9 (27.3)
Disease progression	5 (15.2)
Other	4 (12.1)
Requirement for alternative therapy	3 (9.1)
Administrative decision	1 (3.0)
Consent withdrawn	1 (3.0)

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The primary analysis occurred when all subjects had the opportunity to complete 57 days of treatment. At that time, 31 (94%) of the subjects had terminated the study and the median (range) time on study was 1.8 (0 to 23) months.

Rapporteurs comment:
In total 31 subjects had discontinued by the primary analysis data cutoff date with19 subjects having discontinued the study at or before 57 days on study where of 4 subjects had ≤ 10 days on study.

Recruitment

Study Population

Study 20070315 enrolled subjects with cancer and a screening CSC concentration > 12.5 mg/dL (3.1 mmol/L; CTCAE grade 3) despite IV bisphosphonates administered ≥ 7 days and ≤ 30 days prior to the screening CSC.

Enrollment and Disposition

This was a multicentre study conducted at 12 study centres in the United States, France, Italy, and Poland. A total of 35 subjects were screened for participation and 33 subjects enrolled, all of whom received ≥ 1 dose of denosumab and were evaluated for efficacy. Of the 33 enrolled subjects, 23 (70%) were from the United States, 8 (24%) from France, and 1 (3%) subject each from Italy and Poland.

Conduct of the study

Study protocol amendments

The original protocol (dated 31 March 2009) was modified twice; Amendment 1 (14 May 2010), (2 subjects enrolled between the original date and the date of the first amendment) and Amendment 2 (05 May 2011) (10 subjects enrolled between this date and the date of the next amendment).

Amendment 1: The primary reason for this amendment was to delete the exclusion of a prior history or current evidence of ONJ, and related factors.

Amendment 2: modified the pre-study window for treatment with other therapeutic agents for hypercalcemia such that the determination for evaluating the expected potentially effective therapeutic window of these agents was at the discretion of the physician.

Rapporteurs comment: The amendment 2 possibly increased the possible confounding from other therapeutic agents for hypercalcemia to the study results.

Baseline data

Demographic and Baseline Characteristics

Most subjects were men (64%, 21 subjects) and most (70%) were white; median (range) age was 63 (22 to 89) years, with 14 subjects (42.4%) ≥ 65 years of age and 3 subjects (9.1%) ≥ 75 years of age. Mean (standard deviation [SD]) weight and body mass index were 65.4 (18.0) kg and 22.5 (5.2) kg/m2, respectively.

Twenty-six (79%) subjects had advanced solid tumors and 7 (21%) subjects had advanced hematologic malignancies. Metastatic disease was present in 30 subjects (91%) and metastatic bone disease in 13 subjects (39%) at baseline.

Twenty-five subjects (76%) had poor performance status (Eastern Cooperative Oncology Group ≥ 2) at baseline; 19 subjects (58%) reported symptoms related to HCM at baseline. Metastatic disease was present in 30 (91%) subjects and metastatic bone disease in 13 (39%) subjects at baseline. Three (9%) subjects had non-metastatic disease, 2 with myeloma and 1 with non-Hodgkin's lymphoma.

Twenty-four subjects (73%) were classified as having refractory HCM (previous IV bisphosphonate treatment did not lower CSC to ≤ 11.5 mg/dL), 7 subjects (21%) were classified as having relapsed HCM (previous IV bisphosphonate treatment did normalize CSC, but CSC was > 12.5 mg/dL despite IV bisphosphonates administered ≥ 7 days and ≤ 30 days before the screening CSC), and 2 subjects were not classified by the site, although they did meet inclusion criteria.

Calcium data were not obtained by Amgen from the time period before each subject was screened for the study. These data could not be retrospectively obtained because collection of these data was not covered by the original informed consent form. The only calcium laboratory values that were recorded in the CRF during the screening period (≤ 28 days before day 1 of the study) following informed consent and before study enrolment were those that were used by the investigator to determine subject eligibility. All study subjects had documented hypercalcemia and investigator-reported use of bisphosphonates before study entry.

At enrollment,

- median CSC was 13.7 mg/dL (range: 11.9 to 17.3 mg/dL),
- median PTHrP was 4.2 pmol/L (range: 0.5 to 24.0),
- median calculated creatinine clearance was 76.0 mL/min (range 13 to 311).

Calculated creatinine clearance level was 30 - < 60 mL/min in 10 subjects and < 15 mL/min in one subject.

Prior Bisphosphonate Use (Full Analysis Set) (20070315 Primary Analysis)

	Denosumab 120 mg Q4W (N=33)
Duration of prior bisphosphonate use (months)	
n	33
Mean	7.5
SD	8.8
Median	4.0
Q1, Q3	2.0, 11.0
Min, Max	1, 41
Number of prior IV bisphosphonate use	
n	33
Mean	8.5
SD	9.4
Median	5.0
Q1, Q3	3.0, 11.0
Min, Max	1, 42
Number of prior IV bisphosphonate use	
1 dose	5 (15.2)
2 - 5 doses	13 (39.4)
6 - 10 doses	5 (15.2)
11 - 15 doses	5 (15.2)
≥ 16 doses	5 (15.2)
Time from last IV bisphosphonate to enrollment (days)	
n	33
Mean	18.3
SD	6.7
Median	17.0
Q1, Q3	13.0, 22.0
Min, Max	8, 34

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N = Number of subjects enrolled

Nineteen subjects (58%) reported a total of 48 symptoms related to HCM at baseline. The most commonly (> 10%) reported symptoms were fatigue (9 subjects), anorexia (5 subjects), nausea (4 subjects), lethargy (4 subjects), and constipation (4 subjects).

Rapporteurs comment:

A total of 9 of 33 subjects in the study had not a refractory HCM to bisphosphonate treatment (proposed indication) or the type HCM was not defined. Six subjects had missing central baseline CSC values.

There was a significant variation in prior bisphosphonate treatment history among the study subjects. The MAH has no systematic data on calcium values before or after IV bisphosphonate treatment, except the screening values for the study. The MAH states that these data could not be retrospectively obtained.

The type of IV bisphosphonate treatment and the time point of CSC evaluation is of great importance in trying to define the target group “refractory HCM to IV to intravenous bisphosphonate. As an example, in the pivotal clinical studies with Zolendronic acid, the mean time for relapse after treatment was 30-40 days and 17 days for pamidronate. A large proportion of the patients who got a second treatment course due to relapse or because they were refractory, did have a treatment response.

Of note, the choice of effective therapeutic window for prior IV bisphosphonates administration/treatment was changed from the pre-specified 7 to 30 days to be up to the investigator in amendment 2. The potential carry over effect of previous recent bisphosphonate treatments should also be discussed **(OC)**.

In conclusion, the number of fully assessable individuals with documented refractory HCM in the study is considered low for an application of a new indication. The submission would be strengthened if MAH have had complementary data on the treatment of hypercalcaemia and calcium data for the last two-three months prior to enrolment in the study. Based both on the uncontrolled study design and the limited sample size there will be doubts regarding to what extent the outcome seen can serve as basis for generalisation to the intended patient population.

At the time of the primary analysis data cut-off date, 31 subjects (94%) were discontinued from treatment and the study, while 2 subjects (6%) continued the study. Results for the 2 subjects who were alive and continued the study after the primary analysis data cut-off date are reported in the final analysis CSR (Study 20070315FA; dated 01 April 2014). The additional safety and efficacy data for these 2 subjects do not alter the safety and efficacy conclusions from the primary analysis CSR (Study 20070315; dated 01 April 2013).

The most common reasons for discontinuation were disease progression (progression of HCM), death, and adverse events.

Numbers analysed

The full analysis set included all enrolled subjects.

The response analysis subset included all subjects who received at least 1 dose of denosumab and had a screening CSC (from local lab) > 12.5 mg/dL (3.1 mmol/L). This subset was used to analyze CSC response-related endpoints.

The efficacy analysis subset included all subjects who received at least 1 dose of denosumab. This subset was used for other efficacy analyses.

The safety analysis subset was the same as the efficacy analysis subset.

Rapporteurs comment:

No subjects were excluded from the response analysis subset.

Outcomes and estimation

Primary endpoint:

Proportion of subjects with a response, defined as (one measurement of) CSC ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after the first dose of denosumab:

- 21 of the 33 subjects had achieved a response as defined above (63.6%; 95% exact CI: 45.1%, 79.6%). The KM estimate for proportion of subjects with a response by day 10 was 59.0% (95% CI using bootstrap method: 41.5%, 74.5%).

Secondary endpoints:

• *Proportion of subjects with a response (ie, CSC ≤11.5 mg/dL [2.9 mmol/L]) by visit*

Overall, 23 subjects (69.7%) achieved a response and the median time to response was 9 days.

The proportion of subjects with a response increased cumulatively by visit up to day 19: 9%, 24%, 49%, 64%, 64%, and 70% by days 2, 4, 8, 10, 15, and 19, respectively. After day 19, the proportion of responders did not increase.

• *Duration of response defined as the number of days from the first day of CSC ≤ 11.5 mg/dL (2.9 mmol/L) to the last day of CSC ≤11.5 mg/dL (2.9 mmol/L)*

In subjects who achieved a response, the estimated median duration of first response was 104 days (95% CI: 9.0, not estimable) based on KM estimates.

The median duration of best response (defined as the maximum duration of any response) was 43 days (defined as the maximum duration of any response) was 43 days

Time to Response, Duration of Response and of Best Response

			KM Estimate (days)	
	N	**n**	**Median**	**95% CI** [a]
Time to response	33	23 [b]	9.0	5.0, 19.0
Duration of response	23	10 [c]	104.0	9.0, NE
Duration of best response	23	10 [c]	43.0	26.0, 192.0

[a] Confidence interval was calculated using bootstrap method
[b] Number of subjects who had a response
[c] Number of subjects whose CSC level reached > 11.5 mg/dL after the first response
Response was defined as on-study CSC ≤ 11.5 mg/dL.
CI = confidence interval; CSC = corrected serum calcium; KM = Kaplan-Meier; NE = not estimable

• *Proportion of subjects with a complete response (CR) (ie, CSC ≤10.8 mg/dL [2.7 mmol/L]) by visit*

Twelve subjects (36.4%) had a complete response by study day 10 (95% CI: 20.4%, 54.9%).

The KM estimate for proportion of subjects with a complete response by day 10 was 34.3% (95% CI using bootstrap method: 19.3%, 52.7%).

• *Duration of CR defined as the number of days from the first day of CSC ≤ 10.8 mg/dL (2.7 mmol/L) to the last day of CSC ≤10.8 mg/dL (2.7 mmol/L)*

Median time to complete response was 23 days.

The median duration of both first and best complete response was 34 days.

Time to Complete Response, Duration of Complete Response, and Duration of Best Complete Response:

			KM Estimate (days)	
	N	**n**	**Median**	**95% CI** [a]
Time to complete response	33	21 [b]	23.0	11.0, 43.0
Duration of complete response	21	14 [c]	34.0	1.0, 134.0
Duration of best complete response	21	14 [c]	34.0	1.0, 185.0

[a] Confidence interval was calculated using bootstrap method.
[b] Number of subjects who had a complete response
[c] Number of subjects whose CSC level reached >10.8 mg/dL after the first complete response
Complete response was defined as on-study CSC by albumin ≤ 10.8 mg/dL (2.7 mmol/L).
CI = confidence interval; CSC = corrected serum calcium; KM = Kaplan-Meier

• *Time to relapse/nonresponse of HCM*

The KM estimate for median time to relapse/nonresponse of HCM in all 33 subjects was 19 days (95% CI: 5, 114). The time to relapse in the 23 subjects with a response was a median of 114 days (95% CI: 19.0, not estimable) based on KM estimates.

Rapporteurs comment:

Given the uncontrolled design, the risk for confounding (concomitant treatments and the underlying disease) and the limited sample size it is not possible to draw any firm conclusions on efficacy based on Study 20070315. Analyses were descriptive in nature and were applicable Kaplan-Meier estimates has been provided. Inference based on KM estimates is however not considered very meaningful due to few numbers and a high level of censoring.

This study enrolled 33 subjects. Of those, 23 were classified as responders while on study whereof 21 within 10 days after the first dose. In this study subjects were considered to have a response once CSC was ≤ 11.5 mg/dL regardless of whether the CSC increased to a higher level on subsequent days. Among the 23 responders 10 had a documented relapse whereof 4 subjects ≤ day 10. The clinical importance of an early response to treatment regardless of whether the CSC increases to a higher level on subsequent days (here, even before day 10) has seemingly not been discussed. With regard to responders without a documented relapse (13/23) this may imply long response duration but may also be due to premature discontinuation.

In total, 10 subjects were non-responders where of 6 discontinued study treatment according to protocol due to progression of HCM/lack of response, i.e., CSC > 12.5 mg/dL after 4 doses of denosumab or by day 57.

In addition, the proportion of subjects with a complete response **by visit** is not clearly presented, the Applicant is asked to clarify **(OC)**. The median time to complete response was 23 days which is considered a considerable delay in a condition where approximately 50% of patients die within 30 days.

• *Changes in CSC from baseline*

Serum Calcium Corrected by Albumin by Visit during (the first 10 days) in Standard Units (Descriptive Statistics)

Calcium (Corrected) (mmol/L)	n	Mean	SD	Min	Q1	Median	Q3	Max
Baseline								
Denosumab 120 mg Q4W (N = 33)	33	3.47	0.32	3.0	3.30	3.42	3.55	4.3
Day 2								
Denosumab 120 mg Q4W (N = 33)	32	3.36	0.45	1.9	3.09	3.39	3.56	4.2
Day 4								
Denosumab 120 mg Q4W (N = 33)	32	3.13	0.38	2.4	2.89	3.08	3.29	4.1
Day 8								
Denosumab 120 mg Q4W (N = 33)	27	2.96	0.37	2.3	2.75	2.88	3.10	3.9
Day 10								
Denosumab 120 mg Q4W (N = 33)	28	2.96	0.41	2.4	2.69	2.89	3.15	4.0

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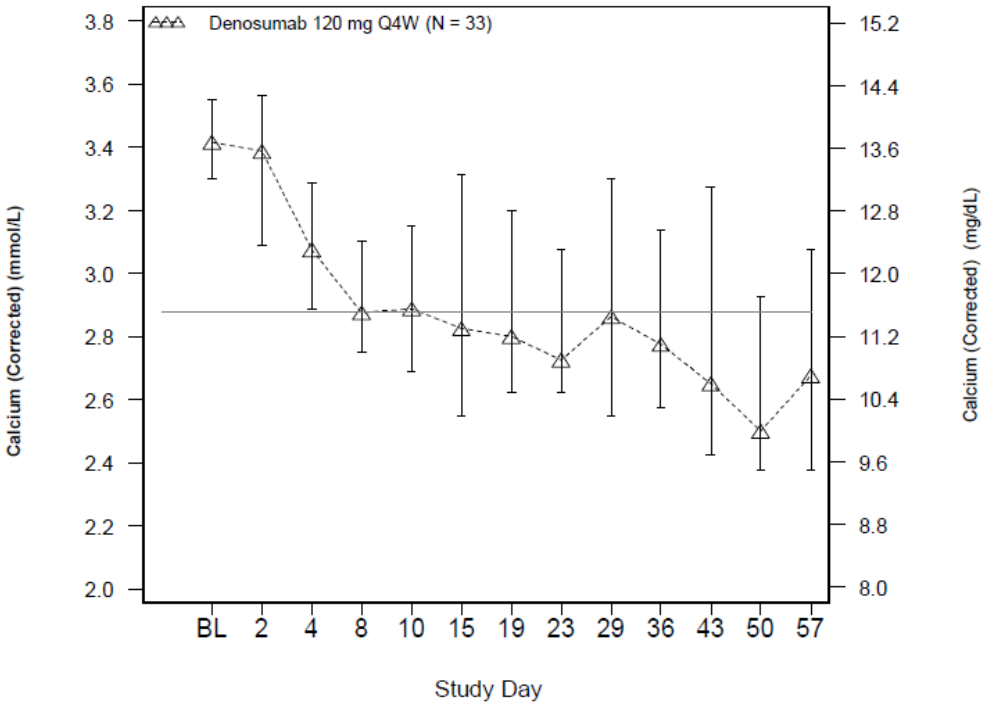
n = Number of subjects with observed data
N = Number of subjects enrolled and received ≥ 1 investigational product
The local baseline corrected serum calcium values were used for 6 subjects due to missing central baseline values.

Serum Calcium Corrected by Albumin by Visit Median and Interquartile Ranges (Efficacy Analysis Subset, Data to 57 Days)



Day	BL	2	4	8	10	15	19	23	29	36	43	50	57
n	**33**	**32**	**32**	**27**	**28**	**24**	**22**	**21**	**22**	**20**	**19**	**15**	**17**

N = number of subjects who received ≥ 1 dose of investigational product
n = number of subjects with observed data

Rapporteurs comment: The Applicant is asked to provide a similar figure with mean (SD) values by visit as for median values above **(OC).**

Subject Profile Plots

The Subject profile plots are discussed in the following comment.

Rapporteurs comment:

Overall, the efficacy analyses were descriptive in nature and no formal hypothesis testing was performed. The number of study subjects was limited and KM estimate analyses with wide confidence intervals might not be the most illustrative way of presenting the results.

The Applicant has submitted subject profile plots of all 33 subjects (Appendix 1, 2.7.3 – Summary of Clinical Efficacy, see two example plot above) and these have been reviewed by the Rapporteur. The findings are summarized below:

- 11/33 subjects had total lack of efficacy in visual examination of the CSC curves.

- 2/33 subjects relapsed back to the baseline CSC levels within 10 days from the last denosumab dose

- Of the remaining 20 subjects, 8 subjects received intravenous sodium chloride and/or furosemide during the first days of the study associated with a rapid decrease in CSC and 8 subjects had on-study systemic steroid use.

- Of the remaining 4 responder subjects, 2 had been previously treated with only one course of bisphosphonate. In addition, 2 subjects got only a single dose of denosumab in the study.

- One responder subject was identified without documented treatments with intravenous fluids, furosemide and systemic corticosteroids, and who had previously got multiple (4) treatment courses with zolendronic acid and who got multiple doses of denosumab in the study. This subject achieved CSC ≤10.8 mg/dL approximately at day 43 and remained in the study over one year.

Given the uncontrolled design and the apparent risk for confounding (e.g. concomitant treatments), the Rapporteur is of the opinion that it is very challenging to draw any firm conclusions on denosumab efficacy on CSC levels in the current study **(MO).**

Exploratory Endpoints:

• Changes in CSC in relationship to uCa/uCr, PTHrP, sCTx, and uNTx/uCr

uCa/uCr: Median uCa/uCr decreased from 0.28 at baseline to 0.075 at day 10 and remained at approximately that level through day 57.

This pattern of decrease starting at day 10 in uCa/uCr was similar to that seen for CSC, hence the relationship between uCa/uCr and CSC was positively correlated at day 10 (correlation coefficient = 0.4331, p =0.0390). When comparing median CSC in subjects with baseline uCa/uCr > 0.285 with those ≤ 0.285 (the median at baseline) by visit, there was no consistent pattern between subgroups.

PTHrP: Median PTHrP decreased only slightly from 4.2 pmol/L at baseline to 3.7 pmol/L at day 29, where it remained at approximately that level through day 57. There was little correlation between PTHrP and CSC. There was no consistent pattern of changes in CSC in relationship to baseline PTHrP in subjects with baseline PTHrP > 4 pmol/L compared with those ≤ 4 pmol/L (the median at baseline).

Changes in CSC in Relationship to sCTx

Median sCTx decreased from 1.215 ng/mL at baseline to 0.348 ng/mL at day 10, then further to 0.250 ng/mL at day 29, where it remained at approximately that level throughout the study). This pattern of decrease starting at day 10 in sCTx and remaining low was similar to that seen for CSC.

Changes in CSC in Relationship to uNTx/uCr

Median uNTx/uCr decreased from 76.9 nmol/mmol at baseline to 19.9 nmol/mmol at day 10, where it remained at approximately that level at day 29 and day 57.

When comparing median CSC in subjects with baseline uNTx/uCr > 76.9 nmol/mmol with those ≤ 76.9 nmol/mmol (the median at baseline) by visit, decreases from baseline in CSC were consistently higher in the > 76.9 subgroup compared with the >76.9 subgroup throughout the study.

• Calcium toxicity grade shift from baseline

In subjects whose CSC was above normal, the toxicity grade improved over time. For example, in evaluable subjects, the number and percentage of subjects with:

- grade 4 CSC decreased from 55% (18 of 33 subjects) at baseline to 14% (4 of 28 subjects) at day 10

- grade 3 CSC decreased from 36% (12 of 33 subjects) at baseline to 11% (3 of 28 subjects) at day 10

• Overall survival

At data cutoff, 5 (15.2%) of the 33 subjects were alive. At the time of analysis, the KM estimate of median overall survival was 71 days (95% CI: 41, 158).

Ancillary analyses

Post-Hoc Efficacy Analyses

Subgroup analyses:

The primary efficacy parameter was examined by various subgroups based on baseline characteristics. These results showed that the proportion of subjects with a response by day 10 was:

- 54% (7 of 13) in subjects with bone metastases at baseline and 70% (14 of 20) in those without bone metastases at baseline
- 83% (10 of 12) in subjects with baseline PRHrP ≤ 4 pmol/L (median) and 50% (6 of 12) in those with baseline PRHrP > 4 pmol/L
- 79% (15 of 19) in subjects who had symptomatic hypercalcemia at baseline and 43% (6 of 14) in those with no symptomatic hypercalcemia at baseline
- 63% (12 of 19) in subjects < 65 years and 64% (9 of 14) in subjects > 65 years.
- 61% (14 of 23) for Caucasian subjects and 70% (7 of 10) for non-Caucasian subjects.

HCM Symptom Improvement

Symptoms associated with hypercalcemia are commonly seen in cancer patients with normal serum calcium concentrations, especially those towards end-stages of the disease. These symptoms include nausea, vomiting, constipation, abdominal pain, fatigue, lethargy, and confusion, among others. Because these symptoms can occur with or without hypercalcemia, correlating HCM symptom improvement with improvements in serum calcium concentrations is confounded.

For this reason, pivotal studies of HCM have employed changes in serum calcium concentration as primary and secondary efficacy endpoints, and change in calcium concentration has served as the regulatory endpoint for bisphosphonates in HCM (Aredia, 2012; Zometa, 2012; Major 2001; Gucalp, 1992).

Nonetheless, as additional supporting data, changes in HCM symptoms were examined. Information on HCM symptoms was collected at baseline, days 4, 8, and 10 using a dedicated HCM symptom CRF; no information was collected after day 10.

A total of 48 HCM symptoms were reported in 19 subjects at baseline. The most commonly reported symptoms were fatigue (9 subjects), anorexia (5 subjects), nausea (4 subjects), lethargy (4 subjects), and constipation (4 subjects). Of the 19 subjects with ≥ 1 symptom, 10 subjects (53%) reported improvement or resolution and 8 (42%) reported resolution of at least 1 symptom by day 10. All symptoms improved or resolved in 6 (32%) subjects and all symptoms resolved in 4 (21%) subjects by day 10. On a symptom level, 15 (31%) of the 48 symptoms present at baseline resolved, 5 (10%) improved, 2 (4%) got worse, and the remainder (26 [54%]) remained stable.

Rapporteurs comment: Information on HCM symptoms was collected at baseline, days 4, 8, and 10 in the study. The Applicant has presented results at baseline for all study subjects but results by day 10 only for subjects with symptoms at baseline.

The Applicant is requested to report the number of symptoms by day 10 for all subjects. The Applicant is also asked to comment if the improvement of symptoms was related to Ca-response in the study **(OC).**

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

Advanced Cancer Studies – Skeletal-related Events Studies 20050136, 20050244, and 20050103

The original marketing approval for XGEVA was supported by results of the primary analysis of 3 identically designed pivotal phase 3 studies in subjects with advanced malignancies involving bone: Study 20050103 (prostate cancer), Study 20050136 (breast cancer), and Study 20050244 (other solid tumors or multiple myeloma). A total of 5723 subjects were enrolled and included in the integrated full analysis set (randomization to the primary analysis data cutoff); 2862 were randomized to receive denosumab and 2861 were randomized to receive zoledronic acid Demographic characteristics and baseline characteristics were balanced overall between the denosumab and zoledronic acid groups within each study and were typical for the advanced cancer patient population.

In addition, denosumab has been studied in a number of other conditions as summarized in the table below:

Number of Subjects Receiving Denosumab and Duration of Cumulative Exposure by Study Type in any Denosumab Clinical Study (All Subjects Population)

	Denosumab						
	≥ 1 Dose	≥ 6 Months	≥ 1 Year	≥ 2 Years	≥ 3 Years	≥ 4 Years	≥ 5 Years
Overall total exposure	15315	13396	11922	8374	6585	4651	4079
Phase 1 studies [a]	925	175	0	0	0	0	0
Postmenopausal osteoporosis studies	8088	7936	7688	6107	5344	4126	3814
Key phase 3 studies [b]	4050	3987	3867	3656	3331	0	0
Additional phase 2 and 3 studies [c]	4038	3949	3821	2451	2013	4126	3814
Phase 3 hormone ablation therapy studies	1045	1014	972	854	486	182	148
Key phase 3 studies [d]	860	830	798	711	483	0	0
Additional phase 3 study [e]	185	184	174	143	3	182	148
Phase 3 advanced cancer studies	4413	3481	2537	1084	494	160	5
Key phase 3 studies [f]	4030	3197	2339	1075	490	160	5
Additional phase 2 studies [g]	383	284	198	9	4	0	0

Other Indications							
Phase 3 male osteoporosis[h]	120	119	116	0	0	0	0
Giant cell tumor studies[i]	547	527	471	329	261	183	112
Hypercalcemia study[j]	33	5	3	0	0	0	0
Other studies[k]	144	139	135	0	0	0	0

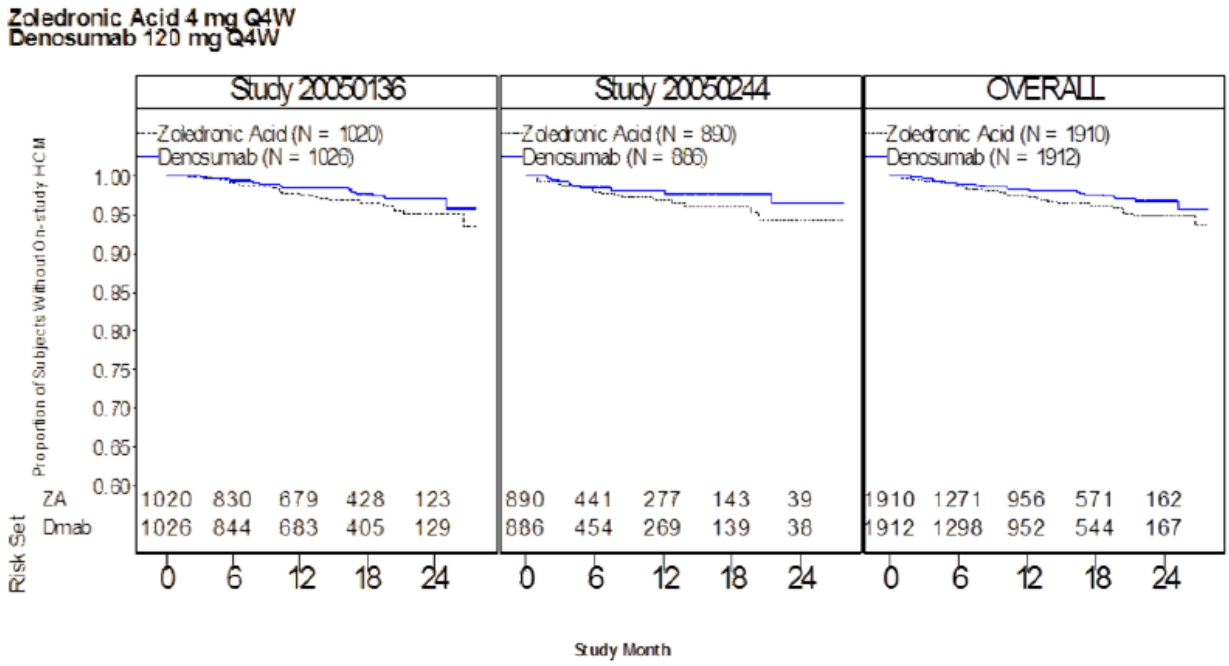
Comparison of Efficacy Results

There were three pivotal phase 3 SRE studies (20050103, 20050136, and 20050244); results from a retrospectively MAH conducted analysis of pooled data from 2 of these studies are summarized below. The retrospective analysis comparing denosumab with zoledronic acid in the prevention of HCM was performed by pooling data from Study 20050136 in subjects with breast cancer and Study 20050244 in subjects with advanced cancer from other solid tumors (excluding breast or prostate cancer) and bone metastases or multiple myeloma.

The results of this analysis demonstrated that denosumab was superior to zoledronic acid in delaying time to first on-study HCM (hazard ratio [HR] = 0.63; 95% CI: 0.41, 0.98; p = 0.042; (Diel et al, 2015).

Study 20050103, conducted in subjects with prostate cancer was not included in the analysis given that hypercalcemia is uncommon in patients with this tumor type.

Figure. Time to First Hypercalcemia of Malignancy Kaplan-Meier Curves (Studies 20050136 and 20050244)



N = Number of subjects randomized.

Program: /stat/amg162/meta/bla_2009onc/analysis/pub/graphs/program/g_20110901_timeto_hcm.sas
Output: g1-23_003_001_20110901_timeto_hcm_Zstdy.cgm (Date Generated: 02SEP2011:16:50:09)
Source Data: ad09css.asleff

Given the uncontrolled design, the risk for confounding and the limited sample size it is very challenging to draw any firm conclusions from the study 20070315. The efficacy of denosumab in the proposed indication needs hence to be supported by other studies/external data.

The MAH refers to three pivotal phase 3 studies on skeletal-related events (SRE) in subjects with advanced malignancies involving the bone; Study 20050103 (prostate cancer), Study 20050136 (breast cancer) and Study 20050244 (other solid tumors or multiple myeloma). In an explorative and retrospectively conducted analysis based on pooled data from two of these three pivotal studies (20050136 and 20050244) it was concluded that denosumab was superior to zoledronic acid in delaying time to first on-study HCM (hazard ratio 0.63, 95% CI: 0.41, 0.98; p=0.042). From the paper (Diel et al., 2015), it is clear that a total of 84 patients experienced at least one HCM event while on antiresorptive therapy, including 32/1910 subjects in the denosumab arm (1.7%) and 52/1912 subjects in the zoledronic acid arm (2.7%). The MAH is asked to present results of an analysis including cases of hypercalcemia including also cases also from prostate cancer study (if any).

The scope in this application is treatment of HCM (in patients that are refractory to bisphosphonates) and not primary prevention of HCM.

The MAH is therefore asked to submit, analyse and discuss all available data with regard to treatment and outcome of first and any subsequent on-study HCM for the subjects diagnosed with HCM in pivotal studies, including data on Ca-levels at diagnosis and at follow-up **(OC).**

Persistence of Efficacy and/or Tolerance Effects

The treatment of HCM is not an indication where long-term exposure is expected in this patient population. Hypercalcemia of malignancy is associated with a poor prognosis and correlates with an advanced cancer stage. The median survival after detection of hypercalcemia in a patient with cancer, despite strategies to lower serum calcium concentrations and treat hypercalcemic symptoms, is approximately 30 days (Ralston et al, 1990). In Study 20070315, the median time on study was 1.8 months (range: 0 to 23 months). Of the 33 subjects who received denosumab, 33 subjects were treated with denosumab for ≥ 1 month, 5 subjects for ≥ 6 months, and 3 subjects for ≥ 1 year.

Comparison of Safety Results

The safety of denosumab has been investigated previously in Osteoporosis (placebo controlled), Bone Loss due to Nonsteroidal Aromatase Inhibitor Therapy, Bone Loss due to Hormone-ablation Therapy, Advanced Malignancies Involving Bone (zolendronic acid as a comparator), Hormone-refractory (Castration-resistant) Prostate Cancer at High Risk of Bone Metastases (placebo-controlled), Multiple Myeloma, Giant Cell Tumor of the Bone, Rheumatoid Arthritis. The Applicant has referred to the respective marketing applications for the detailed safety data.

Rapporteurs comment: For the HCM indication, the duration of treatment is likely to be much shorter (one or two months) than it was for most of the approved indications (up to several years). Long-term effects are of limited interest in the current application.

MAH conclusions

The MAH concludes that denosumab effectively lowered corrected serum calcium in subjects with HCM who did not respond to recent treatment with IV bisphosphonates, and also improved HCM symptoms. The observed safety profile was consistent with that of an advanced cancer population and no new safety signals were identified for denosumab.

2.4.2. Discussion and conclusions on clinical efficacy

Design and conduct of clinical studies

MAH justification of the study design:

1. The sample size of 33 subjects reflects the rareness of HCM (approximately 15 cases per 100,000 people per year; Lumachi, et al, 2009; Lumachi et al, 2008); and the greater rareness of HCM that is refractory to bisphosphonate treatment (approximately 35% of subjects with HCM treated with 4 mg zoledronic acid [Major et al, 2001]). The definition of hypercalcemia required for enrollment (CSC > 12.5 mg/dL) was higher than the definition used for the bisphosphonate studies in HCM (12.0 mg/dL). The study design of Study 20070315 is considered appropriate and sufficient to evaluate efficacy in this patient population based on rarity of the condition, the significant unmet
   medical need in this setting, and because no standard therapy exists

2. The open-label, single-arm design is acceptable since no appropriate comparator exists: placebo was not considered due to ethical reasons; gallium nitrate must be infused over a 5-day period, is associated with significant renal toxicity, and is no longer commercially available; calcitonin has a very limited duration of action; and eligible subjects were refractory to bisphosphonates, which eliminated bisphosphonates from consideration as an appropriate control agent. A placebo control in this setting would be unethical.

3. CSC responses would be unlikely to occur in the absence of treatment.

In the absence of a control group, the study was not designed to assess the effect of denosumab on survival.

Rapporteurs comment:

This was a single-arm proof-of-concept study and designed as such. However, as a pivotal study for a new indication application, the study design has several weaknesses.

1.
Regarding the study size, the Rapporteur does not agree that the sample size is adequate for a new indication application **(OC)**. In comparison, the pivotal study for zoledronic acid for the HCM indication included 275 patients. Even if the incidence of HCM is relatively low, as MAH states, 2% of patients with lung cancer or multiple myeloma experience HCM which should make the recruitment of higher number of patients feasible.

The study was not designed to either confirm earlier findings (within the proposed indication) or for formal testing of a study hypothesis. The sample size was planned to be 33 taking into account a 10% drop-out rate and, hence that approximately 30 subjects were to be evaluable. For some support of the chosen sample size, 95% exact confidence intervals for selected observed response rates were estimated. No discussion with regard to expected outcomes and what would constitute a clinically relevant outcome has been found. In general, any study intended to support treatment efficacy needs to enroll a sufficient number of subjects in a sufficient number of centres in order to be able to provide firm evidence in support of any claims. With a limited sample size the size of any effects attributable to the treatment can rarely be estimated with due precision. From this follows concerns regarding how to relate these effects to their clinical significance. If the sample size is limited there will further be doubts regarding to what extent the outcome seen can serve as basis for generalisation to the intended patient population.

2.
The Rapporteur does not agree with the MAH that no appropriate comparator would exist in this case **(OC)**. A control group receiving a new course of specified potent IV bisphosphonate as or even "standard of care" (intravenous fluids, diuretics and corticosteroids) could have been approvable in a study in these terminally ill patients. Some of the included patients had been treated only once whereas others had up to 16 previous treatment courses with intravenous bisphosphonates.

As a secondary option, if complementary data on the treatment of hypercalcaemia and calcium data for the last two-three months prior to enrolment in the study had been available, the patients could have served as their own controls. Although a "baseline-controlled" design is regarded suboptimal, this could have strengthened the application. The Applicant has declared, however, that this data is not available.

Without a randomised control group there is a risk of selection bias. Further, without a concurrent control group it will not be possible to separate effects attributable to treatment from effects attributable to e.g. study situation, patient/baseline characteristics or natural disease progression. Also in settings with limited patient populations, comparative data obtained from a randomised study design is usually required for firm conclusions of a treatment effect. A randomised design is hence preferable even if underpowered and will (always) be considered a more scientifically valid alternative than a study without a concurrent control group.

3.
MAH states that CSC responses would be unlikely to occur in the absence of treatment. This needs to be further substantiated. The Rapporteur points out that the first line treatment of HCM is hydration and diuresis which can contribute to significant CSC response in the study. Several subjects in the study received both IV sodium chloride and furosemide at the study start. In addition, several study subjects (n=11) also received treatment courses of i.v corticosteroids during the study. It seems very difficult to distinguish the contribution of denosumab to the CSC response in the current study. The MAH should discuss the confounding effect of "standard of care" in these patients and the impact on study results. **(OC)**

The potential carry over effect of previous recent (minimum 8 days) bisphosphonate treatments should also be discussed **(OC)**. For example, approximately 6% of the patients responded between day 7 and 10 in pivotal bisphosphonate studies.

In addition, the observed difference between pre- and post-treatment measurements could, at least to some extent, be due to regression to the mean.

2.5. Clinical safety

Introduction

Study 20070315 provides limited data on long-term denosumab exposure (≥ 1 year), as only 3 subjects received denosumab for ≥ 1 year. A total of 5 subjects were alive at the time of primary analysis. Of these, 3 subjects were discontinued from the study before the primary analysis data cut-off date; however, per protocol, they were followed for up to 6 months for serious adverse events and for up to 12 months for survival after the end-of-study visits. MAH has presented narrative summaries for the 2 subjects who were alive and continued the study after the primary analysis data cut-off date 13 September 2012.

During the primary analysis, a total of 28 deaths were reported. Of the 5 subjects alive at the time of the primary analysis, 3 subjects died after the primary analysis data cut-off date: .

Rapporteurs comment:

The patient population with HCM and advanced cancer is likely to have a high variety of serious and fatal adverse events. In an uncontrolled study, it is virtually impossible to differentiate if adverse events such as nausea, dyspnea, peripheral edema and decreased appetite were related to the investigational product or caused by numerous concomitant treatments and symptoms of the underlying disease itself.

Therefore, the Rapporteur considers that extrapolation of safety data from other studies with other indications is the only possibility to make conclusions on safety regarding this new proposed indication **(OC)**.

Patient exposure

A total of 33 subjects received ≥ 1 dose of denosumab. Four subjects (12%) received only one single dose. As of the data cutoff for this report, the median exposure to denosumab was 4.0 doses, with the longest exposure being 25 doses. The median time on study was 1.8 months, with a range of 0 to 23 months.

Adverse events

Summary of Subject Incidence of Adverse Events

	Denosumab 120 mg Q4W (N=33) n (%)
Adverse events regardless of relationship	
All	32 (97.0)
Serious	30 (90.9)
Fatal	26 (78.8)
Leading to study discontinuation	9 (27.3)
Leading to investigational product discontinuation	11 (33.3)
CTCAE[a] Grade 3, 4, or 5	32 (97.0)
Adverse events related to investigational product [b]	
All	13 (39.4)
Serious	2 (6.1)
Fatal	1 (3.0)
Leading to study discontinuation	0 (0.0)
Leading to investigational product discontinuation	0 (0.0)
CTCAE[a] Grade 3, 4, or 5	7 (21.2)

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

Adverse Events by Preferred Term in Descending Order of Frequency (>5.0% Subject Incidence) (Safety Analysis Set) (20070315 Primary Analysis)

Preferred Term	Denosumab 120 mg Q4W (N=33) n (%)
Number of subjects reporting adverse events	32 (97.0)
Nausea	10 (30.3)
Dyspnoea	8 (24.2)
Headache	8 (24.2)
Oedema peripheral	8 (24.2)
Vomiting	8 (24.2)
Constipation	7 (21.2)
Decreased appetite	7 (21.2)
Diarrhoea	7 (21.2)
Anaemia	6 (18.2)
Cough	6 (18.2)
Fatigue	6 (18.2)
Fluid overload	5 (15.2)
Hypercalcaemia	5 (15.2)
Pyrexia	5 (15.2)
Arthralgia	4 (12.1)
Back pain	4 (12.1)
Confusional state	4 (12.1)
Hypophosphataemia	4 (12.1)
Hypotension	4 (12.1)
Pleural effusion	4 (12.1)
Pulmonary oedema	4 (12.1)
Weight decreased	4 (12.1)
Abdominal distension	3 (9.1)
Abdominal pain	3 (9.1)
Alopecia	3 (9.1)
Epistaxis	3 (9.1)
Haemoglobin decreased	3 (9.1)
Hypocalcaemia	3 (9.1)
Myalgia	3 (9.1)

Preferred Term	Denosumab 120 mg Q4W (N=33) n (%)
Pneumonia	3 (9.1)
Rash	3 (9.1)
Thrombocytopenia	3 (9.1)
Asthenia	2 (6.1)
Breast cancer	2 (6.1)
Dehydration	2 (6.1)
Depressed level of consciousness	2 (6.1)
Dizziness	2 (6.1)
Dry mouth	2 (6.1)
Dysphonia	2 (6.1)
Fall	2 (6.1)
Febrile neutropenia	2 (6.1)
Head and neck cancer	2 (6.1)
Hyperkalaemia	2 (6.1)
Hypokalaemia	2 (6.1)
Hyponatraemia	2 (6.1)
Insomnia	2 (6.1)
Lethargy	2 (6.1)
Lung neoplasm malignant	2 (6.1)
Multiple myeloma	2 (6.1)
Musculoskeletal pain	2 (6.1)
Neutropenia	2 (6.1)
Non-small cell lung cancer	2 (6.1)
Oropharyngeal pain	2 (6.1)
Pain in extremity	2 (6.1)
Palmar-plantar erythrodysaesthesia syndrome	2 (6.1)
Rash pruritic	2 (6.1)
Renal failure acute	2 (6.1)
Rhinorrhoea	2 (6.1)
Tachycardia	2 (6.1)
Urinary tract infection	2 (6.1)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 adverse event
Includes only treatment-emergent adverse events

Most subjects (32 of 33, 97%) experienced ≥ 1 adverse event during their participation in the study, with the most common events being categorized within the MedDRA SOCs of gastrointestinal disorders, general disorders and administration site conditions, and metabolism and nutrition disorders (each 61% of subjects)

By preferred term, the most frequently experienced adverse events were nausea (30%); and dyspnea, headache, peripheral edema, and vomiting, each of which occurred in 24% of subjects.

Thirteen of 33 subjects (39%) experienced ≥ 1 adverse event that was considered by the investigator to be related to denosumab; the most frequently reported (≥ 10%) treatment-related adverse events were hypophosphatemia (12%) and nausea (12%).

The subject incidence of adverse events with CTCAE grades 3, 4, or 5 was 97% (32 subjects). The most frequently reported (> 3 subjects) CTCAE grade 3, 4, or 5 adverse events were dyspnea (6 subjects, 18%), decreased appetite and fatigue (both occurring in 4 subjects, 12%), and confusional state, diarrhea, hypercalcemia, and hypophosphatemia (each occurring in 3 subjects, 9%). A total of 7 subjects (21%) had CTCAE grade 3, 4, or 5 adverse events that were considered by the investigator to have a causal relationship with denosumab. The most commonly reported treatment-related grade 3, 4, or 5 adverse event was hypophosphatemia (3 subjects, 9%). The others each occurred in 1 subject.

Adverse events of interest:

Hypocalcemia

Adverse event preferred terms corresponding to hypocalcemia were reported in 3 subjects (9%), and each of these 3 subjects had 2 occurrences. In each case the second occurrence was of a lower severity grade, decreasing from either CTCAE grade 2 to 1 or grade 3 to 1. The CTCAE laboratory criteria for grade 1 hypocalcemia is CSC ≤ 2.0 mmol/L (8 mg/dL) (Cancer Therapy Evaluation Program, 2006). Of the 3 subjects with hypocalcemia (total of 6 events), 1 subject (2 events) had CSC values ≤ 2.0 mmol/L (8 mg/dL). The other 2 subjects had CSC > 2.0 mmol/L, and therefore did not meet the criteria for any grade of hypocalcemia based on laboratory assessment.

None of these events were serious adverse events, and none of the 3 subjects had symptomatic hypocalcemia.

Two of the 3 subjects received calcium supplements for the event. No subjects discontinued denosumab treatment due to hypocalcemia.

Osteonecrosis of the Jaw

No events of ONJ (investigator reported or positively adjudicated) occurred in this study.

Musculoskeletal Pain

Adverse events of musculoskeletal pain were reported for 11 subjects (33%) in Study 20070315: arthralgia and back pain (4 subjects, 12% each); myalgia (3 subjects, 9%); musculoskeletal pain and pain in extremity (2 subjects, 6% each); and bone pain, coccydynia, flank pain, and neck pain (1 subject, 3% each).

Hypersensitivity

Adverse events potentially associated with hypersensitivity were reported in 6 subjects

(18%); of these events, all were CTCAE grade 1 or 2, none were serious, and none led to discontinuation of denosumab. Of the events potentially associated with hypersensitivity, rash and pruritic rash were the most frequently reported preferred terms, occurring in 3 and 2 subjects, respectively. Other events included dermatitis, dermatitis contact, iodine allergy, and swelling face in 1 subject each. Three of the 6 subjects had 4 adverse events potentially associated with hypersensitivity that were considered by the investigator to be related to denosumab: rash (2 cases) and pruritic rash (2 cases).

Eczema

Adverse events of eczema were reported by 2 subjects (6%): dermatitis and dermatitis contact (contact dermatitis from pleural catheter tape). Neither event was serious nor considered by the investigator to be related to denosumab treatment. One was CTCAE grade 1 and the other grade 2.

Infection including Skin Infection

Infection adverse events were reported for 11 subjects (33%), the most frequent events being pneumonia (3 [9%]) and urinary tract infection (2 [6%]). All other events were reported in 1 subject

each. Two subjects (6%) had events of infection that were serious adverse events, which included 1 event of urinary tract infection and 1 event of septic shock, neither of which was considered by the investigator to be related to denosumab treatment. The subject with septic shock died. In 6 subjects the infection was grade 3, in 1 (septic shock) it was grade 5, and in the remaining 4 subjects the events were grade 1 or 2. Except for 1 subject with septic shock, none of the subjects with infection adverse events discontinued treatment with denosumab due to the events. Five subjects had adverse events of infection that were considered by the investigator to be related to denosumab treatment.

Adverse events of skin infection were reported in 1 subject (3%); the preferred term for this event was cellulitis. It was not serious, not related to treatment, and did not result in discontinuation of denosumab.

Cardiovascular Events

The incidence of adverse events in the cardiac disorders SOC was 15% (5 subjects). The incidence of serious cardiac disorders was 9% (3 subjects) and included 2 subjects with tachycardia, both considered unrelated to denosumab by the investigator, and 1 subject with cardiac arrest for which causality to denosumab could not be ruled out; however, the investigator stated that the fatal event could have been related to progression of the subject's underlying malignancy. The incidence of adverse events in the vascular disorders SOC was 18% (6 subjects) and included 4 subjects with hypotension. Of these, 1 case of hypotension was serious and treatment related. None of the other events in the vascular disorders SOC was either serious or treatment related. No vascular events led to discontinuation of denosumab.

Serious adverse event / deaths / other significant events

Serious Adverse Events

Serious adverse events were reported for 29 subjects (88%). Serious adverse events occurred most frequently in the following SOCs: neoplasms (17 subjects, 52%), respiratory and thoracic disorders (9 subjects, 27%), and metabolic and nutritional disorders (8 subjects, 24%).

In all 17 subjects with neoplasms, the neoplasms were related to the underlying cancer. The most frequently reported serious adverse events by preferred term were worsening hypercalcemia (5 subjects, 15%) and dyspnea (3 subjects, 9%). All other serious adverse events were reported in 1 or 2 subjects. Two of the serious adverse events were considered related to denosumab treatment by the investigator: cardiac arrest and colitis).

Deaths

Twenty-four subjects (73%) experienced an adverse event with a fatal outcome. Of the subjects with fatal adverse events, the most common SOC was neoplasms in 16 (49%) of the 24 subjects. In all 16 subjects, these neoplasms were related to the underlying cancer. Of the 24 events with a fatal outcome, 1 event concerned a Subject (315102005) who had a fatal cardiac arrest at home (no autopsy available). The investigator stated that the fatal event could have been related to progression of underlying malignancy, but causality to denosumab could not be ruled out.

Laboratory findings

Calcium

Change from baseline in serum calcium was an efficacy parameter in this study. For subjects whose CSC was below the normal range (eg, hypocalcemia), based on laboratory values 2 subjects had decreases in CSC, both CTCAE grade 2. No subject experienced a grade 3 or 4 decrease in serum calcium.

Phosphorus

Denosumab administration was associated with decreases in serum phosphorus in Study 20070315. Serum phosphorus decreased from baseline by up to 12.3% up to day 10, then returned to baseline levels from days 19 to 29.

Clinical Chemistry and Hematology

Other than changes in serum calcium and phosphorus levels, no trends indicative of denosumab-related effects on laboratory parameters were evident. There were no clinically meaningful changes over time in the other laboratory parameters.

Vital Signs, Physical Findings, and Other Observations Related to Safety

No clinically relevant changes were observed in body weight or blood pressure in Study 20070315. Heart rate, respiratory rate, and body temperature were not recorded. Electrocardiogram (ECG) assessments were not conducted. Summaries of systolic and diastolic blood pressure over time showed no consistent pattern of increases or decreases from baseline to day 57.

Safety in special populations

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Ten subjects (30%) experienced adverse events that resulted in discontinuation of investigational product and 8 subjects had adverse events that resulted in withdrawal from the study. Six of these 8 patients' adverse events led to discontinuation from both investigational product and from the study; 2 subjects had an adverse event that led to discontinuation of denosumab, but did not result in study withdrawal.

None of the adverse events (different cancer, pulmonary oedema, hypoxia, vomiting, hepatic failure, septic schock and hypercalcaemia) leading to withdrawal from the study or to discontinuation of denosumab was experienced by > 1 subject and none was considered by the investigator to be related to denosumab.

2.5.1. Discussion and conclusions on clinical safety

In the current study, virtually all subjects had serious adverse events and most subjects had a fatal outcome. Two were considered related to the denosumab treatment by the investigator: cardiac arrest and colitis. The most frequently reported (> 3 subjects) adverse events were dyspnea (6 subjects, 18%), decreased appetite and fatigue (both occurring in 4 subjects, 12%), and confusional state, diarrhea, hypercalcemia, and hypophosphatemia (each occurring in 3 subjects, 9%).

In the Xgeva SmPC, very common adverse reactions include musculoskeletal pain, diarrhoea and dyspnoea. In the RMP, important identified risks for denosumab 120 mg per month in cancer patients include hypocalcemia, hypersensitivity reactions and musculoskeletal pain. Atypical femoral fracture and osteonecrosis of the jaw are likely less relevant risks in the current patient population with limited life expectancy and treatment duration.

The patient population with HCM and advanced cancer is likely to have a high variety of serious and fatal adverse events. In an uncontrolled study, it is virtually impossible to differentiate if adverse events such

as nausea, dyspnea, peripheral edema and decreased appetite were related to the investigational product or caused by concomitant treatments and symptoms of the underlying disease itself. The company should discuss the expected rates of these events if these subjects were treated with standard of care only or with another course of zolendronic acid, if possible.

Extrapolation of safety data from other studies with other indications may be the only possibility to make any conclusions on safety regarding this new proposed indication The Applicant is asked to summarize adverse events during the first month of treatment for pooled placebo-controlled and Zolendronic acid-controlled studies.

The HCM population with advanced disease may be more sensitive to adverse events than the previously studied populations. An increase in dose dependent side-effects cannot be excluded compared to the common approved once-a-month regimen.

In the RMP, the important potential risks for denosumab 120 mg per month in cancer patients include infection, cardiovascular events, malignancy, osteonecrosis outside the jaw including external auditory canal, immunogenicity and thyroid function disorder.

In summary, due to the uncontrolled design, limited sample size and confounding due to severe underlying disease, it is difficult to draw any firm conclusions on safety based on the Study 20070315.

2.5.2. PSUR cycle

The PSUR cycle is proposed to remain unchanged.

2.6. Risk management plan

The risk management plan (RMP) has been updated to capture the new indication. The changes within the RMP since the last approved version have been presented by the Applicant. No additional risk minimization activities have been proposed.

Safety concerns

Table. Summary of the Safety Concerns

Important identified risks	hypocalcemia, osteonecrosis of the jaw, hypersensitivity reactions, atypical femoral fracture, musculoskeletal pain, hypercalcemia following treatment discontinuation in patients with growing skeletons
Important potential risks	infection, cardiovascular events, malignancy, osteonecrosis outside the jaw including external auditory canal, immunogenicity, cataracts in men with prostate cancer undergoing androgen deprivation therapy, thyroid function disorder, delay in diagnosis of primary malignancy in giant cell tumor of bone
Missing information	risks during pregnancy and lactation, pediatric patients, patients with multiple myeloma, patients with hepatic impairment, and patients with prior IV bisphosphonate treatment, safety with long-term treatment and with long-term follow--up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone, off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

Considering the data in the safety specification, the safety concerns listed by the MAH are appropriate at this time point of the procedure.

Pharmacovigilance plan

There are several on-going and planned studies in the post-authorisation pharmacovigilance development plan of Xgeva, regarding GCTB indication and long-term safety follow-up of risks ONJ and cataracts.

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product in the currently approved indications.

No additional studies regarding the proposed new indication are proposed which needs to be further discussed later in the procedure.

Risk minimisation measures

No additional risk minimization activities have been proposed by the applicant regarding the new proposed indication. This need to be further discussed later in the procedure.

Elements for a public summary of the RMP

The following text has been added to the section: “Overview of Disease Epidemiology”

Hypercalcemia of malignancy

High blood calcium due to cancer may occur in patients with cancer at any time during the course of their disease, and it occurs more frequently in some cancers (eg, breast cancer, multiple myeloma, and squamous cell carcinoma of the lung) than in others.

The elements for a public summary of the RMP may require revision following the conclusion of the procedure.

Annexes

The annexes (SmPC) should be updated appropriately.

Overall conclusion on the RMP

is pending depending on the overall benefit/risk assessment of the proposed new indication.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 5.1, 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The following additions are proposed:

4.1 Therapeutic indications
Treatment of hypercalcaemia of malignancy refractory to intravenous bisphosphonate.

4.2 Posology and method of administration
Hypercalcaemia of malignancy refractory to intravenous bisphosphonate
The recommended dose of XGEVA is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy.

5.1 Pharmacodynamic properties
Clinical efficacy in patients with hypercalcaemia of malignancy refractory to intravenous bisphosphonate
The safety and efficacy of XGEVA was studied in a phase 2 open-label, single-arm trial (Study 6) that enrolled 33 patients with hypercalcaemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate. Patients received XGEVA subcutaneously every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy.
In this study, refractory hypercalcaemia of malignancy was defined as an albumin-corrected calcium of > 12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate in the last 7-30 days. The primary endpoint was the proportion of patients achieving a response, defined as corrected serum calcium (CSC) ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after XGEVA administration. XGEVA was associated with rapid and sustained decreases in serum calcium in the majority of patients including those with or without bone metastases (see Figure 2 and Table 4).

Figure 2: Corrected serum calcium by visit (median and interquartile range)
N = Number of subjects who received at least 1 dose of denosumab
n = Number of subjects who had no missing data at baseline and the timepoint of interest14

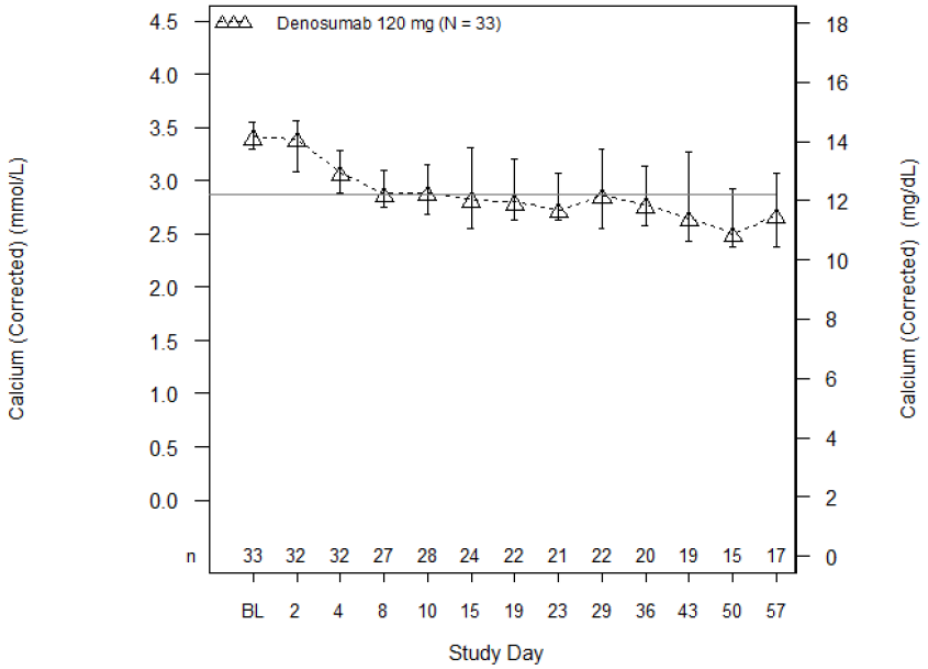


Table 4: Efficacy results in patients with skeletal or humoral hypercalcaemia of malignancy refractory to treatment with intravenous bisphosphonate

	Number of patients evaluable for the endpoint/ Number of patients with the endpoint		Proportion (%) (95% CI)	KM estimate (median) (95% CI)
Response by Day 10a	33	21	63.6 (45.1, 79.6)	--
Overall on-study response	33	23	69.7 (51.3, 84.4)	--
Duration of response (days)b	23	10	--	104 (9.0, NE)
Complete response by Day 10c	33	12	36.4 (20.4, 54.9)	--
Overall on-study complete response	33	21	63.6 (45.1, 79.6)	--
Duration of complete responsed	21	14	--	34 (1.0, 134.0)

a CSC ≤ 11.5 mg/dL (2.9 mmol/L)
b Number of days from the occurrence of first response until last CSC ≤ 11.5 mg/dL (2.9 mmol/L)
c CSC ≤ 10.8 mg/dL (2.7 mmol/L)
d Number of days from the occurrence of first complete response until last CSC ≤ 10.8 mg/dL (2.70 mmol/L)

Rapporteurs comment:

The RSI includes questions on the proposed indication and posology and those are not repeated here. The presentation and wording of study results in the SmPC 5.1 is not assessed in detail at this stage of the

procedure, however, it is noted that the uncertainties in the results due to the study design pointed out by the Rapporteur are not mentioned in the current text. The scale of the figure 2 seems not optimal. Mean values would be preferred instead of median values. The results table 4 is difficult to interpret and could be omitted **(OC).**

5.3 Preclinical safety data

The role of osteoclast-mediated hypercalcaemia was evaluated in 2 murine models of humoral hypercalcaemia of malignancy through the use of osteoprotegerin (OPG), an endogenous decoy receptor that binds and neutralises RANKL. In one model, mice were inoculated with syngeneic colon adenocarcinoma cells, and in the other mice were injected with high-dose parathyroid hormone-related protein (PTHrP) (0.5 mg/kg, SC, twice per day). In both models, a single injection of OPG caused more rapid reversal of established hypercalcaemia and longer lasting suppression of hypercalcaemia than high-dose bisphosphonates.

Rapporteur's comment: It is not clear if the proposed text refers to studies submitted in the original MAA, or if these are new studies. The Applicant is asked to clarify. If these studies have not been previously submitted, they should be submitted for assessment (**OC)**.

2.7.1. User consultation

Rapporteur's comment: No User testing or justification for not providing one has been submitted by the MAH. This should be addressed with the responses to the Request for Supplementary Information **(OC)**.

3. Benefit-Risk Balance

The benefit-risk balance of XGEVA for the approved indications remains unchanged.

The purpose of this application is to add the following new indication to the XGEVA Summary of Product Characteristics (SmPC): "Treatment of hypercalcemia of malignancy (HCM) refractory to intravenous bisphosphonate."

Benefits

Beneficial effects

The new indication application is based on one single arm open-label study with 33 subjects out of whom 24 with classified as refractory HCM (proposed new indication). The subjects had a corrected serum calcium (CSC) > 3.1 mmol/l and have had IV bisphosphonates administered ≥ 7 days and ≤ 30 days prior to the screening CSC.

Decreases in mean CSC were seen from 3.47 mmol/l at baseline to 2.96 mmol/l by the day 10. Mean CSC value at day 57 of the study was 2.76 mmol/l (n= 17).

A total of 21 of the 33 included subjects had a measurement of CSC ≤ 2.9 mmol/l within 10 days after the first dose of denosumab (primary endpoint).

A total of 12 of the 33 included subjects had a measurement of CSC ≤ 2.7 mmol/l within 10 days after the first dose of denosumab (primary endpoint in pivotal zolendronic acid study in HCM).

Denosumab treatment has been shown to be associated with hypocalcemia in all currently approved indications and there is a mechanistic rationale for a calcium lowering effect of denosumab in subjects without HCM.

Uncertainty in the knowledge about the beneficial effects

For a new indication application, the study included only a very limited number of subjects and there was no control group. No discussion with regard to expected outcomes and what would constitute a clinically relevant outcome has been found in the protocol.

The results in the study are likely confounded by standard treatment for hypercalcemia. Intravenous fluids, diuretics and corticosteroids that were frequent in the current study and likely contributed to decreased CSC values. Furthermore, carry over effect of previous recent bisphosphonate treatment is also a possible confounding factor. In addition, the observed difference between pre- and post-treatment measurements could, at least to some extent, be due to regression to the mean.

Both bisphosphonates and denosumab are inhibitors of bone resorption. The rationale on why denosumab would be expected to be effective especially in patients who are refractory to intravenous bisphosphonate is unclear. A total of 11 of the 33 did not have any tendency to decreases in CSC values.

The classification of study subjects as refractory to bisphosphonates was not defined in detail and 9 of the 33 included subjects did not meet the criteria of refractory. No longitudinal data on Ca-levels during previous bisphosphonate treatments are available, only the baseline value for the current study. Six subjects had missing baseline CSC values. Five of the subjects had only received one previous treatment course of bisphosphonates which makes their classification as refractory uncertain.

Treatment of HCM should concentrate on palliative treatment of symptoms. Correlating serum calcium concentration changes with improvements in HCM symptoms is confounded as symptoms associated with hypercalcemia are commonly seen in cancer patients also with normal serum calcium concentrations, especially those towards end-stages of the disease. The presentation of HCM related symptoms in the current study need to be clarified.

The dosage (120 mg x3 during the first month) is higher than the dosage approved for SRE indications (120 mg x1). The rationale of choosing the proposed loading dose regimen needs further justification.

Risks

Unfavourable effects

In the current study, virtually all subjects had serious adverse events and most subjects had a fatal outcome. Two were considered related to the denosumab treatment by the investigator: cardiac arrest and colitis. The most frequently reported (> 3 subjects) adverse events were dyspnea (6 subjects, 18%), decreased appetite and fatigue (both occurring in 4 subjects, 12%), and confusional state, diarrhea, hypercalcemia, and hypophosphatemia (each occurring in 3 subjects, 9%).

In the Xgeva SmPC, very common adverse reactions include musculoskeletal pain, diarrhoea and dyspnoea. In the RMP, important identified risks for denosumab 120 mg per month in cancer patients include hypocalcemia, hypersensitivity reactions and musculoskeletal pain. Atypical femoral fracture and osteonecrosis of the jaw are likely less relevant risks in the current patient population with limited life expectancy and treatment duration.

Uncertainty in the knowledge about the unfavourable effects

The patient population with HCM and advanced cancer is likely to have a high variety of serious and fatal adverse events. In an uncontrolled study, it is virtually impossible to differentiate if adverse events such as nausea, dyspnea, peripheral edema and decreased appetite were related to the investigational product or caused by concomitant treatments and symptoms of the underlying disease itself. The company should discuss the expected rates of these events if these subjects were treated with standard of care only or with another course of zolendronic acid, if possible.

Extrapolation of safety data from other studies with other indications may be the only possibility to make any conclusions on safety regarding this new proposed indication The Applicant is asked to summarize adverse events during the first month of treatment for pooled placebo-controlled and Zolendronic acid-controlled studies.

The HCM population with advanced disease may be more sensitive to adverse events than the previously studied populations. An increase in dose dependent side-effects cannot be excluded compared to the common approved once-a-month regimen.

In the RMP, the important potential risks for denosumab 120 mg per month in cancer patients include infection, cardiovascular events, malignancy, osteonecrosis outside the jaw including external auditory canal, immunogenicity and thyroid function disorder.

Benefit-Risk Balance

Discussion on the Benefit-Risk Balance

It is recognized that there may be an unmet medical need in the proposed target population refractory to intravenous bisphosphonate and potentially also in patients who cannot tolerate bisphosphonates. However, given the uncertainties regarding the refractory definition in the current study, the uncontrolled design, the risk for confounding (concomitant treatments and the underlying disease) and the limited sample size it is difficult to draw any conclusions on efficacy and safety based on the Study 20070315, the only study performed in the proposed target group.

Conclusion

The application for Xgeva in the proposed new indication: “Treatment of hypercalcaemia of malignancy refractory to intravenous bisphosphonate” is not approvable.

4. Recommendations

The application for:

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

Extension of Indication to include treatment of hypercalcemia of malignancy refractory to intravenous bisphosphonate for XGEVA; as a consequence, sections 4.2, 4.3, 4.8, 5.1 and 5.3 of the SmPC are

updated. The Package Leaflet is updated in accordance.

☒ is not approvable since a major objection and other concerns have been identified, which preclude a recommendation at the present time.

☐ could be approvable since other concerns <has><have> been identified, which preclude a recommendation at the present time.

The details of these <major objections>< other concerns> are provided in Annex <> (RSI 1) and should be addressed in writing <and in an oral Explanation>.

☐ is approvable <since other concerns <major objections> <has><have> all been resolved>.

Annex 1: Rapporteurs proposed Request for Supplementary Information

Major objections

Clinical efficacy

1. Given the uncontrolled design, doubts on the refractory status of the selected population, the risk for confounding (concomitant hypercalcemia treatments, carry-over effect of previous bisphosphonates and the underlying disease, regression to the mean) and the limited sample size it is very difficult to draw any firm conclusions on efficacy based on the Study 20070315 . The MAH should further justify why the submitted data could be considered to support the proposed indication considering all the limitations listed above.

Other concerns

Non-clinical aspects

2. The Applicant is asked to provide documentation in support of the proposed addition to section 5.3 of the SmPC.

Clinical aspects

Clinical Pharmacology

3. The Applicant considers it appropriate to target the same steady-state serum denosumab concentrations in HCM patients as in patients with bone metastases from solid tumors, and to facilitate a rapid attainment of steady-state concentrations with the additional doses on days 8 and 15 of treatment, as used in the treatment of GCTB. It would have been informative to compare denosumab concentrations in previous patient populations with the HCM patient population to verify the targeted denosumab exposure levels in the new patient population. The Applicant is asked justify the lack of PK/PD data in HCM patients and to discuss whether there are reasons to believe that the PK/PD relationship differs in the present patient population.
   Data on associations between serum denosumab concentrations and effect is also missing. The Applicant is asked to present any data with Ca-measurement data supporting that current proposed dosing regimen 120 mg X 3 would be more beneficial in hypercalcemia during the first month of treatment compared to a single dose of 120 mg.

Efficacy

4. The proposed indication is treatment of hypercalcemia of malignancy refractory to intravenous bisphosphonate. The subjects Ca responses to previous bisphosphonate treatments were not documented in this single arm pivotal study making the patients classification as refractory uncertain. The Applicant states that primary etiology of both skeletal and humoral HCM is increased bone resorption. Both bisphosphonates and denosumab are potent inhibitors of bone resorption. The Applicant should elaborate the mechanistic rationale for inhibition of the RANK – RANKL axis in bisphosphonate-refractory HCM and whether its efficacy would be expected to differ depending on tumour type and dominant type of HCM, osteolytic vs humoral. Available data, non-clinical and

clinical, supporting a mechanistic rational should be presented.

5. Information on HCM symptoms was collected at baseline, days 4, 8, and 10 in the study. The Applicant has presented results at baseline for all study subjects but results by day 10 only for subjects with symptoms at baseline. The Applicant is requested to report the number of symptoms by day 10 for all subjects. The Applicant is also asked to comment if the improvement of symptoms was related to Ca-response in the study.

6. The proportion of subjects with a complete response by visit is not clearly presented in the results section, the Applicant is asked to provide these numbers in line with the primary endpoint.

7. Six subjects had missing central baseline S-Calcium values. The study subject numbers for these individuals could not be easily found in the documentation. The Applicant is asked to provide the subject numbers for these individuals and comment if using the local values might have had an impact on the main results.

8. The Applicant had originally planned to perform a phase 3 clinical study in order to support a full indication: Treatment of hypercalcemia of malignancy (HCM). The Applicant is asked to clarify in they are planning to perform this study. If not, the Applicant should clarify if the decision was due to any efficacy/safety issues. The Applicant is invited to comment.

Safety

9. With the proposed loading dose regimen, an increase in dose dependent side-effects cannot be excluded compared to the common approved once-a-month regimen. The Applicant states that denosumab has been evaluated across a wide variety of doses and administration schedules in clinical studies: In subjects with advanced cancer, SC doses of up to 180 mg Q4W have been evaluated. In bone loss studies, repeated SC doses of up to 210 mg have been studied. The applicant is asked to present data from these individual studies: with focus on comparisons of effect on the calcium levels and occurrence adverse events between placebo and different denosumab doses.

Product Information

10. The RSI includes questions on the proposed indication and posology and those are not repeated here. The presentation and wording of study results in the SmPC 5.1 is not assessed in detail at this stage of the procedure, however, it is noted that the uncertainties in the results due to the study design pointed out by the Rapporteur are not mentioned in the current text. The scale of the figure 2 seems not optimal. Mean (SD) values by visit should be presented in this figure instead of median values.

11. The results table 4 is difficult to interpret and could be omitted.

12. No User testing or justification for not providing one has been submitted by the MAH. This should be addressed with the responses to the Request for Supplementary Information.