Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for denosumab

Proprietary Product Name: Xgeva

Sponsor: Amgen Australia Pty Ltd

Date of first round CER: 28 June 2013

Date of second round CER: 30 September 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ARTG	Australian Register of Therapeutic Goods
BSAP	Bone specific alkaline phosphatase
CT	X-Ray Computed Tomography
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCTB	Giant Cell Tumour of Bone
LDH	Lactate Dehydrogenase
MRI	Magnetic resonance imaging
ONJ	Osteonecrosis of the jaw
PET	Positron Emission Tomography
PI	Product Information
RANK	Receptor activator of nuclear factor κB
RANK-L	Receptor activator of nuclear factor κB ligand
RECIST	Response evaluation criteria in solid tumours
SAE	Serious Adverse Event
sCTX	Serum C-telopeptide
TGA	Therapeutic Goods Administration
TRAP-5b	Tartrate-resistant acid phosphatase 5 b
uNTX	Urinary N-telopeptide

1. Introduction

The currently approved dose regimen for patients with bone metastases from solid tumours is 120 mg subcutaneously every 4 weeks.

For the new indication, the sponsor is proposing essentially the same regimen, but is proposing the addition of two loading doses of 120 mg each on days 8 and 15 of the initial 4-week period.

The sponsor is proposing changes to the Pharmacology, Clinical Trials, Precautions, Adverse Effects and Dosage and Administration sections of the Product Information (PI), based on the clinical studies submitted in support of the new indication. No other changes to the PI are proposed. Details are beyond the scope of the AusPAR.

2. Clinical rationale

Giant cell tumour of bone (GCTB) is considered to be a benign but locally very destructive neoplasm. The neoplastic cells are thought to arise from primitive mesenchymal stromal cells. These neoplastic cells secrete RANK-L, which stimulates the differentiation and activation of osteoclast-like giant cells. The histological appearance of GCTB is therefore that of a mixture of mononuclear cells (thought to be derived from primitive mesenchymal stromal cells) and the osteoclast giant cells. Contrary to the name of the tumour, the giant cells are not considered to be neoplastic.[1]

GCTB generally occurs in long bones, most commonly around the knee (distal femur, proximal tibia) but also frequently in the distal radius, proximal humerus and proximal fibula. It can also occur in the pelvic bones, sacrum and in the vertebrae. The peak frequency is in the second to fourth decades of life and is slightly more common in females. It is very rare in children unless skeletally mature (that is, with closed epiphyses). On X-ray it appears as a lytic lesion. If left untreated the tumour causes progressive bone destruction. GCTB can also spread to the lungs. In these cases the histology of the pulmonary lesions is identical to that of the primary benign tumour[2] and these lesions are therefore considered to be "benign metastases".

Current treatment of GCTB generally relies on surgical management (curettage of bone, complete resection where possible). Radiotherapy is also considered effective in situations where surgery is not possible.[2] The disease is not considered responsive to chemotherapy. Bisphosphonates may reduce the risk of recurrence following surgery.

Although considered a benign tumour, it has a capacity to undergo malignant transformation. Such transformation is generally only seen in tumours that recur after radiotherapy or surgery. Giant cell tumours that display malignant behaviour de novo are considered to be a form of sarcoma and a separate clinical entity to GCTB.

The clinical rationale for use of denosumab in GCTB is summarised by the sponsor as follows:

> *'In patients with GCTB, the inhibition of RANK-L secreted by the stromal component of the tumor by denosumab significantly reduces or eliminates the osteoclast-like, tumor-associated giant cells. Consequently, osteolysis and the progression of the giant cell tumor are reduced, and proliferative stroma is replaced with nonproliferative, differentiated, densely woven new bone, resulting in improved clinical outcomes.'*

There are currently no other medicines registered for the treatment of GCTB.

[1] Reid R, Banerjee SS, Sciot R. Giant cell tumour. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization Classification of Tumours. Pathology and genetics of tumours of soft tissue and bone. 1st ed. Lyon: IARC Press; 2002; p.310-312.

[2] Szendröi M. Giant-cell tumour of bone [Review]. J Bone Joint Surg (Br). 2004; 86-B: 5-12; Yasko AW. Giant cell tumor of bone. Curr Oncol Rep. 2002; 4: 520-526.

As described above, previous applications for denosumab have been approved by the TGA for use in patients with metastases to bone and for the treatment of bone loss associated with osteoporosis and androgen deprivation therapy.

The following guideline published by the European Medicines Agency (EMA) and adopted by the TGA is considered relevant to the current application:

- Guideline On The Evaluation Of Anticancer Medicinal Products In Man (CPMP/EWP/205/95/Rev.3/Corr.)[3]

Compliance with this guideline will be considered in the relevant sections of this report.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The hard copy of the submission consisted of 15 volumes (6,000 pages) of clinical data. The covering letter gave an assurance that the hard copy and electronic versions of the submission were identical. This reviewer used the electronic version.

The submission contained the following clinical information:

- Clinical study reports for 2 open-label, single-arm studies (20062004 and 20040215) examining the efficacy and safety of denosumab in the treatment of GCTB;
- An integrated analysis of efficacy;
- An integrated analysis of safety;
- Literature references.
- The sponsor's Clinical Overview, Summary of Clinical Efficacy and Summary of Clinical Safety.

3.2. Paediatric data

One of the two submitted clinical trials (20062004) included 10 skeletally mature adolescents (aged between 12 and 18 years). The two trials did not include subjects who were not skeletally mature as GCTB is extremely rare in such subjects.

3.3. Good clinical practice

The study reports for the two submitted clinical trials included assurances that they were conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) guidelines and any regulations applicable in the countries where the trials were conducted. Study protocols, consent forms et cetera were reviewed by independent ethics committees.

[3] <http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm#ewp020595rev4>

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

One of the submitted studies (20040215) included data on trough serum levels of denosumab in 37 subjects receiving the drug for GCTB.

4.2. Evaluator's overall conclusions on pharmacokinetics

The trough level data from Study 20040215 demonstrated that denosumab trough levels do not decline with long-term, 4-weekly dosing in subjects with GCTB, and that use of a loading dose on Days 8 and 15 results in rapid attainment of steady-state levels.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Study 20040215 included data on the effect of denosumab treatment on markers of bone resorption. Results are summarised in the efficacy section of this evaluation report.

6. Dosage selection for the pivotal studies

The sponsor chose to use essentially the same dosage regimen as is currently approved for the treatment of bone metastases 120 mg subcutaneously (SC) every 4 weeks. In a previously submitted Phase II dose ranging Study (20040113) in subjects with breast cancer and bone metastasis, this regimen was associated with the maximum reduction of the bone turnover marker uNTX/Cr (uNTX corrected for urine creatinine) by Week 13 compared with the other dosing regimens tested.

According to the current Australian PI, in patients with bone metastases the half-life of denosumab is approximately 28 days and steady state is achieved after 6 months. The sponsor considered it desirable to achieve target levels within the first month of treatment for patients with GCTB, on the grounds that this may be associated with improved clinical outcomes. For this reason, two loading doses, at Days 8 and 15, were added to the established 4-weekly regimen.

> Comment: Given the rapidly progressive nature of GCTB, the sponsor's justification for the use of the two loading doses is considered acceptable. The PK data from Study 20040215 demonstrated that steady state levels associated with 4-weekly dosing were achieved early with the use of the loading doses.

7. Clinical efficacy

The two submitted studies both provided efficacy data. Although both were single arm, non-comparative Phase II trials, they are both considered pivotal to the submission.

7.1. Pivotal efficacy studies

7.1.1. Study 20040215

7.1.1.1. Study design, objectives, locations and dates

This study was an open label, single arm, Phase II trial. The primary objective of the study was to evaluate the efficacy of denosumab in subjects with recurrent or unresectable GCTB. Secondary objectives included evaluation of safety, pharmacokinetics (trough levels of denosumab), pharmacodynamics (bone markers) and the development of anti denosumab antibodies.

The study was conducted in 8 centres in Australia, France and the United States. The first subject enrolled in July 2006. The submission included two study reports:

- The 'primary analysis' (data cut-off of 7 April 2008, report dated 2 April 2009); and
- A 'final' report (data cut-off of 16 November 2010, report dated of 19 June 2011).

The study has been published.[4]

> Comment: The EMA guideline on anticancer agents generally encourages the use of randomised controlled trials, even in rare tumours. The sponsor justified the use of an open single-arm design on the grounds that there is no active comparator recognised as standard of care, and use of placebo was not considered ethical. Given the aggressive nature of the disease, the justification for not using a placebo arm is considered acceptable.

7.1.1.2. Inclusion and exclusion criteria

It is noted that the study restricted enrolment to patients with unresectable or recurrent disease. The proposed indication in Australia does not restrict use to this population. In the published version of the study the term 'unresectable' is explained as meaning: *'for example, resection could not be done without nerve damage or substantial impairment of joint function.'*

7.1.1.3. Study treatments

All patients received denosumab 120 mg subcutaneously (SC) on days 1, 8, 15 and 29 and once every 4 weeks thereafter. There were no dosage adjustments allowed during the study. Treatment was continued until one of the following occurred:

- The subject had a complete tumour resection;
- Disease progression occurred;
- Either the sponsor or the investigator recommended discontinuation;
- The subject decided to discontinue; or
- The subject received bisphosphonates, calcitonin or interferon alfa-2a.

Daily supplementation with greater than or equal to 500 mg of calcium and 400 IU or more of vitamin D was strongly recommended, except in the case of pre-existing hypercalcemia.

7.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Histopathology. Samples (obtained via biopsy or at the time of any surgical resection) were to be obtained prior to the administration of the first dose of denosumab and again at some

[4] Thomas D et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. Lancet Oncol. 2010, 11: (3): 275-80.

time between weeks 9 and 25. All samples were evaluated both locally and by a blinded central laboratory.

- Tumour imaging (CT or MRI). At baseline, a bone lesion was identified as the target lesion. It was required to be at least 10 mm in its longest diameter and suitable for accurate repeated measurements by CT or MRI. The longest diameter was used as the measurement by which subsequent progression or objective response would be characterised. Imaging was then performed at weeks 13 and 25 and every 12 weeks thereafter. Positron emission tomography (PET) scans were performed at the same time points for additional evaluation of tumour response and bone repair.

The primary efficacy outcome was the proportion of patients who achieved a 'response'. Response was defined as one of the following:

- For subjects who had histopathology samples available:
  - At least 90% elimination of giant cells relative to baseline, or
  - Complete elimination of giant cells in cases where giant cells represented less than 5% of tumor cells at baseline.
- For subjects who did not have histopathology samples available, a response was defined as lack of progression of the target lesion (by CT or MRI) at Week 25 compared with baseline. Progression was defined as a greater than or equal to 20% increase in longest diameter of the target lesion.

Other efficacy outcomes included:

- Changes in concentrations of bone turnover markers, urinary N-telopeptide (uNTx) and serum C-telopeptide (sCTx), compared with baseline;
- The percent change of measurable lesions from baseline in subjects who had multiple lesions and were unable to undergo palliative resection;
- The number and percentage of subjects who had bone calcification, or bone repair in lesions, or clinical benefit.

7.1.1.5. Randomisation and blinding methods

There was no randomisation in the study. Patients and investigators were not blinded to treatment.

7.1.1.6. Analysis populations

The efficacy analysis set (also referred to as evaluable subjects) included those subjects who had a baseline histology assessment and at least 1 post-dose histology assessment between Weeks 5 and 25; or a baseline radiology assessment and at least 1 post-dose radiology assessment between Weeks 5 and 25. Evaluable subjects had to be on study for at least 28 days after administration of the first dose of denosumab.

The safety analysis set included all subjects who received at least one dose of denosumab.

7.1.1.7. Sample size

A response rate of greater than 11% was chosen as clinically meaningful, and a true response rate of 30% was anticipated. The planned sample size was 35 subjects. With this sample size, if a successful result was defined as an observed response rate of 23% or more, the study had a probability of less than 0.05 of concluding denosumab was efficacious when the true response rate was less than 11%. If the true response rate was at least 30%, then the probability of concluding denosumab is not efficacious was less than 0.15.

7.1.1.8. Statistical methods

Descriptive statistics were used. Frequencies and percentages were provided for all categorical variables. Continuous variables were summarized using mean, standard deviation (SD), and minimum and maximum values. Median and other selected percentiles were substituted for mean and SD for parameters exhibiting a lack of normality. For parameters that were required by the protocol to have multiple baseline measurements, the mean of the baseline records was used for calculation of changes from baseline. Otherwise, the baseline value was the observation recorded just before the first dose of denosumab. No imputation of missing values was used.

For the primary endpoint of response rate, 95% confidence intervals were calculated.

7.1.1.9. Participant flow

A total of 37 subjects were enrolled and all received at least one dose of denosumab. At the final analysis, 10 subjects (27%) had proceeded to complete resection and another 12 subjects (32%) had been rolled over into Study 20062004.

7.1.1.10. Major protocol violations/deviations

There were two important protocol violations:

- 1 subject had a diagnosis of osteosarcoma at baseline. The subject was included in the efficacy analysis because a treatment response could still be measured. The study report did not indicate whether this patient had a response or not.
- 1 subject had a GCTB that was not at least 10mm in size at its longest diameter. This subject was not included in the efficacy analysis because it was not possible to accurately determine a treatment response.

Both subjects were included in the safety analysis.

7.1.1.11. Baseline data

The demographic characteristics are consistent with a typical population of patients with GCTB in that the median age was 30.0 years and there was a slight female predominance. The baseline disease characteristics are not typical for GCTB in that only a minority of subjects had target lesions in long bones and 9/37 (24%) patients had pulmonary disease. This may reflect the fact that most patients enrolled had unresectable disease.

7.1.1.12. Results for the primary efficacy outcome

Of the 37 subjects enrolled, 2 were excluded from the efficacy analysis. One subject did not meet the entry criterion of having a GCTB that was at least 10mm in size at its longest diameter. The other subject had not completed 25 weeks on study by the data cut-off.

The percentage of patients who achieved a response was 85.7% (95% CI: 69.7 95.2%). Among patients who had sufficient histology samples for assessment of response (n = 20), 100% achieved a response. Among those without sufficient histology (n = 15), 66.7% achieved a response (that is, the disease did not progress) as measured by CT or MRI.

Similar response rates were observed between subjects who were younger than the median age and those who were older or the same as the median age (88% versus 84%). Subjects with and without prior bisphosphonate use also had similar response rates (80% versus 87%, respectively).

7.1.1.13. Results for other efficacy outcomes

7.1.1.13.1. Markers of bone turnover (secondary endpoint)

There were reductions from baseline of up to 80% in urinary N-telopeptide and serum C-telopeptide.

7.1.1.13.2. Exploratory endpoints

The sponsor also examined change from baseline in the following other markers of bone turnover:

- Bone specific alkaline phosphatase (BSAP) a marker of bone formation;
- Osteocalcin also a marker of bone formation; and
- Tartrate-resistant acid phosphatase 5 b (TRAP-5b) a marker for bone resorption.

Following treatment with denosumab, levels of these markers all decreased significantly.

As an exploratory endpoint the sponsor conducted an analysis of the percentage change from baseline in the size of all measurable lesions (target plus non-target) in the subpopulation of patients who had multiple lesions and were unable to undergo palliative resection. From the tables in the study report it appears that there were 27 subjects who fell into this subgroup. Results were presented for the average per cent change at each point in time for which were data available. The results were highly variable and the sponsor drew no conclusions.

Investigators also assessed bone lesions for evidence of clinical benefit (reduced pain or improvement in functional status), and evidence of bone repair and calcification of bone. A total of 31 subjects provided data for these analyses.

> Comment: Although the result for clinical benefit (83.9%) appears impressive, it should be noted that the methods used for bone lesion assessment were not described in either the study protocol or the study report. The validity of these endpoints is therefore uncertain.

7.1.2. Study 20062004

7.1.2.1. Study design, objectives, locations and dates

This study was an open-label, single-arm, Phase II trial, with 3 cohorts:

- Cohort 1 included subjects with surgically unsalvageable GCTB (for example sacral, spinal disease, or multiple lesions including pulmonary metastases);
- Cohort 2 included subjects with GCTB that was considered surgically salvageable, but whose planned initial on-study surgery would be associated with severe morbidity (for example joint resection, limb amputation, or hemipelvectomy). According to the study report these subjects had “an immediate need for surgery to treat their disease”.
- Cohort 3 included subjects who had been rolled over from Study 20040215.

The primary objective was to evaluate the safety of denosumab in subjects with GCTB.

Secondary objectives were:

- The evaluation of time to disease progression in subjects with unsalvageable GCTB treated with denosumab (Cohort 1 of the study); and
- The evaluation of the proportion of subjects who did not require surgery in denosumab-treated subjects with salvageable GCTB (Cohort 2 of the study).

There were also a number of exploratory objectives related to various exploratory efficacy variables described below.

The study is being conducted at 29 centres in North America, Europe and Australia. The first patient was enrolled on 9 September 2008. The study report presented was based on an interim analysis (the 3rd interim analysis) with a data cut-off of 25 March 2011. The study report itself was dated 29 February 2012. The study is ongoing, and does not appear to have been published other than as conference abstracts.

7.1.2.2. Inclusion and exclusion criteria

Comment: Patients in whom surgical resection without severe morbidity was possible, were not included. The proposed indication in Australia would include such patients. Unlike Study 20040215, this trial included adolescent subjects provided they were skeletally mature and weighed at least 45 kilograms.

7.1.2.3. Study treatments

Patients in Cohorts 1 and 2 received denosumab 120 mg subcutaneously on days 1, 8, 15 and 29 and once every 4 weeks thereafter. Subjects in Cohort 3 continued with the dose regimen they had received in Study 20040215 and did not receive new loading doses.

There were no dosage adjustments allowed during the study.

If a subject underwent a complete tumor resection during the study, denosumab treatment continued for 6 doses after this resection. In all other cases, denosumab treatment continued until:

- Disease progression occurred;
- An investigator's or the sponsor's recommendation of discontinuation;
- Subject's decision to discontinue;
- Lack of clinical benefit in the investigator's judgment; or
- Administration of any proscribed therapy (bisphosphonates, chemotherapy, embolization of the tumour, radiation therapy or an investigational treatment for GCTB).

Daily supplementation with greater than or equal to 500 mg of calcium and greater than or equal to 400 IU of vitamin D was strongly recommended, except in the case of pre-existing hypercalcemia.

7.1.2.4. Efficacy variables and outcomes

Determination of efficacy was only a secondary objective in this study. The main efficacy outcomes were:

- For Cohort 1, the time to disease progression.
- For Cohort 2, the proportion of subjects without any surgery at 6 months.

Evaluations of efficacy were based on assessments of target lesions. Target lesions were chosen by the investigator and were required to be both measurable and accessible for biopsy. Subjects were reviewed at 4-weekly intervals. There was no schedule of investigations to determine the main efficacy outcomes. Similarly there were no standard criteria defined for determining disease progression. Histopathology and imaging studies were performed if and when required as part of standard management. Reports of these studies had to be submitted to the sponsor, however the determination of what constituted disease progression and when it occurred was a matter for each investigator. Data on occurrence and type surgery performed were also collected.

There were a large number of 'exploratory' efficacy outcomes.

Several of exploratory outcomes relate to pain score, which was measured using the Brief Pain Inventory Short Form (BPI-SF). The BPI-SF is a validated, widely used, self-administered questionnaire that assesses the severity of pain and the impact of pain on daily activities. It contains 4 questions on pain severity and 7 questions on how pain has interfered with daily activities. The score for each question ranges from 0 (no pain or interference) to 10 (pain as bad as can be imagined complete interference). A minimally important difference was considered to be 2 points. Patients were asked to recall pain in either the preceding 24 hours or preceding week. The BPI-SF was administered at each visit up to 25 weeks and then every 12 weeks.

Analgesic scores were also measured every 4 weeks by use of the Analgesic Quantification Algorithm (AQA), an 8-point scale ranging from 0 to 7 (corresponding to no analgesic use, non-opioid analgesics, weak opioids only, less than or equal to 75 mg, greater than 75 mg up to 150 mg, greater than 150 mg up to 300 mg, greater than 300 mg up to 600 mg, and greater than 600 mg oral morphine equivalents/day, respectively).

7.1.2.5. Randomisation and blinding methods

There was no randomisation in the study. Patients and investigators were not blinded to treatment.

7.1.2.6. Analysis populations

The Efficacy Analysis Set comprised all enrolled subjects who were eligible for the study and received at least 1 dose of denosumab. The Safety Analysis Set included all enrolled subjects who received at least 1 dose of denosumab. The Patient Reported Outcome (PRO) Set included all subjects in the efficacy analysis set that had at least one PRO assessment (BPI-SF, AQA) and used consistent recall periods throughout the study. The Interim Analysis Set comprised the respective analysis sets of all enrolled subjects up to the time of the interim analysis.

7.1.2.7. Sample size

The sample size was not determined by any considerations related to hypothesis testing. It was decided simply by estimating the number of subjects that could be recruited (approximately 500).

7.1.2.8. Statistical methods

The statistical analyses performed were descriptive in nature. Categorical data were presented by number and percentage. Continuous data were provided as descriptive statistics (n, mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum, and maximum).

For Cohort 1, Kaplan-Meier estimate of time to disease progression[5] were displayed graphically.

Kaplan-Meier event rates at various time points (for example month 3, month 6) with 2-sided confidence intervals (CIs) were summarised. In addition, Kaplan-Meier estimates of quartiles (median, 25th and 75th percentiles) with 2-sided 95% CIs were calculated, if applicable.

For Cohort 2, crude estimates of the proportion of patients without any surgery at 6 months (with 2-sided exact 95% CIs) were summarized for subjects who completed 6 months of treatment in the Efficacy Analysis Set.

Similar methods were used for analysing the exploratory efficacy endpoints.

7.1.2.9. Protocol changes

A total of six changes to the study protocol were made after the study commenced.

> Comment: These changes are considered unlikely to have affected any conclusions regarding efficacy.

7.1.2.10. Participant flow

By the data cut-off for the 3rd interim analysis, a total of 313 subjects had been screened for enrolment. Of these, 6 decided not to participate while a further 21 did not meet the eligibility criteria (most commonly due to not having a pathologically confirmed GCTB). A total of 286 subjects were therefore enrolled. Of these, 15 were subjects rolled over from Study 20040215 into Cohort 3, and 4 of these had completed their denosumab treatment and were rolled over to complete their 2-year safety follow-up. These 4 subjects did not receive denosumab in

[5] The Kaplan–Meier estimator, also known as the product limit estimator, is an estimator for estimating the survival function from lifetime data.

20062004 and hence were not included in the Efficacy Analysis Set (EAS). The EAS therefore comprised 282 subjects.

A total of 170 subjects were enrolled in Cohort 1 and 101 subjects in Cohort 2. At the time of the data cut-off, 238/282 subjects (84%) were still receiving denosumab.

7.1.2.11. Major protocol violations/deviations

Seven subjects had 8 protocol deviations. One subject did not provide written informed consent before enrolment. Four patients became pregnant and were withdrawn. The other deviations were receipt of denosumab before enrolment approval, missed initial dose and receipt of incorrect dose.

Comment: These protocol violations would not have affected the outcomes of the study.

7.1.2.12. Baseline data

The age and gender distributions of the study population were consistent with the known demographics of GCTB patients.

The location of target lesions was consistent with the entry criteria, with the majority of Cohort 2 having lesions in long bones, and the majority of Cohort 1 having lesions in the axial skeleton or lungs.

The majority of patients (61.7%) had had prior surgery.

7.1.2.13. Results for the efficacy outcomes

Median (range) time on-study was 12.98 (0.3, 29.1) months for Cohort 1, 9.23 (0.0, 28.0) months for Cohort 2, and 5.36 (4.5, 6.2) months for Cohort 3. Median for the whole study population was 10.4 (0.0 29.1) months.

7.1.2.13.1. Time to disease progression (Cohort 1)

Only 6 of 169 treated subjects (4%) in Cohort 1 had disease progression. Median time to progression could therefore not be estimated.

Kaplan-Meier estimates of the probability of disease progression were 1.4% (95% CI: 0.0 3.4) at Week 25, 4.0% (95% CI: 0.5 7.5) at eek 49 and 5.6% (95% CI: 1.0 10.2) at Week 73.

7.1.2.13.2. Proportion of subjects without any surgery at 6 months (Cohort 2)

There were 71 subjects in Cohort 2 who had been on study for at least 6 months. Of these, 64 subjects (90.1%; 95% CI: 80.7 95.9) had not received surgery.

7.1.2.13.3. Results for exploratory efficacy outcomes

There were a large number of exploratory endpoints. Notable findings are below.

7.1.2.13.3.1. Need for surgery

As indicated above, in Cohort 2, 90.1% of subjects (64/71) who had completed 6 months of treatment did not receive surgery.

For the whole of Cohort 2 (n = 100), 74.0% avoided surgery and 26.0% received some form of surgery. Of the 26 subjects who did receive surgery, median time to surgery was 723 days (that is, 2 years). Sixteen of these were able to undergo a surgical procedure that was less morbid than that which was planned at baseline. The limited procedure of curettage was performed in 13 of these, replacing planned en bloc resection (n = 6), joint or prosthesis replacement (n = 4), amputation (n = 2) and joint resection (n = 1).

Nine of the remaining subjects underwent their planned procedures while 1 subject underwent a more morbid procedure than originally planned.

7.1.2.13.3.2. Disease status changes best response

In Cohorts 1 and 2 combined, a total of 9.9% of subjects achieved a "complete response" and 37.3% of subjects achieved a "partial response".

> Comment: The meanings of these terms was not defined and the results are therefore of uncertain clinical significance.

Of the 25 subjects who achieved a "complete response", none had disease recurrence.

7.1.2.13.3.3. Pathological response

A total of 40 subjects in Cohorts 1 and 2 had a post-baseline histopathology specimen obtained. Of these 19 (47.5%) had no evidence of tumour found.

7.1.2.13.3.4. Radiological changes over time

Imaging of target lesions over time showed stable or improved appearance, with very few instances of worsening.

7.1.2.13.3.5. Clinical benefit

According to the subjective assessment of the investigators, 47.6% of subjects in Cohorts 1 and 2 experienced some form of clinical benefit during the study. Pain reduction occurred in 36.4%, improved mobility in 26.4% and improved function in 20.4%.

7.1.2.13.3.6. Pain scores and analgesic scores

These scores generally showed improvement in pain over time compared to baseline, without any significant increase in analgesic use.

> Comment: As the trial did not include a placebo arm for comparison and patients were not blinded, any conclusion that treatment results in pain relief would not be reliable.

7.1.2.13.3.7. Results in adolescents

The study included 10 adolescent subjects, 8 in Cohort 1 and 2 in Cohort 2. Eight of these were continuing to receive denosumab at the time of the data cut-off. One subject was withdrawn due to pregnancy and one was lost to follow up. There were 8 females and 2 males and age ranged from 13 to 17 (median 16).

Median follow-up was 9.02 months (range 3.3 to 17.3 months). No subject had (subjectively assessed) progressive disease. Neither of the two patients in Cohort 2 had undergone surgery.

7.1.3. Analyses performed across trials

The sponsor presented an "Integrated Analysis of Objective Tumour Response" in the Summary of Clinical Efficacy This analysis was conducted after discussions and agreement with the FDA. It was a retrospective analysis of imaging results collected during Studies 20040215 and 20062004. An independent company conducted the analysis. The sponsor provided all CT, MRI and 18FDG-PET scans.

The sponsor states in the submission that it considers this integrated analysis to be the primary evaluation of efficacy for this marketing application. Efficacy results from the individual studies are supportive efficacy evaluations".

7.1.3.1. Methods

GCTB tumour response and progression were assessed using three differing methodologies:

- Assessment of tumour size using modified RECIST (Response Evaluation Criteria In Solid Tumours) criteria (version 1.1) based on CT or MRI imaging.

  > Comment: The RECIST criteria are a standard method of assessing tumour response/progression and the EMA anticancer guideline recommends their use in Phase

II oncology studies. The RECIST criteria require that any tumour response should be confirmed with a repeat scan, but this was not a requirement in this integrated analysis.

In the original RECIST criteria[6] published in 2000 (version 1.0) tumours in bone were considered non-measurable and hence progression and response could not be assessed. In the revised version[7] published in 2009 (version 1.1) lytic bone lesions with identifiable soft tissue components that can be assessed by CT or MRI are considered as measurable. The two submitted studies were commenced prior to 2009. The integrated analysis was conducted in 2012.

- Evaluation of metabolic response using 18FDG-PET scans and assessed using a modified version of criteria published[8] by the European Organisation for Research and Treatment of Cancer (EORTC). The Standardised Uptake Value (SUV) is a measure of the uptake of 18FDG by tumour tissue. Higher values reflect greater uptake. Maximum SUV for each lesion in a patient was measured and then all values summed.

  Comment: Regulatory authorities such as the EMA as do not yet accept 18FDG-PET scan as an acceptable measure of tumour response/progression. However, the degree of 18FDG uptake is considered to be a measure of the number of viable cells in a tumour, and 18FDG-PET scan may be a useful tool for situations in which drug activity is not associated with reductions in size of the tumour (for example cytostatic agents).

- Assessment of tumour size (based on CT or MRI) and tumour density (based on CT) using a modified version of published criteria[9] (the 'Choi criteria'). The Choi criteria were originally proposed for response assessment in gastrointestinal stromal tumour (GIST), a malignancy in which the conventional RECIST criteria were found to be insensitive. Smaller changes in tumour size than those required by RECIST, or reductions in tumour density, predicted benefits in long-term prognosis of GIST patients. For this analysis, changes in tumour size were measured by CT or MRI. Changes in tumour density were assessed by CT and measured in Houndsfield Units (HU)[10]. In GIST, treatment with an active agent such as imatinib resulted in a decrease in tumour density. In GCTB, it was anticipated that successful treatment would be associated with an increase in bone density (replacement of tumour soft tissue with new bone).

  Comment: The Choi criteria are less stringent than RECIST for achievement of a response based on decrease in size, and also allow a response based on change in density of the tumour, without any decrease in size. They have also not yet been accepted as a valid measure of clinical efficacy by regulatory authorities. The supporting papers from the literature provided by the sponsor related to their use in GIST and soft tissue sarcomas only.

[6] Therasse P et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumours. J Natl Cancer Inst. 2000, 92 (3): 205-216.

[7] Eisenhauer EA et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009, 45: 228-247.

[8] Young H et al. Measurement of Clinical and Subclinical Tumour Response Using [18F]-fluorodeoxyglucose and Positron Emission Tomography: Review and 1999 EORTC Recommendations. Eur J Cancer. 35 (13): 1773-1782.

[9] Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol. 2007. 25:1753-1759.

[10] The Hounsfield unit (HU) scale is a linear transformation of the original linear attenuation coefficient measurement in one in which the radiodensity of distilled water at standard pressure and temperature (STP) is defined as zero Hounsfield units (HU), while the radiodensity of air at STP is defined as -1000 HU. For a material X with linear attenuation coefficient μX, the corresponding HU value is therefore given by where is the linear attenuation coefficient of water. Thus, a change of one Hounsfield unit (HU) represents a change of 0.1% of the attenuation coefficient of water since the attenuation coefficient of air is nearly zero. It is the definition for CT scanners that are calibrated with reference to water.

The integrated analysis also included an 'imaging control group'. This was to consist of at least 20 subjects from the two trials who had at least 3 images performed prior to treatment with denosumab. The pre-treatment imaging would be assessed using the same criteria for response or progression described above. Radiologists interpreting the imaging for the integrated analysis were blinded as to whether imaging was done pre- or post- treatment with denosumab. The purpose of the control group was to *'help distinguish a true effect of denosumab from any bias in the evaluation process, natural progression of the disease, and artifacts such as regression to the mean.'*

For the purposes of the analysis, an 'objective tumour response' was defined as a complete or partial response determined using any of the above three methodologies. Descriptive statistics were used in the analysis and there was no hypothesis testing.

7.1.3.2. Results

A total of 303 subjects were eligible for entry in the two studies and received at least 1 dose of denosumab. Of these, 190 subjects were included in the integrated analysis. Non-inclusion was generally due to inability to re-consent the subject or non-availability of imaging.

The demographic and baseline disease characteristics for the 190 subjects were broadly consistent with those for the entire population enrolled in the two studies. The median time on study was 13.4 months.

Among the 190 subjects, 187, 26, and 176 subjects were evaluable by the modified RECIST, the modified EORTC criteria, and the density/size evaluations, respectively. Subjects could be evaluated according to more than 1 response criteria. Non-target lesions could be evaluated by RECIST, whereas such lesions were not evaluable by density/size criteria. Thus, there were more evaluable subjects by modified RECIST than by density/size evaluations.

The overall objective response rate was 71.6% (95% CI: 64.6 77.9). Median time to response for responders was 2.8 months.

Results for the three individual methodologies were as follows:

7.1.3.2.1. RECIST 1.1 Criteria

The response rate according to RECIST criteria was 25.1% (95% CI: 19.1 32.0). All responses were partial responses. Of the 47 subjects who achieved a response, only 3 subjects subsequently developed progressive disease. Hence median duration of response could not be determined. Median time to response was also not estimable.

Effective treatment of tumours in bone may not be associated with reduction in size of the lesion on CT or MRI, and therefore according to the original RECIST 1.0 criteria, bone lesions were considered unmeasurable, and not suitable for documenting a response to treatment. However, the RECIST 1.1 criteria indicate that lytic bone lesions with identifiable soft tissue components (greater than 10 mm in diameter on CT) may be considered measurable. The sponsor conducted an ad hoc analysis of the subgroup of patients who had a soft tissue lesion, or a lesion with a soft tissue component (n = 49). The response rate in this subgroup using RECIST 1.1 criteria was 57.1% (95% CI: 42.2 71.2). In contrast, the subgroup of patients who had bone lesions with no soft tissue component (n = 126) had a response rate of 15.4% (95% CI: 9.6 23.1).

> Comment: Response rate using RECIST criteria is the only efficacy measure used in this submission that is accepted by regulatory authorities such as the TGA and the EMA. According to RECIST 1.1, only those bone lesions with a soft tissue component are considered measurable. The response rate of 57.1% obtained for this subgroup therefore represents perhaps the best estimate of efficacy available in the submission using conventional efficacy endpoints. A response rate of 57.1%, in a neoplastic disorder for which there is no accepted therapy apart from surgery, is clinically significant.

However, it should be noted that the responses were not confirmed by follow-up scans, the RECIST 1.1 analysis was done retrospectively as was the subgroup analysis of subjects with a soft tissue component.

7.1.3.2.2. EORTC Criteria (18FDG-PET scans)

The response rate according to EORTC criteria was 96.2% (95% CI: 80.4 99.9). Complete response was recorded in 30.8% of subjects and partial response in 65.4%. Of the 25 subjects who achieved a response, none subsequently developed progressive disease and hence median duration of response could not be calculated. Median time to response was 2.7 months.

Comment: These data demonstrate a notable reduction in metabolic activity within GCTB lesions following denosumab treatment. This is most likely due to reduced activity of osteoclast-like giant cells within the tumour.

7.1.3.2.3. Choi Criteria (Size/density)

The response rate according to the Choi criteria was 76.1% (95% CI: 69.1 82.2). All responses were partial responses. Of the 134 subjects who achieved a response, only one subsequently developed progressive disease and hence median duration of response could not be calculated. Median time to response was 3.0 months.

In an ad hoc analysis of all responders for the density/size evaluation, 41.8% of responses were based on both density and size, 30.6% of responses were based on density component alone, and 27.6% of responses were based on size alone. A total of 124 subjects had sufficient imaging data available for assessment of changes in lesion density following denosumab. Treatment was generally associated with an increase in lesion density, which would be consistent with new bone formation.

The secondary endpoints for the integrated analysis included the proportion of subjects with sustained objective responses. This was analysed using data from subjects who had at least two assessments that were at least 4, 8, 12 or 24 weeks apart during treatment. The proportion of subjects with a response remained fairly constant up to 24 weeks. An analysis of sustained tumour control (that is, complete response, partial response or stable disease) showed a similar pattern.

A total of 26 subjects were included in the imaging control group. The overall response rate was 34.6% (95% CI: 17.2 55.7). For RECIST 1.1 the response rate in the control group was 8.0% (95% CI: 1.0 26.0) and for the Choi criteria 37.5% (95% CI: 18.8 59.4). None of the control group subjects had 18FDG-PET scans. All responses were partial responses. Overall a total of 9 subjects achieved some form of response prior to denosumab treatment. Seven of these subjects had had surgery for their GCTB that would explain the apparent responses. If these 7 subjects were excluded, the overall response rate in the imaging control group fell from 34.6% to 10.5%.

7.2. Evaluator's conclusions on clinical efficacy for GCTB

The evidence for efficacy contained in the submission is limited. Trial 20040215 enrolled only 37 subjects. In Trial 20062004, evaluation of efficacy was only a secondary objective, no efficacy hypothesis was tested and assessments of efficacy were not standardised and were made subjectively by the investigators. The integrated analysis of objective tumour response was conducted retrospectively and, apart from RECIST 1.1 criteria, used efficacy endpoints not usually accepted by regulatory authorities. The limitations in the efficacy data probably reflect the rarity of GCTB and the belief at the time the two trials began that bone tumours were not amenable to study with conventional oncology efficacy endpoints. Despite the limitations, the following conclusions can be drawn:

- Treatment with denosumab results in at least 90% clearance of osteoclast-like giant cells from tumours (20040215). These cells are believed to be the causative agents of bone destruction in GCTB.
- In 47.5% of GCTB subjects treated with denosumab, no evidence of tumour cells could be found on biopsy (20062004).
- Treatment with denosumab is associated with a marked reduction in markers of bone resorption such as uNTX and sCTX (20040215) and a notable reduction in metabolic activity in the tumour as assessed by 18FDG-PET scan (integrated analysis).
- Treatment with denosumab is associated with an increase in the density of tumour lesions, which may be reflective of new bone formation (integrated analysis).
- In patients with unresectable disease, treatment with denosumab is associated with a low rate of subjectively assessed disease progression 4% after a median follow up of approximately 13 months (20062004 Cohort 1). In the literature GCTB is described as a rapidly progressive disease.
- In patients with resectable disease, requiring 'immediate' surgery, treatment with denosumab resulted in only 26% of subjects actually proceeding to surgery. The majority of these (16/26 or 62%) underwent surgical procedures that were less extensive than those originally considered necessary (20062004 Cohort 2). This suggests that the drug may be of benefit as neoadjuvant therapy.
- Using conventional RECIST criteria, treatment with denosumab is associated with a 25.1% response rate. In the subgroup of patients with tumours with a soft tissue component (and hence more amenable to accurate tumour measurement) the response rate was 57.1%. These response rates are considered clinically significant.
- Responses to denosumab are sustained with response rates being maintained up to 24 weeks, and only a small proportion of patients developing progressive disease following commencement of treatment.

The drug is intended for the treatment of a serious disease and the available treatments (principally surgery) may be associated with significant morbidity. Overall, despite the limitations of the data, this reviewer concludes that there is sufficient evidence of efficacy to support approval of denosumab for the treatment of GCTB.

8. Clinical safety

8.1. Studies providing evaluable safety data

Both of the submitted studies provided evaluable safety data. The sponsor's summary of clinical safety of the submission presented a pooled analysis of safety data from the two studies and this has been used as the basis for assessing safety in this evaluation report.

8.1.1. Pivotal efficacy studies

In the two efficacy studies, the following safety data were collected:

- General adverse events (AEs). The method of eliciting AEs from subjects was not described.
- The following AEs of particular interest were assessed: hypocalcaemia, osteonecrosis of the jaw, hypersensitivity AEs, infections, malignancies and cardiovascular AEs.
- Laboratory tests. In 20040215 these included full blood count and biochemistry (urea, creatinine, glucose, total protein, albumin, alkaline phosphatase, LDH, bilirubin, AST, ALT,

sodium, potassium, chloride, bicarbonate, calcium, magnesium and phosphate). These were measured at 4-weekly intervals. In 20062004 only creatinine, albumin, calcium, magnesium were measured at 4-weekly intervals.

- Physical examination findings (including vital signs in 20040215).

There were no other studies in the submission.

8.2. Patient exposure

For the pooled analysis, the population consisted of all subjects who received at least one dose of denosumab. A total of 304 subjects were included. Of these, 147 subjects received denosumab for ≥ 1 year, 46 subjects for ≥ 2 years and 15 subjects for ≥ 3 years.

The median number of denosumab doses received was 14.0.

8.3. All adverse events (irrespective of relationship to study treatment)

Overall a total of 85.2% of subjects experienced an AE while on study. The most common adverse events were arthralgia, headache, nausea and back pain.

8.3.1. Treatment-related adverse events (adverse drug reactions)

The incidence of adverse drug reactions (AEs for which the investigators indicated there was a reasonable possibility that they may have been related to denosumab) was 49.0%.

The most common events were fatigue, headache and nausea. Notable other treatment-related events included hypocalcaemia (3.6%) and ONJ (1.3%).

8.3.2. Deaths and other serious adverse events

One death occurred during treatment with denosumab.

- A 32-year old male in Study 20062004 who had a GCTB originating in the femur approximately 12 years previously and had extensive metastatic lung disease prior to enrolment. After approximately 9 months of denosumab treatment he developed respiratory failure and died. The investigator did not consider the event related to denosumab.

Deaths occurring in the safety follow-up phase in the two studies (that is, more than 30 days after completion of denosumab treatment) were as follows:

- 5 deaths in Study 20040215: 2 subjects who died of disease progression, 1 from congestive cardiac failure and 1 due to ventricular tachycardia. These deaths were considered unrelated to denosumab. 1 other death in the follow-up phase was due to the development of a pleomorphic sarcoma, which the investigator considered possibly related to denosumab treatment.
- 3 deaths in Study 20062004: 2 subjects due to progressive disease and 1 due to the development of pleomorphic sarcoma. All were considered unrelated to treatment.

The overall incidence of serious AEs (other than death) was 11.2% and the overall incidence of treatment-related serious AEs was 1.0%. The only individual SAEs reported in more than 1 subject were ONJ and osteomyelitis, both of which occurred in only 2 subjects each.

8.3.3. Discontinuation due to adverse events

The proportion of patients who discontinued denosumab due to AEs was 5.3%. Only 3 subjects (1.0%) discontinued due to AEs that were considered related to denosumab (2 cases of ONJ and 1 case of arthralgia).

8.3.4. Adverse events of special interest

8.3.4.1. Hypocalcaemia

Hypocalcaemia is a known AE with denosumab. The overall incidence of hypocalcaemia was 4.9% (n = 15). There were no serious AEs of hypocalcaemia. In 14 of the 15 subjects the maximum severity was Grade 1 (n = 14) or 2 (n = 1). One subject developed Grade 3 hypocalcaemia.

> Comment: According to the currently approved Australian PI, the incidence of hypocalcaemia in patients with bone metastases treated with denosumab was 9.6%, compared with 5.0% in patients treated with zoledronate. The incidence in GCTB patients appears to be lower than this.

8.3.4.2. Osteonecrosis of the Jaw (ONJ)

ONJ is also a known AE with denosumab. For the submitted studies, adverse events considered as potential ONJ cases were identified using a broad search strategy and sent for adjudication by an external panel of independent experts who used a predefined set of criteria for diagnosis. The overall incidence was 1.3% (n = 4). Of note, 3 of the 4 cases resolved with discontinuation of denosumab.

> Comment: According to the currently approved Australian PI, the incidence of ONJ in patients with bone metastases treated with denosumab is 1.8%, compared with 1.3% in patients treated with zoledronate. The incidence of ONJ in patients with GCTB treated with denosumab is therefore comparable.

8.3.4.3. Hypersensitivity

As a foreign protein, denosumab might be expected to cause hypersensitivity reactions. The overall incidence of AEs suggestive of hypersensitivity events was 9.9% (n = 30). Of these 30 subjects, 29 experienced a maximum severity of Grade 1 and one subject experienced a Grade 2 event. The most common individual events were rash, face oedema and eczema. There were no serious hypersensitivity AEs and none of the events resulted in discontinuation of denosumab.

> Comment: The incidence of hypersensitivity in GCTB subjects appears to be higher than that observed in patients with bone metastases (5.8% with denosumab versus 3.8% with zoledronate).

8.3.4.4. Infection

The current Australian PI documents for Xgeva and Prolia contain statements regarding an increased incidence of skin infections observed with denosumab in controlled clinical trials. In the GCTB trials the overall incidence of infections was 35.9%. There were various types of infection observed. The incidence of serious infections was 3.0% (n = 9) and there were 10 infections of Grade 3 severity and 1 infection of Grade 4 severity.

> Comment: In the absence of a control group it is difficult to draw any conclusions regarding the role of denosumab in causing these infections.

8.3.4.5. Malignancy

Malignant transformation of GCTB can occur. However it is considered to be rare, occurring in less than 1% of giant cell tumours,[11] and mostly in patients who have received radiotherapy. Across the two studies there were 9 subjects who developed bone malignancies (sarcomas or spindle cell tumours in bone). Only one of these subjects had received prior radiotherapy.

[11] Bullough PG, Bansal M. Malignancy in giant cell tumour. In: Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization Classification of Tumours. Pathology and genetics of tumours of soft tissue and bone. 1st ed. Lyon: IARC Press; 2002; p.313.

Comment: The incidence of bone malignancies (9/304 = 3%) appears higher than expected, especially as the duration of follow-up of subjects in the two studies is relatively short (median = 11.2 months). The sponsor provided a brief analysis of these 9 cases. In the sponsor's opinion, 4 were due to malignant transformation of GCTB and the remainder were essentially cases of incorrect GCTB diagnosis at baseline. This reviewer could only locate individual case narratives for 3 of 9 the subjects. It is recommended that the sponsor be asked to provide a more detailed assessment of the risk of malignant transformation of GCTB, including detailed individual case narratives for all subjects.

One subject in Study 20062004 developed thyroid cancer. It was not considered to be related to denosumab.

8.3.4.6. Cardiac disorders

The overall incidence of cardiac AEs was 3.9%. None of the events were serious AEs and none were considered related to denosumab according to the investigators.

8.3.4.7. Vascular disorders

The overall incidence of vascular AEs was 5.9%. None of the events were serious AEs. Eight events of hot flush/flushing were considered related to denosumab according to the investigators.

8.3.4.8. Other AEs

An increased incidence of pancreatitis was observed among denosumab-treated subjects in one study in osteoporosis and this finding is included in the current PI. There were no cases of pancreatitis in the two GCTB studies.

8.4. Laboratory tests

8.4.1. Calcium and Phosphorus

The incidence of Grade 2 hypocalcaemia (using albumin-corrected calcium levels) was 2.6%. There was no Grade 3 or 4 hypocalcaemia detected on laboratory testing. Denosumab treatment was associated with mild transient decreases in average calcium levels.

The incidence of Grade 3 hypophosphatemia was 9.5%. No Grade 4 decreases were observed. Median values decreased with denosumab treatment but remained within the normal range.

8.4.2. Other laboratory tests

Grade 3 or 4 abnormalities were uncommon for other laboratory parameters.

8.4.3. Vital signs

No clinically relevant changes were observed in body weight, blood pressure, pulse, or body temperature in Study 20040215. Vital signs and body weight were measured only at screening in Study 20062004.

8.5. Post-marketing experience

No post-marketing data were included in the submission.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

Denosumab has not previously been associated with hepatic toxicity. All these events were Grade 1 or 2 in severity and none were considered serious. One subject in 20040215 had an isolated Grade 3 elevation of alanine amino transferase.

8.6.2. Haematological toxicity

Only one serious haematological adverse event was reported. This was a case of Grade 3 anaemia in Study 20062004 thought to be due to intra-tumoural bleeding. The investigator considered it unrelated to denosumab.

8.6.3. Serious skin reactions

There were no severe cutaneous adverse reactions reported in the two submitted studies.

8.6.4. Cardiovascular safety

As described under 'Adverse events of special interest' above, no significant cardiovascular toxicity was observed.

8.6.5. Unwanted immunological events - Anti-denosumab antibodies

In Study 20040215, serum samples were to be collected at baseline, Week 25, Week 49, at the end of study visit and at the safety follow up visit. Of the 37 subjects enrolled, 33 had at least one post-baseline test result. All tests were negative for anti-denosumab antibodies.

In Study 20062004, serum samples were tested on day 1, at the end of study and at follow up visits every 6 months. A total of 267 subjects were tested at baseline and all were negative for anti-denosumab binding antibodies. Results were available for only 28 subjects at the end of study and 5 subjects at the 6-month follow-up. All tests were negative.

8.7. Other safety issues

8.7.1. Safety in special populations

Study 20062004 enrolled 10 adolescents. There were no deaths, serious adverse events or discontinuations due to adverse events among these subjects. The submission included a table of the individual AEs experienced by these subjects. The pattern of AEs was broadly consistent with that seen in adults.

8.7.2. Safety related to drug-drug interactions and other interactions

In the summary of clinical safety, the sponsor briefly refers to a recently completed study examining potential interactions between denosumab and midazolam (Study 20101131). The study apparently showed no interaction, however it has not been submitted for evaluation in the current application.

8.8. Evaluator's overall conclusions on clinical safety

The safety of denosumab has previously been documented in large randomised controlled trials in patients with bone metastases (compared to zoledronate) and patients with bone loss (compared to placebo). Safety in GCTB patients has been studied for a much smaller number of subjects (n = 304) and only in open, single-arm trials. The absence of a comparator group in these studies makes interpretation of the data more difficult, especially with regard to assigning causality.

However, the overall safety profile of denosumab observed in these studies appears broadly comparable to that seen in patients with bone metastases. The sponsor should provide further

information on the issue of bone malignancies. Apart from this issue there do not appear to be any new safety concerns arising from use of denosumab in the GCTB population.

Only 5.3% of subjects had to discontinue treatment due to AEs and only 1.0% of subjects had to discontinue due to AEs that were thought to be related to denosumab. Treatment related Grade 3 or 4 AEs only occurred in 5.3% of subjects and treatment-related serious AEs in 1.0% of subjects.

Assuming the issue of bone malignancies can be resolved, and given the serious nature of the disease, this reviewer considers that the safety profile of denosumab in patients with GCTB is acceptable.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The clinical benefits of denosumab in the proposed usage are:

- A reduction in size of GCTB lesions in a significant proportion of patients (approximately 25 to 57%);
- A low incidence of disease progression after commencement of treatment, in a disease that is generally described as rapidly progressive;
- A possible reduction in the extent of surgery (and therefore resultant morbidity) in GCTB subjects proceeding to surgical excision.

9.2. First round assessment of risks

The risks of denosumab in the proposed usage are:

- Osteonecrosis of the jaw (occurring in approximately 1.0% of subjects);
- Hypocalcaemia, occurring in approximately 5% of subjects and generally of mild or moderate severity;
- Hypophosphataemia, occurring in approximately 10% of subjects;
- Hypersensitivity events (generally mild or moderate in severity) occurring in approximately 10% of subjects;

There is an unresolved question regarding a possible increased risk of malignant transformation of GCTB/bone malignancy. The sponsor should address this question with further information.

9.3. First round assessment of benefit-risk balance

Assuming that the question regarding malignant transformation/bone malignancy can be satisfactorily resolved, the benefit-risk balance of denosumab for the treatment of GCTB is considered favourable.

10. First round recommendation regarding authorisation

Assuming that the question regarding malignant transformation/bone malignancy can be satisfactorily resolved, it is recommended that the application should be approved.

11. Clinical questions

11.1. Pharmacokinetics

Not applicable.

11.2. Pharmacodynamics

Not applicable.

11.3. Efficacy

Not applicable.

11.4. Safety

11.4.1. Question one

In Study 20040215 a total of 37 subjects received denosumab. In Study 20062004, 169 and 101 subjects received denosumab in Cohorts 1 and 2 respectively. The total number of subjects who received denosumab was therefore 307. The safety database described in the sponsor's Summary of Clinical Safety only includes 304 subjects. Please provide reasons for the exclusion of the 3 subjects from the safety analysis.

11.4.2. Question two

According the Clinical Summary of Safety there were 9 cases of bone malignancy. The overall incidence of bone malignancy (9/304 or 3%) appears high, especially as the median time on study was only 11.2 months. The clinical evaluator could only locate case narratives for 3 of these 9 subjects.

Please provide more detailed information on all cases of bone malignancies/malignant transformation of GCTB observed during the two submitted studies, including individual case narratives. The following information should be provided for each case if available: age, sex, site of original GCTB, time between original diagnosis of GCTB and trial enrolment, previous treatments for GCTB, duration of denosumab treatment prior to onset of malignancy, any information on the histology of the malignancy and whether the investigator considered the malignancy to be related to denosumab.

There appear to be other cases in the trials (for example, Subject ID [information redacted]) where subjects discontinued or died due to "disease progression". Is the sponsor able to exclude malignant transformation in these subjects?

12. Second round evaluation of clinical data submitted in response to questions

12.1. Question one

The sponsor has provided an explanation for the apparent discrepancy in the total number of subjects in the safety database. Three subjects who were included in Study 20040215 were subsequently enrolled in Cohort 1 of Study 20062004 and were given new subject ID numbers. Therefore, the total number of unique individuals in the safety database was 304. The sponsor's response is acceptable.

12.2. Question two

The sponsor's response to the safety concern relating to bone malignancies is summarised as follows:

Malignant GCTBs can be classified as either primary malignant GCTB (PMGCTB) or secondary malignant GCTB (SMGCTB). PMGCTB is a high-grade sarcoma that arises side-by-side with a benign GCTB. It may be difficult to diagnose because it contains areas of benign GCTB, and a biopsy may not detect the malignant portion. SMGCTB arises at the site of a previously treated GCTB. There is usually an interval of several years between initial diagnosis of GCTB and the development of SMGCTB. It most commonly follows prior radiotherapy treatment, but can occur after surgical treatment.[12] The sponsor also refers to a subtype of SMGCTB called 'sarcomatous transformation' (ST) which is a SMGCTB that does not have a clear residual GCTB lesion or is not associated with multinucleated giant cells. The term 'ST' also appears to refer to lesions that have become malignant at sites not previously treated with radiotherapy or surgery.

The sponsor provided a tabulation of the frequency of malignant GCTB among GCTB patients as reported in the literature. Reported frequencies varied from 1.8% to 18.9%.

> Comment: The observed frequency in the submitted studies was approximately 3% (9 cases in 304 subjects).

The sponsor then presented an analysis of all cases of bone malignancy, or subject discontinuation due to disease progression, reported in the two studies up to a cut-off date of 31 August 2012. A total of 20 such cases had been reported by this date, including the previously reported 9 cases of bone malignancy. By 31 August 2012, a total of 494 subjects had received at least one dose of denosumab in the two studies, with a median time on study of 15.44 months (range 0.1 to 71.4) and a median number of doses of 18.0 (range 1 to 78).

Five of the 20 cases were excluded from the analysis (2 subjects had histologically proven primary sarcoma prior to study enrolment, 2 subjects had no histology to confirm the presence of bone malignancy and 1 subject had disease progression without evidence of malignancy). The calculated incidence of bone malignancy was therefore 3% (15 cases in 494 subjects).

On review of the 15 cases, the sponsor concluded that 10 were cases of PMGCTB (and hence these would have had malignancy prior to denosumab exposure), 3 were cases of SMGCTB and 2 were cases of ST.

> Comment: Details of the individual cases have been reviewed and the sponsor's conclusions appear reasonable. Of the 10 cases assessed as PMGCTB, several had histological or clinical features at baseline, which in retrospect were suggestive of the presence of malignancy (for example atypical features on baseline histology, invasive disease at baseline). Others had unusually rapid disease progression after initial diagnosis. A number of patients had relatively short periods of treatment with denosumab (for example 29, 30, 38 days) prior to malignancy being detected. As described above, diagnosis of PMGCTB may be difficult, as a biopsy may not detect the malignant portion of the tumour. The three cases assessed as SMGCTB all had radiotherapy treatment for GCTB several years previously.

The time between initial diagnosis of GCTB and initial diagnosis of malignancy in the clinical studies was consistent with reports in the literature, suggesting that the administration of denosumab did not precipitate the development of malignancy. The clinical features of the subjects who developed bone malignancies were also consistent with series reported in the literature.

[12] Bertoni F, Bacchini P, Staals EL. Malignancy in giant cell tumor of bone. Cancer. 2003; 97(10): 2520-2529.

As requested, the sponsor reviewed other reports of discontinuation or death due to 'disease progression' for potential evidence of the development of bone malignancy following denosumab therapy. The additional cases identified (n = 6) either had documented bone malignancy prior to denosumab, or did not have histopathological specimens available to confirm the development of malignancy.

The sponsor also argued that malignant transformation of a benign GCTB by denosumab is not biologically plausible. The evidence cited in support of this position included:

- Preclinical data do not provide evidence for a neoplastic effect of the drug;
- In clinical studies in other settings (subjects with bone metastases from solid tumours, osteoporosis) the incidence of new malignancies was comparable in the denosumab and comparator arms.

Comment: The sponsor has adequately addressed the safety question raised. In patients diagnosed with GCTB, the incidence of bone malignancies in the literature varies widely. The incidence observed in the two submitted studies (3%) is within the range reported in the literature. In addition, several of the patients diagnosed with bone malignancy during the two studies probably had the disease prior to denosumab treatment and others had received prior radiotherapy, a known risk factor. It is noted that malignancy is listed as a potential risk in the proposed Risk Management Plan and that therefore the issue will continue to be monitored by the sponsor.

13. Second round benefit-risk assessment

The benefit-risk balance of denosumab for the treatment of GCTB is considered favourable.

14. Second round recommendation regarding authorisation

It is recommended that the application should be approved.

15. References

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