24 July 2014
EMA/CHMP/468730/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

XGEVA

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/002173/II/0016

Note

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

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 6 December 2012 an application for a variation.

This application concerns the following medicinal product:

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

The following variation was requested:

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

The MAH applied for an Extension of indication to add treatment of giant cell tumour of bone in adults or skeletally mature adolescents. As a consequence, it was proposed to update sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and to update the Package Leaflet accordingly. Further, the MAH proposed to update section 4.6 of the SmPC with further guidance regarding pregnancy.

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

Rapporteur: Kristina Dunder

Co-Rapporteur: Jan Mueller-Berghaus

1.2. Steps taken for the assessment

Submission date:	6 December 2012
Start of procedure:	21 December 2012
Rapporteur's preliminary assessment report circulated on:	11 February 2013
PRAC Rapporteur's preliminary RMP assessment report circulated on:	18 February 2013
Rapporteur's updated assessment report circulated on:	15 March 2013
PRAC Rapporteur's updated RMP assessment report circulated on:	4 March 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 March 2013
MAH's responses submitted to the CHMP on:	19 July 2013
PRAC Rapporteur's preliminary RMP response assessment report circulated on:	19 August 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	20 August 2013
PRAC Rapporteur's updated RMP response	26 August 2013

assessment report circulated on:	
Rapporteur's final assessment report on the MAH's responses circulated on:	13 September 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	19 September 2013
MAH's responses submitted to the CHMP on:	21 March 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 April 2014
PRAC Rapporteur's RMP response assessment report circulated on:	21 April 2014
Rapporteur's final assessment report on the MAH's responses circulated on:	16 May 2014
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	22 May 2014
MAH's responses submitted to the CHMP on:	23 June 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	1 July 2014
PRAC Rapporteur's preliminary RMP response assessment report circulated on:	1 July 2014
PRAC Rapporteur's updated RMP response assessment report circulated on:	4 July 2014
CHMP opinion:	24 July 2014

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0211/2012 was not yet completed as some measures were deferred.

2. Scientific discussion

2.1. Introduction

Giant cell tumour of the bone (GCTB) is a rare tumour with an incidence of about 800, 800, 80, and 30 cases are newly diagnosed yearly in the United States (US), European Union (EU), Canada, and Australia, respectively. Diagnosis is made at a mean age of about 33 years with the bulk of patients between 15 and 55 years although younger and elderly patients are diagnosed. The primary tumour is in the majority of cases found in femur or tibia. GCTB is a locally aggressive tumour with at least two distinct cellular components: the neoplastic mononuclear stromal cells and the secondarily activated multinuclear giant cells. Standard of care is surgical resection either by curettage, usually complemented by various local procedures such as freezing and cementing, or by complete resection. Curettage has a high incidence of recurrence and is accompanied by malignant transformation in about 10% of subjects. Pulmonary metastases are rare (1-4%) but can be seen also with this otherwise benign neoplastic disease.

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator nuclear receptor kappa ligand). RANKL is produced by the neoplastic mononuclear stromal cells of GCTB. RANKL binds to and activates RANK on monocyte/macrophage cells that mature to giant cells with osteoclast

function. Denosumab binds to RANKL and thereby prevent binding of RANKL to RANK. It is hypothesised that this mechanism of action will lead to reduced osteolytic activity of GCTB and thereby prevents disease progression. It is also hypothesised that the extent of orthopaedic surgery needed will be reduced.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical Pharmacology aspects

Pharmacokinetics

Basic pharmacokinetics of denosumab have been evaluated in previous marketing authorisation applications (Xgeva and Prolia). New pharmacokinetic data for the current variation application is limited to serum trough levels of denosumab in patients with GCTB in one of the two efficacy/safety trials (study 20040215).

The proposed dosing regimen for denosumab in treatment of GCTB is the same as the previously approved for prevention of skeletal related events in adults with bone metastases from solid tumours, i.e. 120 mg administered as a single subcutaneous injection once every 4 weeks. However, for GCTB the treatment is intended to have a direct effect on the tumour, as opposed to impacting the bone complications associated with metastatic disease, and a more rapid achievement of steady state is desirable at treatment of GCTB. Therefore, additional loading doses of 120 mg are given at Day 8 and Day 15 of treatment. The aim of the pharmacokinetic evaluation in GCTB was primarily to confirm that use of the loading doses is appropriate.

Study 20040215

Study 20040215 was a phase 2, open-label, single-arm study in adult subjects with unresectable or recurrent GCTB. The dosing schedule was 120 mg administered subcutaneously (SC) every 4 weeks (Q4W), with additional 120-mg loading doses administered on study days 8 and 15. One secondary objective of the study was to measure serum trough levels of denosumab. Blood samples for measurement of serum denosumab concentrations were collected at days 1 (baseline), 8, 15 and weeks 5 (day 29), 9, 13, 25, 49 and end of study.

Summary statistics are presented in the table below:

Summary Statistics for Serum Denosumab Trough Concentrations (ng/mL) in Subjects with Giant Cell Tumor Following SC Dosing of Denosumab 120 mg Q4W with Additional Doses on Days 8 and 15

Summary Statistic	Day 1	Day 8	Day 15	Day 29 (Week 5)	Day 57 (Week 9)	Day 85 (Week 13)	Day 169 (Week 25)	Day 337 (Week 49)
N	32	32	28	33	32	26	24	17
Mean	BQL	19000	31600	36400	27500	23400	20100	19000
SD	BQL	24100	27300	20600	17300	12100	9580	9600
Geometric Mean	BQL	14300	25300	31900	24300	20300	17200	15700
%CV	BQL	127	86.4	56.7	63.1	51.9	47.6	50.3
Min	BQL	4430	8840	8260	6860	4840	3620	2780
Median	BQL	14400	25400	29600	23900	22800	23100	22000
Max	2.29	145000	142000	113000	106000	57500	34200	32800

BQL = Below the lower limit of quantification (LLOQ = 0.8 ng/mL)
%CV = Percent coefficient of variation (calculated as: (SD/Mean)*100)

Mean and median trough serum denosumab concentrations at the end of the loading dose (Week 5) were approximately 2-fold those following the first dose (predose on Day 8), indicating that the loading dose regimen increased systemic exposure to target levels as anticipated. Between Weeks 9 and 49, mean and median trough levels varied by less than 22% and 10%, respectively. Thus, exposures remained stable

during the Q4W dosing period, indicating that denosumab pharmacokinetics did not change with time or upon multiple dosing.

Previous data have indicated that in patients with bone metastases from solid tumours (not receiving additional loading doses), steady-state denosumab levels are reached in approximately 4 to 6 months with 120 mg Q4W dosing. The Company therefore considers the 120 mg Q4W dose regimen, with120-mg loading doses on days 8 and 15 of treatment, to be the appropriate dosing regimen for patients with GCTB.

Safety of the use of loading doses has been assessed in the two pivotal studies in GCTB. Additional pharmacokinetic data is not considered necessary for approval of this new indication.

Special populations

Previously, denosumab has not been indicated in children and there is no pharmacokinetic data in children. The new indication GCTB is proposed to include skeletally mature adolescents. In study 20062004, a total of 10 patients in the age range ≥12 years to <18 years were included, but pharmacokinetics was not evaluated in this study.

Pharmacokinetics of an antibody is not expected to differ relevantly between skeletally mature adolescents and adults. The lack of pharmacokinetic data in adolescents is therefore acceptable.

2.4. Clinical Efficacy aspects

Introduction

Denosumab treatment of giant cell tumour of the bone was studied in two clinical trials (Studies 20040215 and 20062004) using a fixed dose regimen based on experience from clinical use of denosumab for preventing cancer related skeletally related events (SRE).

The dosing regimen was 120 mg denosumab administered SC Q4W, with 120-mg loading doses on days 8 and 15 of treatment. The 120 mg Q4W maintainance dose is the same as the approved for denosumab for prevention of SREs in patients with bone metastases from solid tumors while the use of loading doses of denosumab is used for the first time in the treatment of GCTB, the intention being a rapid attainment of steady-state concentrations. The dose was selected based on earlier clinical experience in cancer patients treated for SRE and a theoretical consideration on the degree of receptor binding needed for a clinically maximal effect. No clinical dose-finding study for denosumab in GCTB was done. Patients were treated until progression.

Denosumab has been investigated in two clinical studies both open, single-arm studies. Study 20040215, is completed. Study 20062004 is ongoing data are provided from a planned interim analysis including efficacy data up to 25 March 2011 and a safety update including data up to August 31 2012.

A pooled analysis of radiological data from studies 20040215 and 20062004 to assess efficacy was carried out.

In response to the second RSI a summary of updated efficacy and safety results from study 20062004 with 507 enrolled patients and a data “snap-shot”, cut-off date 30 Aug 2013 was provided.

Clinical Studies in the GCTB Development Program

Title: An Open-Label, Multicenter, Phase 2 Safety and Efficacy Study of Denosumab (AMG 162) in Subjects With Recurrent or Unresectable Giant Cell Tumor (GCT) of Bone		
Study identifier	20042015	
Design	Open-label, phase 2 single arm study of denosumab enrolled subjects with recurrent or unresectable giant cell tumor of bone. All eligible subjects received 120 mg denosumab subcutaneously every 4 weeks (Q4W) starting with study day 1, with additional doses administered on study days 8 and 15, until one of the following: complete tumor resection; disease progression; investigator's or Amgen's recommendation for discontinuation; the subject's decision to discontinue; administration of bisphosphonates, calcitonin, or interferon alfa-2a; or rollover to Study 20062004.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	Until complete resection, disease progression, withdrawal; treatment with proscribed therapies; or roll over to Study 20062004. After the last dose of denosumab, safety data were collected every 6 months for up to 2 years. <time> <not applicable> <time> <not applicable>
Hypothesis	Denosumab will cause apoptosis of giant cells within the tumor(s) and inhibit further osteolysis to delay progression of disease, resulting in a response rate of greater than 11%. A true response rate of at least 30% is anticipated. If the lower bound of the 2-sided 95% confidence interval of the observed response rate is above 11%, the null hypothesis of the response rate ≤ 11% will be rejected.	
Treatment groups	Single arm, international, multi-center, openlabel study in subjects with recurrent or unresectable giant cell tumor of bone	Thirty-seven subjects enrolled in this study, and all subjects received at least one dose of denosumab. All eligible subjects received 120 mg denosumab subcutaneously (SC) every 4 weeks (Q4W) starting with study day 1, with additional doses on study days 8 and 15, until complete tumor resection; disease progression; investigator's or Amgen's recommendation for discontinuation; the subject's decision to discontinue; administration of isphosphonates, calcitonin, or interferon alfa-2a; or rollover to study 20062004.

Study No.	Study Objectives	Study Design and Type of Control	Regions	No. Subjects Enrolled (No. Subjects Exposed)	Key Entry Criteria	Duration of Study (including follow-up)	Study Status; Type of Report
20040215	Efficacy (elimination of giant cells, lack of progression), pharmacodynamics, PK, safety, antibody response	Phase 2, open-label, single-arm	United States, Australia, France	37 (37 denosumab SC 120 mg Q4W with 120-mg loading doses on days 8 and 15[a])	Men or women with histologically confirmed GCTB Age: ≥ 18 yr	Until complete tumor resection; progression; withdrawal; treatment with bisphosphonates, calcitonin, or interferon alfa-2a; or rollover to Study 20062004	Complete Full (primary) Complete Abbreviated (final)

Title: An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Tumor of Bone			
Study identifier	20062004		
Design	Phase 2, international, multi-center, open-label study in subjects with GCTB, receiving 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		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		4 years of enrollment plus 5 years of treatment and follow-up. <time> <not applicable> <time> <not applicable>
Hypothesis	The study tests the hypothesis that denosumab, a RANKL inhibitor, can inhibit ongoing osteolysis and progression of GCTB		
Treatment groups	Cohort #1:		263 enrolled subjects with surgically unsalvageable (unresectable) disease (eg, sacral or spinal GCTB, or multiple lesions including pulmonary metastases)
	Cohort #2:		Cohort 2: 232 enrolled subjects with surgically salvageable (resectable) disease whose planned on-study surgery was associated with severe morbidity (eg, joint resection, limb amputation, or hemipelvectomy). Treatment with denosumab continued for 6 doses after complete tumor resection per protocol.
	Cohort #3:		Cohort 3: 12 enrolled subjects with recurrent or unresectable GCTB who rolled over from Study 20040215 for continuation of denosumab treatment
Endpoints and definitions	Primary endpoint	<label>	Safety profile of denosumab characterized in terms of the type, frequency, and severity of adverse events and laboratory abnormalities for each cohort.
	Secondary endpoint	<label>	Time to disease progression in cohort 1
	Secondary endpoint	<label>	Proportion of subjects without any surgery at month 6 for cohort 2
Database lock	30 August 2013		
Results and analysis			
Analysis description	**Primary analysis**		
Note	Primary analysis is safety profile of denosumab characterized in terms of the type, frequency, and severity of adverse events and laboratory abnormalities for each cohort. Therefore, the results are not included in this table.		

2.4.1. Study 200401215

2.4.1.1. Study Participants and inclusion criteria

Study 20040215 was an open-label, single-arm, phase 2 study to evaluate the tumour response to treatment with denosumab, measured by histopathology (at least 90% elimination of giant cells relative to baseline, or complete elimination of giant cells in cases where giant cells represented < 5% of tumour cells) or radiography (lack of progression of the target lesion at week 25 as determined by the investigator), and the safety of denosumab in subjects with GCTB.

To be included patients needed to have histologically confirmed GCTB, measurable (≥10 mm in the greatest dimension) recurrent GCTB confirmed by radiology, or unresectable GCTB.

Table 8-4. Baseline Disease Characteristics (Enrolled Subjects, Primary Analysis)

	Denosumab 120 mg Q4W (N = 37)
GCT disease type - n (%)	
Primary unresectable	13 (35)
Recurrent unresectable	18 (49)
Recurrent resectable	6 (16)
ECOG performance status - n (%)	
0	13 (35)
1	21 (57)
2	1 (3)
Missing	2 (5)
Percent of apoptotic bodies in tumor on pre-treatment biopsy	
n	35
Mean	2.3
SD	4.9
Median	0.1
Q1, Q3	0.0, 1.0
Min, Max	0, 20
Percent of giant cells in tumor on pre-treatment biopsy	
n	35
Mean	28.7
SD	16.1
Median	30.0
Q1, Q3	20.0, 40.0
Min, Max	0, 60

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N = Number of subjects enrolled
*Other includes 9 subjects with pulmonary disease, 1 subject with dorsal vertebrae and 1 subject with pelvic region.

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Output: t14-02_004_base_dis_char.rtf (Date Generated: 17JUL2008:10:10:40) Source Data: adam.aslbase, adam.als, adam.ahist
Table appears in Section 14 as Table 14-2.4

The majority of the patients had unresectable disease.

2.4.1.2. Efficacy endpoints

The major efficacy endpoints in Study 20040215 were:

- Primary
  - Response rate with response defined as: 90% elimination of giant cells or if giant cells represent less than 5% of tumour, complete elimination of giant cells, or
  - Lack of investigator-assessed progression at Week 25 compared with baseline
- Exploratory
  - Investigator-assessed clinical benefit, bone calcification, bone repair
  - Changes in bone turnover markers (sCTX, uNTX, BSAP, TRAP-5b, OC) (partly secondary objective)

The study protocol was amended on 31 July 2007 after the first unplanned interim analysis. Due to feedback from investigators and observations made during this interim analysis, the definition of response was redefined from elimination of giant cells, or doubling of the percentage of apoptotic giant cells, relative to baseline to as above criteria of radiologic progression was changed from 25% increase volumetric measurement to 20% change in longest dimension. The rationale for the change was “the pathologists, who were blinded to specimen identification, would search an entire sample for a single osteoclast, therefore, the original criteria could never be met” and “study centres reported that volume measurements were difficult to obtain”.

Furthermore PET imaging that was optional in the original protocol was made a requirement (most study centres were already providing PET scans). Also a re-treatment option was added to allow subjects to continue receiving denosumab after disease recurrence following a response to denosumab treatment. It was anticipated that only a small number of subjects would require re-treatment and therefore, should not impact the results or conclusions.

The safety follow-up period was shortened from 3 years to 2 years because 2 years was considered to be sufficient and consistent with other denosumab clinical studies.

2.4.1.3. Statistical methods

The study had a single treatment arm and no control group. A total of 37 subjects with recurrent or un-resectable GCTB enrolled in the study. Efficacy results are reported as of the primary analysis with a data cut-off date of 07 April 2008. No formal statistical hypothesis testing was made.

2.4.1.4. Results

Participant flow

The subject disposition in study 20040215 is summarised in the table below.

Table 8-1. Subject Disposition as of the Data Cut-off Date (07 April 2008)

	Denosumab 120 mg Q4W	
	n	(%)
Enrolled	37	
Received ≥ 1 dose of denosumab	37	(100.0)
Subjects still on-study	26	(70.3)
Denosumab treatment ongoing	23[a]	(62.2)
Completed denosumab because of complete resection or anticipation of a complete resection	8[b]	(21.6)
Discontinued denosumab for reasons other than complete resection	6[a]	(16.2)
Disease progression	2	(5.4)
Administrative decision	1	(2.7)
Adverse event	1	(2.7)
Consent withdrawn	1	(2.7)
Requirement for alternative therapy	1	(2.7)

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Percentages based on number of subjects enrolled.

[a] Subject 215108002 incorrectly reported to have discontinued denosumab for reason "other," but still receiving denosumab as of the data cut-off date (Listing 1-2)

[b] Subject 215108005 completed denosumab before the data cut-off date in anticipation of complete resection that occurred after the data cut-off date (data on file at Amgen)

Sources: Tables 14-1.2 and 14-1.3, Listing 1-2, and data on file at Amgen.

The subject discontinuing due to administrative reason stopped treatment due to complete response and was transferred to study 20062004 for follow-up.

Summary of Main Efficacy Results

A total of 37 subjects with primary unresectable (n=13), recurrent unresectable (n=18) and recurrent resectable (n=6) enrolled in the study, and all subjects received at least 1 dose of denosumab. Efficacy results are reported with a cut-off date of 07 April 2008. Of the 35 subjects included in the efficacy analysis set, 20 subjects had sufficient histology data while for 15 subjects the response criteria were based on radiology data alone.

Of those 35 in the efficacy analysis, 30 met the efficacy criteria, 20 of 20 subjects with sufficient histology, and 10 of 15 subjects with only radiology data .Radiographic measurements of changes in longest lesion dimensions were generally consistent with the primary used volumetric endpoint analysis.

The response rate was similar regardless of age (above or below median; 84 and 88% respectively) or prior bisphosphonate use (prior/ no prior; 80 and 87% respectively.

Response as defined by the primary endpoint (at least 90% elimination of giant cells relative to baseline, or complete elimination of giant cells if giant cells < 5% of tumour cells, or lack of progression at week 25 by radiography if histopathology not available) was 86% with a considerable difference whether based on

histology (100%) or radiology (66.7%). The radiological response rate in subjects with histological data (10/13) is comparable with those without histological data (9/12).

The quantitative histological response indicate the presence of giant cells, which are not the neoplastic cells but rather normal cells that are recruited by RANKL excreted by neoplastic stromal cells and "used" by the neoplastic cells to create expansion space. There is support for the reduction in giant cell activity by both glucose utilisation and reduced levels of different bone metabolism markers. There is also a reduction of the neoplastic stromal cell area relative to the total tumour area compared to baseline and an increase in the extracellular matrix composed of collagen and osteoid and woven bone.

Summary of percent reduction in the fraction of mononuclear tumour stromal component in GCTB

(Study 20040215 Subjects with Evaluable Histopathology Result)

	Tumor Area (mm^2)		Tumor Stroma Area (mm^2)		Baseline Giant Cell Area (mm^2)	On-study Acellular Matrix (mm^2)	Fraction of GCTB Tumor Area Represented by Mononuclear Tumor Cell Stroma		
	Baseline	On-Study	Baseline	On-Study			Baseline	On-Study	%Reduction
n	20	20	20	20	20	20	20	20	20
mean	21.344	39.004	20.009	13.238	1.336	25.766	93.897	24.745	69.152
SD	25.744	58.56	24.124	38.703	2.449	45.985	6.685	28.37	28.803
median	10.805	10.87	8.625	1.33	0.33	9.24	94.31	11.755	84.23
Q1	3.635	3.525	3.305	0.475	0.055	2.64	91.57	3.66	53.535
Q3	26.47	49.61	24.73	4.645	1.565	38.75	98.965	37.78	91.03
Min	1.24	0.79	1.21	0.01	0.02	0.19	71.5	0.79	1.47
Max	81.09	209.99	79.69	172.71	10.03	205.89	99.92	92.55	95.41
p-value[a]									<.0001

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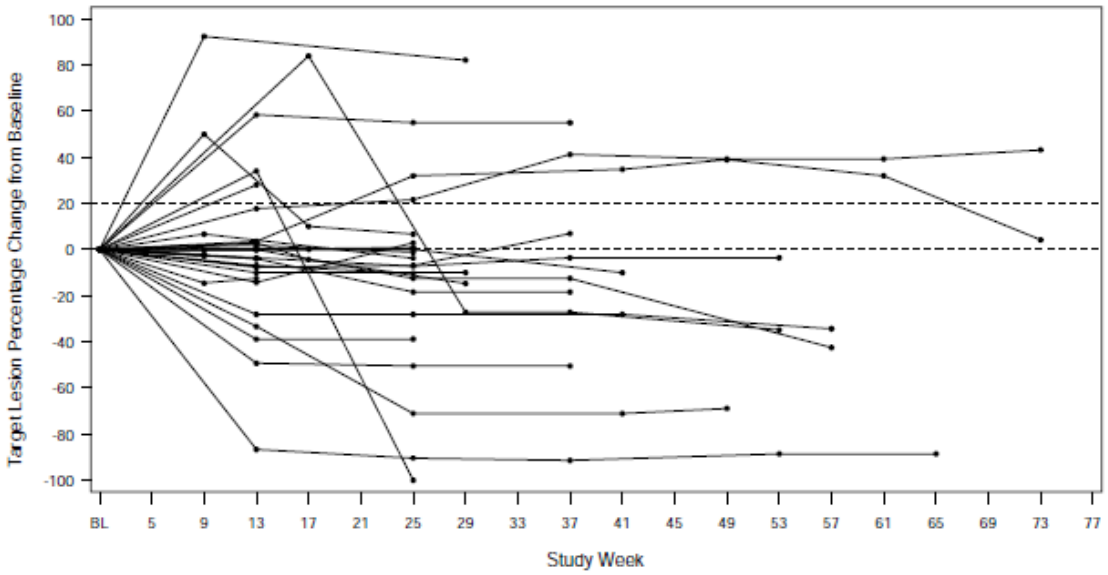
The baseline acellular matrix and on-study giant cell tumor areas were both near 0.
Mean tumor area for on-study samples is larger because some subjects underwent complete resection, resulting in a larger tissue sample provided for analysis. At baseline, most tumor samples provided for analysis were needle biopsies or surgical biopsies.
[a] Based on paired t-test comparison of % of GCTB tumor area represented by mononuclear tumor cell stroma at baseline and on-study

Table 1 OC5

The longest dimension of the target lesion decreased from baseline or did not change in 29 out of 37 subjects (83%). Eight subjects had increases in the longest dimension ≥ 20% from baseline; of these subjects, 3 had longest dimensions that remained ≥ 20% above baseline at the time points assessed.

Figure 9-6. Target Lesion Percent Change of Longest Dimension From Baseline Line Plot by Visit (Safety Analysis Set)



Note: one record (percent change from baseline=882%) is out of the graph range.
Detail information: subject ID=215201006, the longest dimension of the target lesion at week 13 was 56mm, and the longest dimension of the target lesion at baseline was 5.7mm.

Program: /stat/amg162/therapeutic/20040215/analyses/final/adhocs/program/g_ah_lmc_les
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Source: /stat/amg162/therapeutic/20040215/analyses/final/sasdata/adam/adt.sas7bdat

Percentage changes from baseline in the longest dimensions of target lesions and non-target lesions were highly variable in subjects who had multiple lesions and who were unable to undergo palliative resection.

Biomarkers:

Urinary NTX/Cr and CTX were consistently suppressed (approximately 80% below baseline) from week 5 onward. Other bone turnover markers (BSAP, osteocalcin, and TRAP-5b) also decreased from baseline and remained below baseline throughout the study.

All mean values of the markers at baseline were in the range of the reference values except TRAP-5b that was increased at baseline.

Clinical benefit, increased bone calcification and bone repair at the lesion were observed with denosumab treatment (see table below). (NB clinical benefit is the investigator ticking Y with a free written motivation to the column entry “clinical benefit”, examples include positive evaluation of radiological examination data as well pain reduction and improved mobility).

Table 14-4.7.1. Bone Lesion Evaluation
(Efficacy Analysis Set)
(20040215 Primary Analysis)

	Clinical Benefit		Calcification		Bone Repair	
	n/N1 (%)	(95% CI)	n/N1 (%)	(95% CI)	n/N1 (%)	(95% CI)
Baseline						
Denosumab 120 mg Q4W (N = 31)	-	-	4/31 (12.9)	(3.6, 29.8)	0/31 (0.0)	(0.0, 11.2)
Post-dose						
Denosumab 120 mg Q4W (N = 31)	26/31 (83.9)	(66.3, 94.5)	6/31 (19.4)	(7.5, 37.5)	9/31 (29.0)	(14.2, 48.0)

N = Number of subjects with non-missing baseline and ≥ 1 non-missing post baseline evaluation and in the efficacy analysis set

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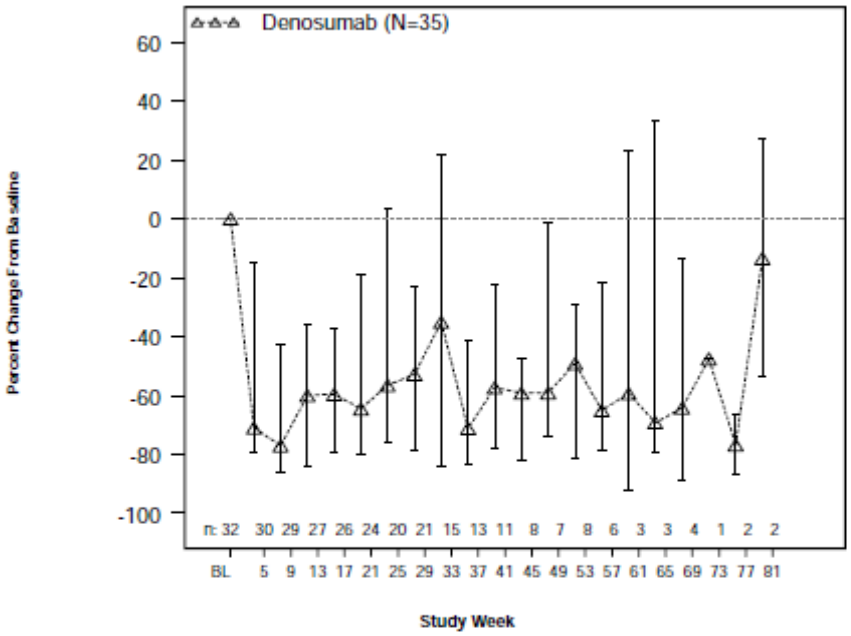
Output: t14-04_007_001_bone_les_eff.rtf (Date Generated: 17JUL2008:10:10:50) Source Data: adam.atmrev, adam.aslinfo

Figure 9-1. uNTX Corrected by Creatinine Percent Change from Baseline Visit Median and Interquartiles (Efficacy Analysis Set)



N = Number of subjects who (1) are on study for >= 28 days after the first dose of denosumab; and (2) have at least one baseline tissue and at least one post-dose tissue between week 5 and week 25, or have at least one baseline radiograph and at least one post-dose radiograph between week 5 and week 25.

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Output: g14-06_004_001_untx_pchg_eff.cgm (Date Generated: 29JAN2009:15:59:31)
Source Data: adam.albbnsp, adam.aslinl

Figure appears in Section 14 as Figure 14-6.4.1.

Obviously the effects on bone metabolism markers are not clearly due to effects on the tumours as the levels may well be determined by the activity in the remaining and healthy skeletal tissue.

2.4.2. Study 20062004

2.4.2.1. Study Participants and inclusion criteria

Study 20062004 is an ongoing phase 2, open-label, single-arm study in adult and skeletally mature adolescent subjects with GCTB, designed to primarily evaluate the safety of denosumab, as well as tumour response as determined by the investigator. Three cohorts have been enrolled:

Cohort 1: subjects with surgically unsalvageable (unresectable) disease (e.g, sacral or spinal GCTB, or multiple lesions including pulmonary metastases).

Cohort 2: subjects with surgically salvageable (resectable) disease whose planned on-study surgery was associated with severe morbidity (eg, joint resection, limb amputation, or hemipelvectomy).

Cohort 3: subjects who rolled over from Study 20040215.

No patients with primary resectable disease were included.

Patients were treated with denosumab Q4W (with an initial loading dose on day 8 and 15) until progression or complete resection. After complete resection 6 further doses were given.

2.4.2.2. Efficacy endpoints

The major efficacy endpoints in Study 20062004 were:

- Secondary
  - Time to disease progression (Cohort 1)
  - Proportion of subjects without any surgery at month 6 (Cohort 2)
- Exploratory
  - Investigator-assessed clinical benefit
  - Time to disease progression (All subjects)
  - Change in BPI-SF “worst” pain score from baseline
  - Change in analgesic score from baseline
  - Proportion of subjects able to undergo a less morbid surgical procedure compared to planned surgical procedure at baseline (Cohort 2)

A copy of imaging reports and all available pathology reports within a year before enrollment as performed as per standard of care were to be provided. During the study pathology samples, pathology reports and imaging reports were to be submitted if performed as standard of care. Pathology samples and pathology reports were to be provided at end of study to a central imaging vendor for evaluation of disease response as per amendment 5 (05 May 2011).

Imaging reports (PET, CT, PET/CT, MRI or X-ray were included only if as performed as local standard of care and at intervals as per local standard of care.. Efficacy assessments were based upon lesions which were selected by the investigator using the criteria that target lesions should be both measurable and accessible for biopsy. All tumour assessments were based on investigator´s evaluation.

As the primary objective of study 20062004 was to evaluate the safety of denosumab efficacy was not up-front systematically evaluated.

A pooled radiological analysis was performed.

2.4.2.3. Statistical methods

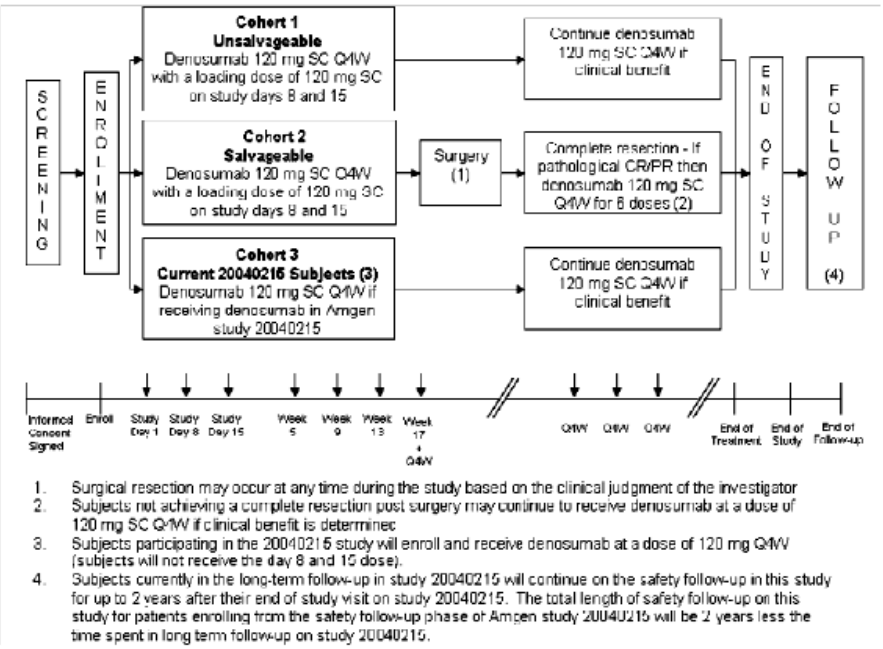
The study 20062004 had a single treatment arm and no control group.

As of 25 March 2011 (date of pre-planned interim analysis 3), 286 subjects were enrolled. In Cohort 1 (unresectable), n = 170, in Cohort 2 (resectable) n = 101 and in Cohort 3 (i.e. roll-over from study 20040215) n = 11. Four subjects from Study 20040215 were enrolled directly into the safety follow up phase; these subjects were not included in the treatment phase analysis presented.

A safety up-date was performed for data up to August 31 2012 and included 251 subjects in Cohort 1, 209 subjects in Cohort 2 and 12 subjects in Cohort 3.

In response to the second RSI a summary of updated efficacy and safety results from study 20062004 with 507 enrolled patients at a data "snap-shot" cut-off date 30 Aug 2013 was provided. (See below.)

No formal statistical hypothesis testing was made.



1. Surgical resection may occur at any time during the study based on the clinical judgment of the investigator
2. Subjects not achieving a complete resection post surgery may continue to receive denosumab at a dose of 120 mg SC Q4W if clinical benefit is determined
3. Subjects participating in the 20040215 study will enroll and receive denosumab at a dose of 120 mg Q4W (subjects will not receive the day 8 and 15 dose).
4. Subjects currently in the long-term follow-up in study 20040215 will continue on the safety follow-up in this study for up to 2 years after their end of study visit on study 20040215. The total length of safety follow-up on this study for patients enrolling from the safety follow-up phase of Amgen study 20040215 will be 2 years less the time spent in long term follow-up on study 20040215.

2.4.2.4. Results

Participant flow

Table 8-3. Baseline Demographics (Enrolled Subjects) (20062004 Interim Analysis 3)

	Cohort 1 (N = 170)	Cohort 2 (N = 101)	Cohort 3 (N = 11)	All (N = 282)
Sex - n (%)				
Female	102 (60.0)	57 (56.4)	5 (45.5)	164 (58.2)
Male	68 (40.0)	44 (43.6)	6 (54.5)	118 (41.8)
Ethnic group / race - n (%)				
White or Caucasian	135 (79.4)	85 (84.2)	10 (90.9)	230 (81.6)
Black or African American	10 (5.9)	6 (5.9)	0 (0.0)	16 (5.7)
Hispanic or Latino	11 (6.5)	3 (3.0)	1 (9.1)	15 (5.3)
Asian	8 (4.7)	4 (4.0)	0 (0.0)	12 (4.3)
American Indian or Alaska Native	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.4)
Other	5 (2.9)	2 (2.0)	0 (0.0)	7 (2.5)
Age (years)				
n	170	101	11	282
Mean (SD)	36.1 (14.3)	34.8 (11.4)	34.7 (14.9)	35.5 (13.3)
Median	33.0	34.0	30.0	33.0
Q1, Q3	26.0, 45.0	25.0, 43.0	24.0, 44.0	25.0, 44.0
Min, Max	13, 83	16, 69	22, 63	13, 83
Age group - n (%)				
< 18 Years	8 (4.7)	2 (2.0)	0 (0.0)	10 (3.5)
18 - 40 Years	106 (62.4)	67 (66.3)	8 (72.7)	181 (64.2)
41 - 60 Years	44 (25.9)	31 (30.7)	1 (9.1)	76 (27.0)
> 60 Years	12 (7.1)	1 (1.0)	2 (18.2)	15 (5.3)
Weight (kg)				
n	165	97	10	272
Mean (SD)	75.76 (21.30)	74.72 (17.72)	78.38 (21.36)	75.48 (20.04)
Median	70.00	74.00	67.50	72.37
Q1, Q3	58.23, 87.73	60.00, 87.00	63.64, 90.00	59.00, 87.87
Min, Max	46.0, 155.4	40.5, 130.0	58.5, 123.6	40.5, 155.4

N = Number of subjects enrolled
Four subjects from study 20040215 were directly enrolled into the safety follow-up phase in study 20062004 and were excluded from the treatment phase analysis.
Source: Modified from Table 14-2.1.1 and Table 14-2.1.2

Most of the subjects had not previously received biphoshonates (3% oral and 15% iv).

Table 8-4. Baseline Disease Characteristics (Enrolled Subjects) (20062004 Interim Analysis 3)

	Cohort 1 (N = 170)	Cohort 2 (N = 101)	Cohort 3 (N = 11)	All (N = 282)
GCT disease type - n (%)				
Primary resectable	0 (0.0)	63 (62.4)	0 (0.0)	63 (22.3)
Primary unresectable	48 (28.2)	0 (0.0)	2 (18.2)	50 (17.7)
Recurrent resectable	0 (0.0)	38 (37.6)	0 (0.0)	38 (13.5)
Recurrent unresectable	122 (71.8)	0 (0.0)	9 (81.8)	131 (46.5)
Longest dimension of target lesion (mm)				
n	170	101	11	282
Mean	64.8	70.6	38.0	65.8
SD	48.5	38.9	28.5	45.0
Median	53.5	64.0	29.0	58.5
Q1, Q3	28.0, 93.0	45.0, 86.0	14.0, 67.0	33.0, 89.0
Min, Max	7, 308	7, 221	3, 88	3, 308
Location of target lesion - n (%)				
Sacrum	42 (24.7)	4 (4.0)	2 (18.2)	48 (17.0)
Lung	42 (24.7)	2 (2.0)	3 (27.3)	47 (16.7)
Tibia	9 (5.3)	34 (33.7)	0 (0.0)	43 (15.2)
Pelvic bone	23 (13.5)	12 (11.9)	0 (0.0)	35 (12.4)
Femur	3 (1.8)	21 (20.8)	0 (0.0)	24 (8.5)
Radius	6 (3.5)	10 (9.9)	0 (0.0)	16 (5.7)
Other	8 (4.7)	6 (5.9)	1 (9.1)	15 (5.3)
Thoracic vertebrae	9 (5.3)	2 (2.0)	2 (18.2)	13 (4.6)
Cervical vertebrae	11 (6.5)	0 (0.0)	0 (0.0)	11 (3.9)
Humerus	3 (1.8)	6 (5.9)	0 (0.0)	9 (3.2)
Skull	7 (4.1)	0 (0.0)	0 (0.0)	7 (2.5)
Fibula	1 (0.6)	2 (2.0)	1 (9.1)	4 (1.4)
Lumbar vertebrae	1 (0.6)	1 (1.0)	1 (9.1)	3 (1.1)
Metacarpus	2 (1.2)	1 (1.0)	0 (0.0)	3 (1.1)
Pelvis (soft tissue only)	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.7)
Ulna	0 (0.0)	0 (0.0)	1 (9.1)	1 (0.4)
Patella/knee	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)

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N = Number of subjects enrolled
Four subjects from study 20040215 were directly enrolled into the safety follow up phase in study 20062004 and were excluded from the treatment phase analysis.
Target lesion was measured through imaging procedures including X-ray, CT, MRI etc.
[a] Not expected or available for Cohort 3 subjects

Source: Modified from Table 14-2.1.4

The majority of patients had been treated previously (see below).

Table 13. Recurrent/Disease Progression History Prior to Enrollment (Study 20040215 and Study 20062004 Interim Analysis 3)

	Study 20040215 (N = 37)	Study 20062004 Cohort 1 (N = 167)	Study 20062004 Cohort 2 (N = 101)	Study 20062004 Cohorts 1 and 2 (N = 268)	Overall (N = 305)
Time since initial diagnosis at enrollment (months)[a]					
n (%)	22 (59.5)	150 (89.8)	101 (100.0)	251 (93.7)	273 (89.5)
Mean	20.0	38.6	13.0	28.3	27.6
SD	34.0	57.5	36.0	51.4	50.3
Median	2.8	17.7	2.5	10.0	9.4
Q1, Q3	0.4, 19.9	5.7, 46.2	1.2, 11.3	2.1, 31.3	1.6, 30.6
Min, Max	0, 130	0, 413	0, 335	0, 413	0, 413

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N = number of enrolled subjects
N1=number of subjects with corresponding recurrence
Subjects who were originally enrolled in 20040215 and rolled over or retreated in 20062004 are included only for 20040215
Percentages based on N or N1
Recurrence or disease progression events were counted as separate events if they were >= 30 days apart.
[a]Diagnosis date was used for Cohort 2 and intervention start date was used for Study 20040215 to derive time from initial diagnosis to enrollment.

Table 12. Number of Interventions Prior to Enrollment
(Enrolled Subjects in Study 20040215 And 20062004 Interim Analysis 3)

	Study 20040215 (N = 37)	Study 20062004 Cohort 1 (N = 167)	Study 20062004 Cohort 2 (N = 101)	Study 20062004 Cohorts 1 and 2 (N = 268)	Overall (N = 305)
Any Intervention - N1	31	167	98	265	296
12 months prior to enrollment - n(%)					
1 intervention	10 (32.3)	40 (24.0)	82 (83.7)	122 (46.0)	132 (44.6)
2 interventions	15 (48.4)	67 (40.1)	11 (11.2)	78 (29.4)	93 (31.4)
3 interventions	4 (12.9)	31 (18.6)	1 (1.0)	32 (12.1)	36 (12.2)
4 interventions	1 (3.2)	11 (6.6)	1 (1.0)	12 (4.5)	13 (4.4)
>=5 interventions	1 (3.2)	13 (7.8)	0 (0.0)	13 (4.9)	14 (4.7)
Any time prior to enrollment - n(%)					
1 intervention	2 (6.5)	15 (9.0)	63 (64.3)	78 (29.4)	80 (27.0)
2 interventions	13 (41.9)	31 (18.6)	16 (16.3)	47 (17.7)	60 (20.3)
3 interventions	8 (25.8)	24 (14.4)	10 (10.2)	34 (12.8)	42 (14.2)
4 interventions	5 (16.1)	32 (19.2)	4 (4.1)	36 (13.6)	41 (13.9)
>=5 interventions	3 (9.7)	65 (38.9)	5 (5.1)	70 (26.4)	73 (24.7)

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N = number of enrolled subjects
N1=number of subjects with corresponding interventions
Percentages based on N1
Subjects who were originally enrolled in 20040215 and rolled over or retreated in 20062004 are included only for 20040215

Table 14-2.1.5. Prior Cancer Treatment and Bisphosphonate Use
(Enrolled Subjects)
(20062004 Interim Analysis 3)

	Cohort 1 (N = 170)	Cohort 2 (N = 101)	Cohort 3 (N = 11)	All (N = 282)
Chemotherapy				
Yes	24 (14.1)	2 (2.0)	0 (0.0)	26 (9.2)
No	146 (85.9)	99 (98.0)	11 (100.0)	256 (90.8)
Radiation				
Yes	42 (24.7)	6 (5.9)	0 (0.0)	48 (17.0)
No	128 (75.3)	95 (94.1)	11 (100.0)	234 (83.0)
Surgery				
Yes	130 (76.5)	44 (43.6)	0 (0.0)	174 (61.7)
No	40 (23.5)	57 (56.4)	0 (0.0)	97 (34.4)
Unknown	0 (0.0)	0 (0.0)	11 (100.0)	11 (3.9)
Bisphosphonate (oral)				
Yes	7 (4.1)	1 (1.0)	0 (0.0)	8 (2.8)
No	163 (95.9)	100 (99.0)	11 (100.0)	274 (97.2)
Bisphosphonate (IV)				
Yes	32 (18.8)	10 (9.9)	0 (0.0)	42 (14.9)
No	138 (81.2)	91 (90.1)	11 (100.0)	240 (85.1)

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N = Number of subjects enrolled
Four subjects from study 20040215 were directly enrolled into the safety follow up phase in study 20062004 and were excluded from the treatment phase analysis.

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At the interims analysis 241 enrolled patients were continuing in the study, 41 had discontinued study (reasons see below).

Ten skeletally mature adolscent subjects were included (two had discontinued treatment and study, one due to loss to follow up and one due to pregnancy).

Table 8-2. Reasons for Study Discontinuation and Denosumab Discontinuation (Enrolled Subjects) (20062004 Interim Analysis 3)

	Cohort 1 n (%)	Cohort 2 n (%)	Cohort 3 n (%)	All n (%)
Enrolled	170	101	11	282
Study Participation Status				
Ongoing	149 (87.6)	81 (80.2)	11 (100.0)	241 (85.5)
Discontinued study	21 (12.4)	20 (19.8)	0 (0.0)	41 (14.5)
Protocol-specified criteria [a]	2 (1.2)	10 (9.9)	0 (0.0)	12 (4.3)
Administrative decision	4 (2.4)	4 (4.0)	0 (0.0)	8 (2.8)
Adverse event	7 (4.1)	1 (1.0)	0 (0.0)	8 (2.8)
Consent withdrawn	1 (0.6)	2 (2.0)	0 (0.0)	3 (1.1)
Disease progression	1 (0.6)	2 (2.0)	0 (0.0)	3 (1.1)
Lost to follow-up	2 (1.2)	1 (1.0)	0 (0.0)	3 (1.1)
Requirement for alternative therapy	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.7)
Other	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)
Pregnancy	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)
Investigational Product Status				
Received IP	169 (99.4)	101 (100.0)	11 (100.0)	281 (99.6)
IP ongoing	148 (87.1)	79 (78.2)	11 (100.0)	238 (84.4)
Discontinued IP	21 (12.4)	22 (21.8)	0 (0.0)	43 (15.2)
Protocol-specified criteria [a]	2 (1.2)	11 (10.9)	0 (0.0)	13 (4.6)
Administrative decision	5 (2.9)	4 (4.0)	0 (0.0)	9 (3.2)
Adverse event	7 (4.1)	2 (2.0)	0 (0.0)	9 (3.2)
Consent withdrawn	1 (0.6)	2 (2.0)	0 (0.0)	3 (1.1)
Disease progression	1 (0.6)	2 (2.0)	0 (0.0)	3 (1.1)
Lost to follow-up	1 (0.6)	1 (1.0)	0 (0.0)	2 (0.7)
Requirement for alternative therapy	2 (1.2)	0 (0.0)	0 (0.0)	2 (0.7)
Other	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)
Pregnancy	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)
Never received IP	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)

IP = investigational product
Percentages based on number of subjects enrolled.
Four subjects from study 20040215 were directly enrolled into the safety follow up phase in Study 20062004 and were excluded from the treatment phase analysis.
[a] Complete resection

Source: Table 14-1.1.1 and Table 14-1.1.2

The administrative reasons for discontinuations have been specified, by the applicant. The majority of cases are considered disease related.

Summary of Main Efficacy Results

Cohort 1 (Time to disease progression)

In total seven patients had progressive disease or died. Six of 169 (3.6%) had investigator-determined disease progression and one patient died. For the six subjects with investigator-determined disease progression (none of which were adolescent subjects), the initial clinical determinations of disease progression were made 85 to 498 days after first denosumab.

In cohort 1 the median time to disease progression was not reached.

Table 14-4.1.2. Kaplan-Meier Estimates of the Probability of Subjects with Disease Progression (Efficacy Analysis Set) (20062004 Interim Analysis 3)

	Week 25 % (95% CI)	Week 49 % (95% CI)	Week 73 % (95% CI)
Cohort 1 (N = 169)	1.4 (0.0, 3.4)	4.0 (0.5, 7.5)	5.6 (1.0, 10.2)
Cohort 2 (N = 100)	1.1 (0.0, 3.2)	3.2 (0.0, 7.7)	3.2 (0.0, 7.7)
Cohort 3 (N = 11)	NE	NE	NE
Cohorts 1 and 2 (N = 269)	1.3 (0.0, 2.7)	3.8 (1.0, 6.5)	5.1 (1.3, 8.8)

N = number of enrolled subjects who were eligible for the study and received at least one dose of denosumab
NE = Not estimable

Cohort 2 (Proportion of subjects without any surgery at month 6)

At the time for the interim report, 71 subjects had received > 1 dose of denosumab and had participated in the study for> 6 months. Of these, 64 subjects, 90% (64/71) had not undergone surgery by month 6.

Overall 74 patients had no surgery performed. Twenty-six patients in cohort 2 did undergo surgery, the Kaplan-Meier estimate of median time to surgery was 723 days. Of these 26 subjects, 16 were able to undergo a less morbid procedure compared with the surgical procedure planned at baseline

In total two patients died or had progressive disease in cohort 2.

In total two patients in cohort 1, and ten patients in cohort 2 had a complete resection.

Disease Status with Best Postbaseline Response (patients with more than one postbaseline evaluation) (20062004 Interim Analysis 3)

	N1	Complete response n (%)	Partial response n (%)	Stable disease n (%)	Disease progression n (%)	
Cohort 1 (N = 169)	159	8 (5.0)	57 (35.8	93 (58.5)	1 (0.6)	
Cohort 2 (N = 100)	93	17 (18.3)	37 (39.8)	38 (40.9)	1 (1.1)	
Cohort 3 (N = 11)	11	0 (0.0)	2 (18.2)	9 (81.8)	0 (0.0)	

Table 1. Distribution of Planned Versus Actual Surgical Procedures in Subjects With Giant Cell Tumor of Bone (Cohort 2)

Surgical Procedure	Baseline Planned (N = 100)	Actual Total (N = 26)
Total number of surgeries	100	26
Curettage	13	16
Marginal excision, en bloc excision, or en bloc resection	42	6
Major surgeries	44	3
Joint resection	14	2
Joint/prosthesis replacement	9	1
Amputation	17	0
Hemipelvectomy	4	0
Other	1	1

The MAH has carried out an analysis of recommended surgery by independent orthopaedic oncologists. There was a trend towards recommending less severe surgery. The clinically most important observation being the number of recommended joint resections, or amputations, reduced from 17 to 10.

Table 10. Independent Review of Surgical Procedures in Subjects With Resectable Giant Cell Tumor of Bone (Subjects Evaluable for Orthopedic Adjudication) (Cohort 2 in Study 20062004 Efficacy Analysis Set)

Surgical Procedure	Recommended Surgical Intervention at Baseline (N = 47)	Best Recommended Surgical Intervention On Study (N = 47)
No surgery required	0	1
Curettage	25	31
Marginal excision, en bloc excision, or en bloc resection	5	5
Joint resection, joint resection with prosthesis	16	10
Amputation	1	0
Hemipelvectomy	0	0
Unresectable	0	0

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Pathologic findings:

Forty subjects had on-study histopathology procedures performed (18 subjects in Cohort 1 and 22 subjects in Cohort 2); of these, 24 subjects (5 and 19 respectively) had based on the investigator's assessment a pathologic response to denosumab treatment, and 19 subjects had histopathology findings denoting the absence of active tumour cells, see table below.

Table 9-3. Subject Incidence of Pathologic Response and Proportion of Subjects Without Tumor Observed in Postbaseline Histopathology Specimen (Efficacy Analysis Set) (20062004 Interim Analysis 3)

		Crude Incidence	
	N1	n(%) [a]	(95% CI)
Subject Incidence of Pathologic Response			
Cohort 1 (N = 169)	18	5 (27.8)	(9.7, 53.5)
Cohort 2 (N = 100)	22	19 (86.4)	(65.1, 97.1)
Cohort 3 (N = 11)	1	0 (0.0)	(0.0, 97.5)
Cohorts 1 and 2 (N = 269)	40	24 (60.0)	(43.3, 75.1)
Proportion of Subjects Without Tumor			
	N1	n(%) [b]	(95% CI)
Cohort 1 (N = 169)	18	5 (27.8)	(9.7, 53.5)
Cohort 2 (N = 100)	22	14 (63.6)	(40.7, 82.8)
Cohort 3 (N = 11)	1	1 (100.0)	(2.5, 100.0)
Cohorts 1 and 2 (N = 269)	40	19 (47.5)	(31.5, 63.9)

N = number of enrolled subjects who were eligible for the study and received at least one dose of denosumab
N1 = number of subjects with histopathology procedures performed on study
[a] n=number of subjects with pathologic response, which includes complete response and incomplete response recorded in the histopathology CRF
[b] n=number of subjects with histopathologically tumor absence postbaseline
Percentages based on N1
Confidence intervals are exact

The definition of pathologic response is the same in study 20040215 and 20062004. The reason for histopathological evaluation in 20062004 was driven by clinical questions.

Among subjects in Cohort 1, Cohort 2, and Cohort 3, the respective median (range) time on-study was 12.98 (0.3, 29.1) months, 9.23 (0.0, 28.0) months, and 5.36 (4.5, 6.2) months. The median exposure to denosumab was 13.0 doses, with the longest exposure being 33 doses. For adolescent subjects, the median duration were 9.02 (3.3, 17.3) months.

Table 8-1. Summary of On-study Duration
(Safety Subjects)
(20062004 Interim Analysis 3)

	n(%)
>0 - ≤6 months (N=281)	
Cohort 1	169 (60.1)
Cohort 2	101 (35.9)
Cohort 3	11 (3.9)
Cohorts 1 and 2	270 (96.1)
>6 - ≤12 months (N=281)	
Cohort 1	126 (44.8)
Cohort 2	69 (24.6)
Cohort 3	1 (0.4)
Cohorts 1 and 2	195 (69.4)
>12 - ≤18 months (N=281)	
Cohort 1	92 (32.7)
Cohort 2	31 (11.0)
Cohort 3	0 (0.0)
Cohorts 1 and 2	123 (43.8)
>18 - ≤24 months (N=281)	
Cohort 1	49 (17.4)
Cohort 2	9 (3.2)
Cohort 3	0 (0.0)
Cohorts 1 and 2	58 (20.6)
>24 months (N=281)	
Cohort 1	24 (8.5)
Cohort 2	1 (0.4)
Cohort 3	0 (0.0)
Cohorts 1 and 2	25 (8.9)

N = number of enrolled subjects who were eligible for the study, received at least one dose of denosumab.
n= number of subjects in specific on-study duration
Percentages based on N

C**ohort 3:** No patient had died or had progressive disease at the interims analysis.

Table 9-5. Subject-Reported Clinical Benefit Over Time (Efficacy Analysis Set) (20062004 Interim Analysis 3)

	N1 (%)	Pain Reduction n (%)	Improved Mobility n (%)	Improved Function n (%)	Other n (%)
Cohort 1 (N = 169)	67 (39.6)	48 (28.4)	38 (22.5)	32 (18.9)	6 (3.6)
Cohort 2 (N = 100)	61 (61.0)	50 (50.0)	33 (33.0)	23 (23.0)	10 (10.0)
Cohort 3 (N = 11)	3 (27.3)	3 (27.3)	2 (18.2)	2 (18.2)	1 (9.1)
Cohorts 1 and 2 (N = 269)	128 (47.6)	98 (36.4)	71 (26.4)	55 (20.4)	16 (5.9)

N = number of enrolled subjects who were eligible for the study and received at least one dose of denosumab
N1 = Number of subjects who reported clinical benefit
For an individual subject, within each category, if multiple responses are present in the same time frame, the best response is presented.
Percentages based on N

Pain

For subjects with or without an objective tumour response, the mean and median worst pain scores at baseline were higher than at any time on study. The only exception was day 8 median scores for subjects with an objective tumour response Cohorts 1 and 2 combined, in which the median scores were the same as those observed at baseline.

At study enrolment, 75% (209 of 280) of subjects in the efficacy analysis set had no/low analgesic use (ie, an analgesic score ≤ 2) and 25% (71 of 280) of subjects had strong opioid use (ie, an analgesic score ≥ 3).

Very few subjects shifted from no/low analgesic use to strong opioid use during their participation in the study the proportion of subjects in the PRO analysis set with no/low analgesic use at baseline who shifted to strong opioid use at any study visit was ≤ 5.0% in Cohort 1, ≤5.3% in Cohort 2, and ≤ 4.7% among all subjects (all cohorts combined).

Mean worst pain scores by visit are summarized in the table below.

Table 14-5.1.1. BPI-SF - Worst Pain by Visit
(PRO Analysis Set)
(20062004 Interim Analysis 3)

	n	Mean	SD	Min	Q1	Median	Q3	Max
Baseline								
Cohort 1 (N = 166)	160	4.2	3.2	0	1.0	4.0	7.0	10
Cohort 2 (N = 99)	92	4.4	2.8	0	2.0	5.0	7.0	10
Cohort 3 (N = 11)	10	1.9	2.6	0	0.0	0.0	4.0	7
Cohorts 1 and 2 (N = 265)	252	4.3	3.1	0	1.0	4.0	7.0	10
All (N = 276)	262	4.2	3.1	0	1.0	4.0	7.0	10
Day 8								
Cohort 1 (N = 166)	145	3.8	3.1	0	1.0	4.0	7.0	10
Cohort 2 (N = 99)	93	3.6	2.6	0	2.0	4.0	6.0	9
Cohort 3 (N = 11)	0	-	-	-	-	-	-	-
Cohorts 1 and 2 (N = 265)	238	3.7	2.9	0	1.0	4.0	6.0	10
All (N = 276)	238	3.7	2.9	0	1.0	4.0	6.0	10
Day 15								
Cohort 1 (N = 166)	149	3.4	3.0	0	0.0	3.0	6.0	10
Cohort 2 (N = 99)	89	3.4	2.5	0	1.0	3.0	6.0	8
Cohort 3 (N = 11)	0	-	-	-	-	-	-	-
Cohorts 1 and 2 (N = 265)	238	3.4	2.9	0	1.0	3.0	6.0	10
All (N = 276)	238	3.4	2.9	0	1.0	3.0	6.0	10
Week 5								
Cohort 1 (N = 166)	147	3.3	2.9	0	0.0	3.0	5.0	10
Cohort 2 (N = 99)	84	2.9	2.5	0	0.5	3.0	5.0	8
Cohort 3 (N = 11)	8	4.3	3.2	0	2.5	3.5	6.0	10
Cohorts 1 and 2 (N = 265)	231	3.2	2.8	0	0.0	3.0	5.0	10
All (N = 276)	239	3.2	2.8	0	0.0	3.0	5.0	10
Week 9								
Cohort 1 (N = 166)	137	3.0	2.7	0	0.0	2.0	5.0	10
Cohort 2 (N = 99)	81	2.5	2.2	0	1.0	2.0	4.0	10
Cohort 3 (N = 11)	11	2.6	2.8	0	0.0	2.0	4.0	8
Cohorts 1 and 2 (N = 265)	218	2.8	2.5	0	1.0	2.0	4.0	10
All (N = 276)	229	2.8	2.6	0	0.0	2.0	4.0	10

	n	Mean	SD	Min	Q1	Median	Q3	Max
Week 49								
Cohort 1 (N = 166)	83	2.4	2.7	0	0.0	2.0	4.0	9
Cohort 2 (N = 99)	31	1.6	2.3	0	0.0	1.0	2.0	10
Cohort 3 (N = 11)	0	-	-	-	-	-	-	-
Cohorts 1 and 2 (N = 265)	114	2.2	2.6	0	0.0	1.5	3.0	10
All (N = 276)	114	2.2	2.6	0	0.0	1.5	3.0	10
Week 61								
Cohort 1 (N = 166)	67	2.7	2.8	0	0.0	2.0	5.0	9
Cohort 2 (N = 99)	18	1.7	2.4	0	0.0	0.5	2.0	7
Cohort 3 (N = 11)	0	-	-	-	-	-	-	-
Cohorts 1 and 2 (N = 265)	85	2.5	2.7	0	0.0	1.0	5.0	9
All (N = 276)	85	2.5	2.7	0	0.0	1.0	5.0	9
Week 73								
Cohort 1 (N = 166)	52	2.4	2.7	0	0.0	2.0	4.0	10
Cohort 2 (N = 99)	7	1.4	2.7	0	0.0	0.0	3.0	7
Cohort 3 (N = 11)	0	-	-	-	-	-	-	-
Cohorts 1 and 2 (N = 265)	59	2.3	2.7	0	0.0	1.0	4.0	10
All (N = 276)	59	2.3	2.7	0	0.0	1.0	4.0	10
Week 85								
Cohort 1 (N = 166)	40	2.3	2.5	0	0.0	1.0	4.0	9
Cohort 2 (N = 99)	5	1.4	1.5	0	0.0	1.0	3.0	3
Cohort 3 (N = 11)	0	-	-	-	-	-	-	-
Cohorts 1 and 2 (N = 265)	45	2.2	2.4	0	0.0	1.0	4.0	9
All (N = 276)	45	2.2	2.4	0	0.0	1.0	4.0	9
Week 97								
Cohort 1 (N = 166)	27	2.0	2.5	0	0.0	1.0	3.0	8
Cohort 2 (N = 99)	2	1.0	1.4	0	0.0	1.0	2.0	2
Cohort 3 (N = 11)	0	-	-	-	-	-	-	-
Cohorts 1 and 2 (N = 265)	29	2.0	2.5	0	0.0	1.0	3.0	8
All (N = 276)	29	2.0	2.5	0	0.0	1.0	3.0	8

	n	Mean	SD	Min	Q1	Median	Q3	Max
Week 109								
Cohort 1 (N = 166)	12	2.4	2.4	0	0.0	2.0	4.5	6
Cohort 2 (N = 99)	0	-	-	-	-	-	-	-
Cohort 3 (N = 11)	0	-	-	-	-	-	-	-
Cohorts 1 and 2 (N = 265)	12	2.4	2.4	0	0.0	2.0	4.5	6
All (N = 276)	12	2.4	2.4	0	0.0	2.0	4.5	6
Week 121								
Cohort 1 (N = 166)	2	0.5	0.7	0	0.0	0.5	1.0	1
Cohort 2 (N = 99)	1	0.0	-	0	0.0	0.0	0.0	0
Cohort 3 (N = 11)	0	-	-	-	-	-	-	-
Cohorts 1 and 2 (N = 265)	3	0.3	0.6	0	0.0	0.0	1.0	1
All (N = 276)	3	0.3	0.6	0	0.0	0.0	1.0	1

N = number of enrolled subjects who were eligible for the study, received at least one dose of denosumab, and used consistent recall periods on study
n = number of subjects with data at the visit
The range of worst pain is 0 - 10; a higher score indicates a less preferred health status.

Program: /stat/amg162/therapeutic/20062004/analysis/interim_3/tables/program/t-bpi-byvis.sas
Output: t14-05-001-001-bpi-byvis-wrst.rtf (Date Generated: 11NOV2011:15:11:20) Source Data: adam.aqsbpi, adam.aslinfo

Table 1. Number of Study Discontinuations and Reason for Study Discontinuation by Baseline Pain Level, Number of Subjects (Percent[a]) (Enrolled Subjects, 20062004 Interim Analysis 3)

Subject Pain Level at Baseline[a]	Discontinued Study	Discontinued Due to Adverse Event	Discontinued Due to Disease Progression
Cohort 1			
No/mild (n = 86)	11 (12.8)	4 (4.7)	0 (0.0)
Moderate (n = 26)	2 (7.7)	1 (3.8)	0 (0.0)
Severe (n = 50)	6 (12.0)	1 (2.0)	1 (2.0)
Cohort 2			
No/mild (n = 45)	8 (17.8)	1 (2.2)	0 (0.0)
Moderate (n = 20)	4 (20.0)	0 (0.0)	0 (0.0)
Severe (n = 29)	7 (24.1)	0 (0.0)	2 (6.9)
Cohorts 1 and 2 combined			
No/mild (n = 131)	19 (14.5)	5 (3.8)	0 (0.0)
Moderate (n = 46)	6 (13.0)	1 (2.2)	0 (0.0
Severe (n = 79)	13 (16.5)	1 (1.3)	3 (3.8)

[a] No/mild, moderate, and severe pain defined as worst pain score ≤ 4 points, 5 to 6 points, and ≥ 7 points. respectively.

The applicant has provided an analysis of discontinuations stratified according to baseline pain levels with no indication of a larger drop-out rate in those with severe pain.

Updated efficacy response to second RSI:

In response to the second RSI a summary of updated efficacy and safety results from study 20062004 with 507 enrolled patients and a data "snap-shot" cut-off date 30 Aug 2013 was provided. In total 263 patients in cohort 1, 232 in cohort 2 and 12 patients in cohort 3 (rolled over from study 20040215) were included. The median time on study was for cohort 1 26.7 months (0-58.0), for cohort 2 15.2 months (0.1-57.2) and cohort 3 34.5 months (12.8-35.4). A total of 415 patients were treated >1 year, 222 patients>2 years, 108 patients> 3 years and 37 patients<4 years.

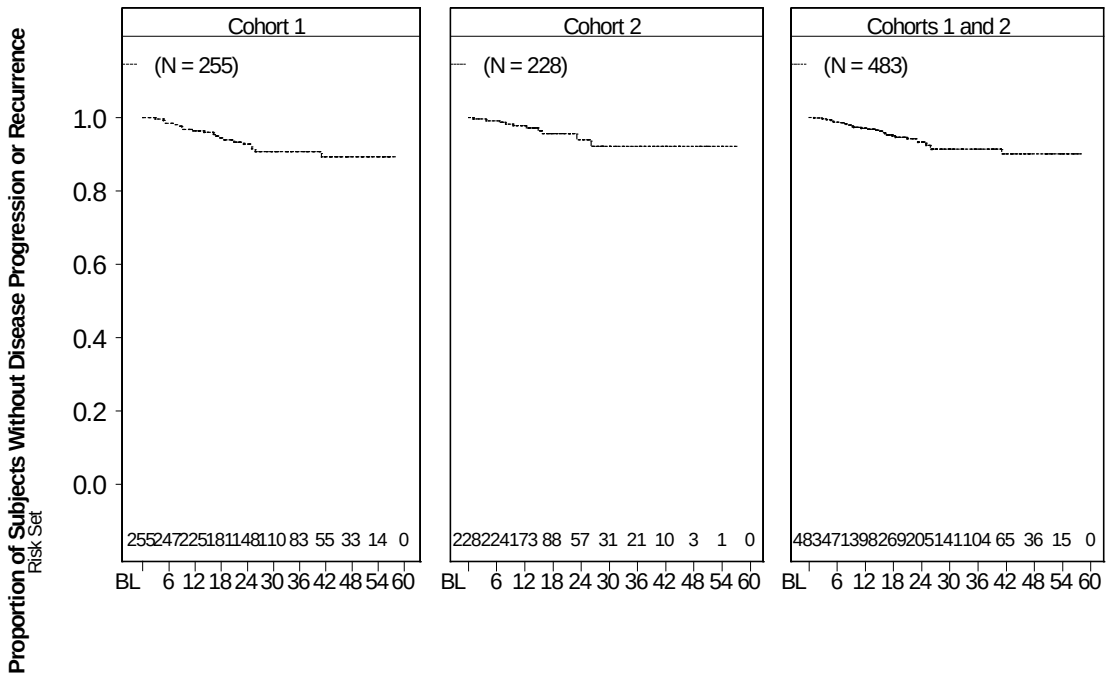
In total 21 of 258 treated subjects (8.1%) in cohort 1, 10 of 228 (4.4%) in cohort 2 and 0 of 11 patients in cohort 3 had disease progression.

Although per eligibility criteria, Cohort 1 subjects did not have surgery planned at baseline, during the course of treatment, 34 subjects became eligible to have surgery. Surgery were in the following locations: lower extremities (8 subjects, 3.1%), upper extremities (7 subjects, 2.7%), and pelvis (6 subjects, 2.4%).

Of the 225 subjects with surgically salvageable disease in cohort 2 (excluding 3 subjects with lung or soft tissue lesions 109 had no GCTB surgery performed over the entire study and 84 underwent a less morbid surgical procedure compared to planned at base line. Twenty six of 225 (11.7%) subjects underwent their originally planned surgery.

The most common locations of on-study GCTB surgery by baseline target lesion were lower extremities (72 subjects, 31.6%), upper extremities (35, 15.4%), and pelvis (11, 4.8%). The Kaplan-Meier estimate of median time to all GCTB surgery in Cohort 2 was 261 days.

Time to Disease Progression or Recurrence <u>On-study</u> Kaplan-Meier Curves (Excluding Subjects Rolled Over From Study 20040215) (Efficacy Analysis Set) (Study 20062004 EU Snapshot, Cutoff of 30 August 2013)



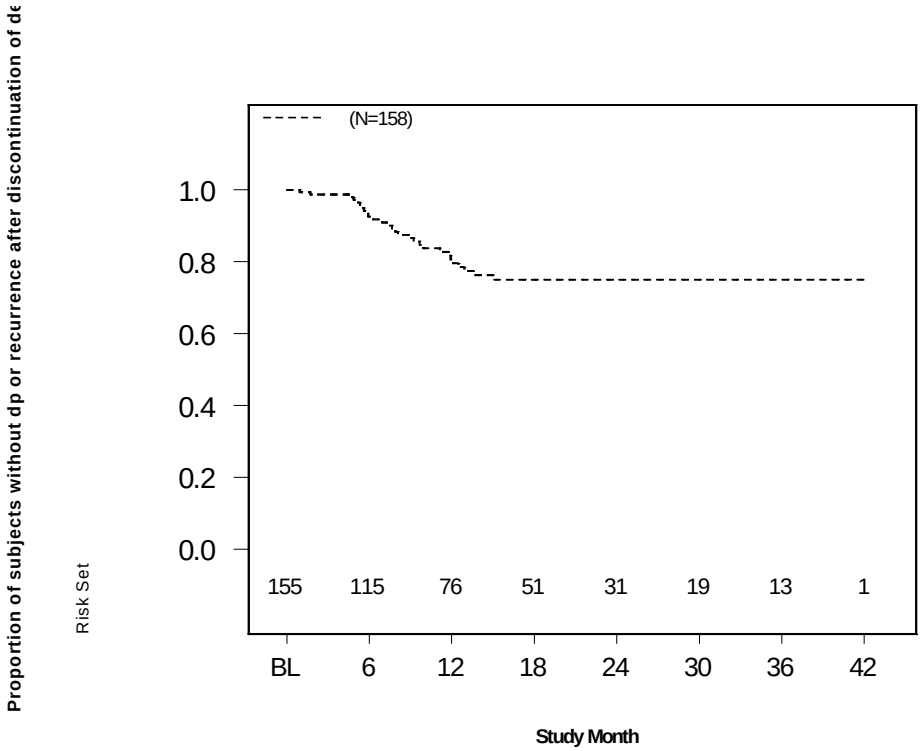
N = number of enrolled subjects who were eligible for the study and received at least one dose of denosuma excluding subjects rolled over from study 20040215

Program: /userdata/stat/amg162/meta/bla_2011gctb/analysis/EU_snapshot_2013/figures/program/f-time-km-strata.sas
Output: f200-04-001-001-time-km-dp.cgm (Date Generated: 10MAR2014:10:51:01)
Source Data: aeu2004.aslinfo, aeu2004.asleff

A total of 13 (23.2%) of 56 subjects who discontinued study drug in Cohort 1 had disease progression or recurrence after discontinuation of denosumab.

Of the 102 subjects, who discontinued denosumab for reasons other than disease progression in cohort 2, fifteen (14.7%) had local recurrence after discontinuation of denosumab. The majority of patients discontinued denosumab based on protocol specific treason complete resection (96 subjects).

Time to Disease Progression or Recurrence <u>After Discontinuation</u> of Denosumab Kaplan-Meier Curves (Excluding Subjects Rolled Over from Study 20040215 and Excluding Subjects With Disease Progression Prior to Discontinuation of Denosumab) (Cohorts 1 and 2 Combined Efficacy Analysis Set) (Study 20062004 EU Snapshot, Cutoff of 30 August 2013 Snapshot)



N = number of enrolled subjects who were eligible for the study and received at least one dose of denosumab, excluding subjects (a) discontinued denosumab due to death or lost to follow up or consent withdrawn or disease progression (b) had disease progression prior to discontinuation of denosumab(c) rolled over subjects from study 20040215

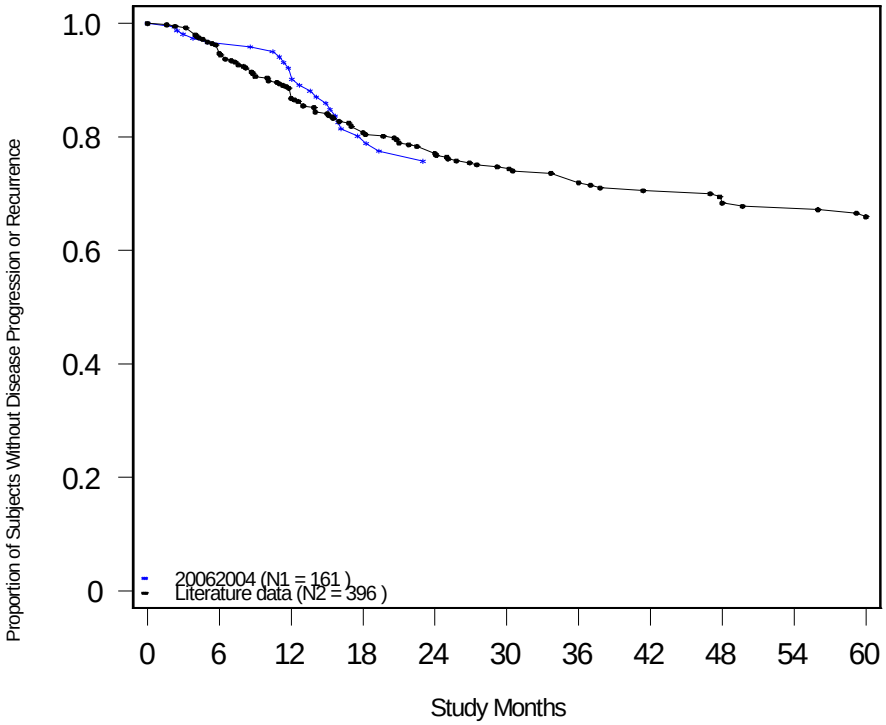
Program: /userdata/stat/amg162/meta/bla_2011gctb/analysis/EU_snapshot_2013/figures/program/f-time-km-2.sas
Output: f200-04-003-003-time-km-2-dp-ip.cgm (Date Generated: 07MAR2014:11:27:46)
Source Data: s042004.df, s062004.suppdf, aeu2004.asleff, aeu2004.aslinfo

Disease progression / recurrence after surgery

Six subjects of 34 subjects with GCTB surgery in Cohort 1 (17.6%) had disease progression or recurrence after GCTB surgery, and 18 subjects of 127 subjects with GCTB surgery in Cohort 2 (14.2%) had disease progression or recurrence after GCTB surgery. The median time to disease progression or recurrence was not reached; Kaplan-Meier estimates showed that the proportion of subjects with disease progression or recurrence over time for Cohort 1 was 3.0% (0.0, 8.9) at week 25, 8.4% (0.0, 20.1) at week 49, and 19.9% (1.9, 37.9) at week 73, and 29.9% (5.7, 54.1) at week 98 for Cohort 2 was 3.4% (0.1, 6.7) at week 25, 5.5% (1.2, 9.8) at week 49, and 18.1% (9.9, 26.2) at week 73, and 21.0% (12.2, 29.9) at week 98.

The applicant has provided a comparison on progression/recurrence post-surgery to literature data.

Kaplan-Meier Estimates of Time to Disease Progression or Recurrence After First On-study GCTB Surgery Adjusted by Lesion Location (Comparison of Data From Study 20062004 With Data From Literature) (Cohorts 1 and 2 Combined Efficacy Analysis Set, Study 20062004 EU Snapshot, Cutoff of 30 August 2013)



N1 = number of subjects at risk with GCTB surgery excluding subjects rolled over from study 20040215 in study 20062004
N2=Eligible subjects from literature at risk
Plot was truncated at year 5.

Program: /userdata/stat/amg162/meta/bla_2011gctb/analysis/EU_snapshot_2013/figures/program/f-time-km-lit-2.sas
Output: f200-04-101-time-km-lit-lesion-surg-adj.cgm.cgm (Date Generated: 13MAR2014:12:38:41)
Source Data: aeu2004.asleff, aeu2004.als, lesion_location_3category.xls, evidera.recurrence

2.5. Clinical studies in special populations

No special populations were investigated for the GCTB indication. Ten subjects in study 20062004 were skeletally mature adolescents. Among the skeletally mature adolescents in cohort 1 (n=8) five had partial response and three had stable disease. In cohort 1 (n=2) two had stable disease. The Kaplan Meier estimate of median time to surgery was 261 days.

After the safety update in August 2012 there are 15 adolescents.

In the data snap-shot August 2013 18 adolescents were included.

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

2.6.1. Outcomes / endpoints

A retrospective independent radiographic review of tumour response was performed by a central imaging vendor for Studies 20040215 and 20062004 to provide further clinical evidence of a denosumab treatment effect on tumour regression. Key design aspects were agreed following consultation with regulatory authorities.

For the retrospective radiographic review CT, MRI, and/or PET were provided (if available) for assessment of tumour response and disease progression. Plain X-ray film, bone scans, or ultrasounds were not evaluated in the independent imaging analysis.

An objective tumour response was defined as either a CR or PR, determined using the best response evaluated by any of the following response criteria: modified RECIST 1.1 (CT/MRI), modified EORTC criteria using ^{18}FDG-PET, and modified inverse Choi criteria (density/size) to evaluate tumour size by CT/MRI and density using Hounsfield units on CT. These 3 response criteria were used to collectively define and characterize objective tumour response in subjects with GCTB.

There are no well-established tumour response criteria in GCTB as RECIST is primarily used in soft tissue tumours, FDG/PET measures the metabolic activity and modified Choi criteria (increase in lesion density and the longest diameter measured on CT or MRI).

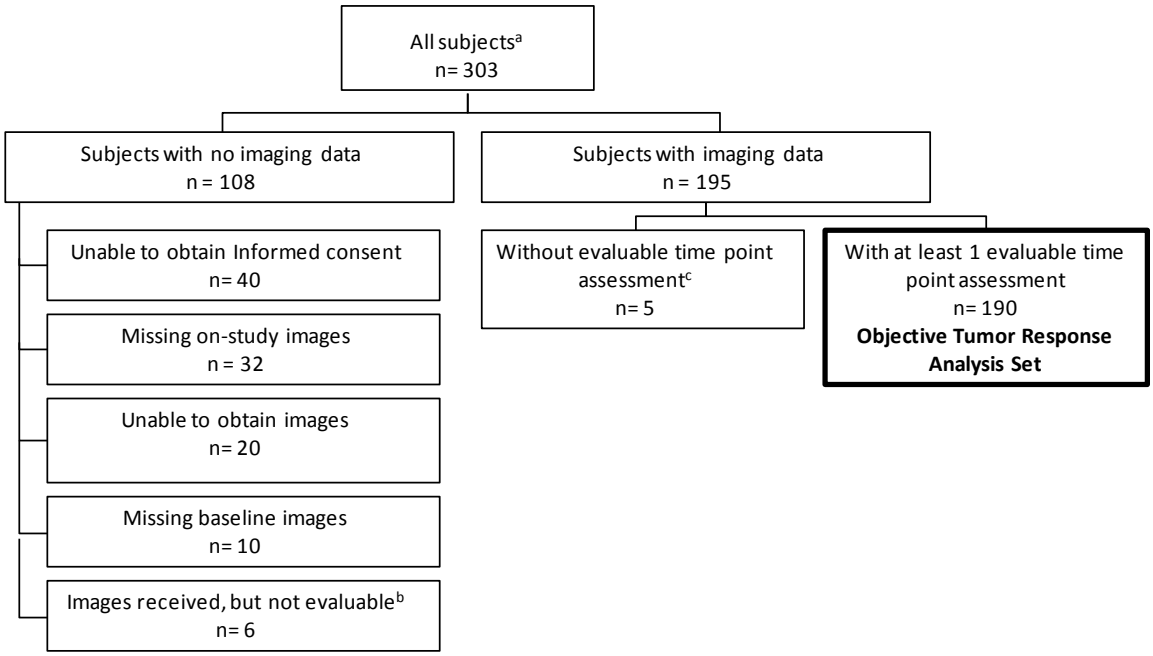
2.6.2. Study Participants

Patients with imaging data from studies 20040215 and 20062004 were included (roll-over patients from study 200415 were only included once). For internal validity an imaging control group was formed from 26 patients with at least 3 pre-treatment images available.

The study population is described below under “Participant flow”.

2.6.3. Participant flow

Disposition of All Potential Imaging Data



[a] Rollover or re-entry subjects from Study 20040215 who were enrolled in Study 20062004 were included only once in the imaging analysis.
[b] X-ray only
[c] Lesions unevaluable due to image quality or determination that subject had surgical resection prior to the time point assessment.

Source: Table tiae1.1.1; Table tiae1.1.2

In total imaging data were not available for 10 patients in study 20040215 and 98 patients in 20062004.

There were no notable differences in baseline demographic and disease characteristics or clinical outcomes between subjects with radiological evaluations and subjects without radiological evaluations in Studies 20062004 and 20040215. Furthermore, when the reasons for missing evaluations were further evaluated, there was no indication of bias in the collection of radiographic evaluations.

In the objective tumor response analysis set, 38 discontinued the study (see below).

In the objective analysis set the median time on study was 13.4 months and median number of doses 16 (4-54 doses).

Table 8. Reasons for Study Discontinuation
(Subjects With At Least One Evaluable Time Point Assessment)
(Efficacy Analysis Set)

	Study 20040215		Study 20062004 Cohort 1		Cohort 2		Cohorts 1 and 2		Overall	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with at least one evaluable time point assessment	27		114		49		163		190	
Ongoing	0	(0.0)	108	(94.7)	44	(89.8)	152	(93.3)	152	(80.0)
Discontinued study	27	(100.0)	6	(5.3)	5	(10.2)	11	(6.7)	38	(20.0)
Protocol-specified criteria[a]	8	(29.6)	2	(1.8)	3	(6.1)	5	(3.1)	13	(6.8)
Rollover to other study	9	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	9	(4.7)
Administrative decision	1	(3.7)	1	(0.9)	2	(4.1)	3	(1.8)	4	(2.1)
Other[b]	4	(14.8)	0	(0.0)	0	(0.0)	0	(0.0)	4	(2.1)
Adverse event	1	(3.7)	2	(1.8)	0	(0.0)	2	(1.2)	3	(1.6)
Disease progression	2	(7.4)	1	(0.9)	0	(0.0)	1	(0.6)	3	(1.6)
Consent withdrawn	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
Noncompliance	1	(3.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)

Percentages based on number of enrolled subjects who were eligible for the study, received at least one dose of denosumab, and had at least one evaluable time point assessment

[a] Complete resection

[b] Discontinued study at investigator's discretion.

Modified from source: Table tiae1.2.1.

Baseline Disease Characteristics Based on CRF Data (Descriptive Statistics) (Subjects with at Least One Evaluable Time Point Assessment) (Efficacy Analysis Set)

		Study 20062004			
	Study 20040215 (N = 27)	Cohort 1 (N = 114)	Cohort 2 (N = 49)	Cohorts 1 and 2 (N = 163)	Overall (N = 190)
ECOG Status - n(%)					
0	9 (33.3)	73 (64.0)	24 (49.0)	97 (59.5)	106 (55.8)
1	16 (59.3)	35 (30.7)	25 (51.0)	60 (36.8)	76 (40.0)
2	0 (0.0)	6 (5.3)	0 (0.0)	6 (3.7)	6 (3.2)
Missing	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)
GCT disease type - n(%)					
Primary resectable	0 (0.0)	0 (0.0)	26 (53.1)	26 (16.0)	26 (13.7)
Primary unresectable	9 (33.3)	34 (29.8)	0 (0.0)	34 (20.9)	43 (22.6)
Recurrent resectable	6 (22.2)	0 (0.0)	23 (46.9)	23 (14.1)	29 (15.3)
Recurrent unresectable	12 (44.4)	80 (70.2)	0 (0.0)	80 (49.1)	92 (48.4)

Study 20062004					
	Study 20040215 (N = 27)	**Cohort 1 (N = 114)**	**Cohort 2 (N = 49)**	**Cohorts 1 and 2 (N = 163)**	**Overall (N = 190)**
Longest dimension of target lesion (mm)					
N	26	114	49	163	189
Median	44.5	50.5	70.0	60.0	56.4
Q1, Q3	29.0, 70.0	29.0, 90.0	49.9, 83.0	34.0, 89.0	33.8, 85.0
Min, Max	6, 130	7, 240	10, 200	7, 240	6, 240
Location of target lesion - n(%)					
Pelvis	7 (25.9)	46 (40.4)	8 (16.3)	54 (33.1)	61 (32.1)
Other[a]	8 (29.6)	36 (31.6)	5 (10.2)	41 (25.2)	49 (25.8)
Lower extremities	6 (22.2)	7 (6.1)	26 (53.1)	33 (20.2)	39 (20.5)
Spine	2 (7.4)	14 (12.3)	2 (4.1)	16 (9.8)	18 (9.5)
Upper extremities	3 (11.1)	6 (5.3)	8 (16.3)	14 (8.6)	17 (8.9)
Head/neck	0 (0.0)	5 (4.4)	0 (0.0)	5 (3.1)	5 (2.6)
Missing	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

(Other= mainly pulmonary metastases)

Tumour Response

Table 11. Proportion of Subjects with an Objective Tumor Response (Subjects With At Least One Evaluable Time Point Assessment) (Efficacy Analysis Set)

	n	N1	Percent	95% CI[a]
Proportion of subjects with an objective tumor response (CR, PR)				
Based on best response	136	190	71.6	(64.6, 77.9)
RECIST 1.1	47	187	25.1	(19.1, 32.0)
EORTC	25	26	96.2	(80.4, 99.9)
Density/size	134	176	76.1	(69.1, 82.2)

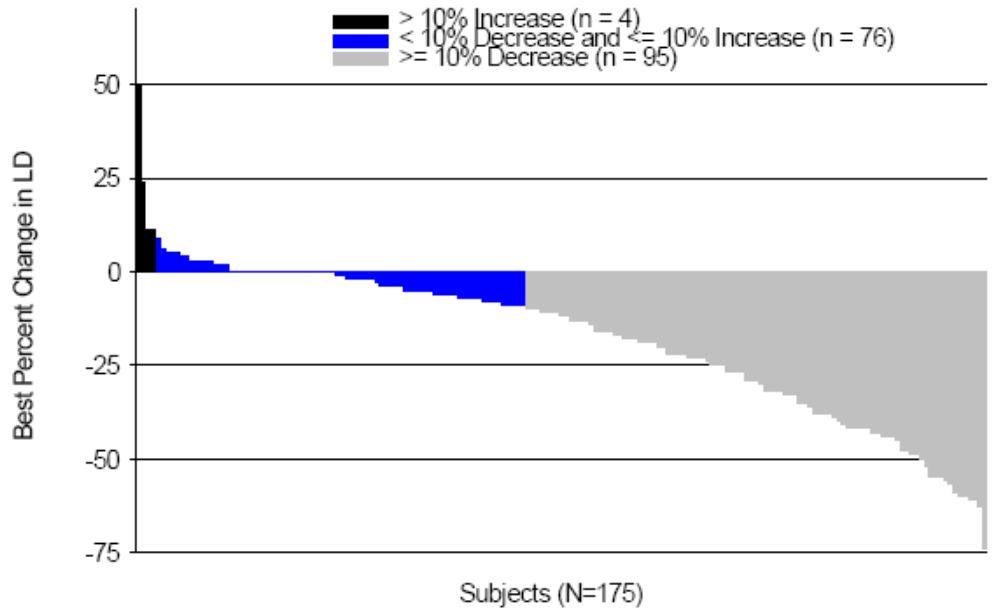
Page 1 of 1

n = number of subjects with a response
N1 = number of subjects with at least one evaluable time point assessment using the respective tumor response criteria
[a] Exact confidence interval

More patients have a response in terms of modified EORTC (FDG/PET) metabolic activity and modified Choi (density/size) than RECIST. The could be explained by the fact that modified Choi could be derived from the density component alone (in an ad hoc analysis 41.8% of responses were based on both density and size,

30.6% on density component alone, and 27.6% on size alone. A partial response by modified RECIST requires at least a 30% reduction in sum of the longest diameter (SLD) for target lesion, whereas a partial response for density/size requires at least a 10% reduction in SLD. The responses above could reflect the less stringent size response criteria and the additional response criteria for density alone.

Longest diameter:



Density:

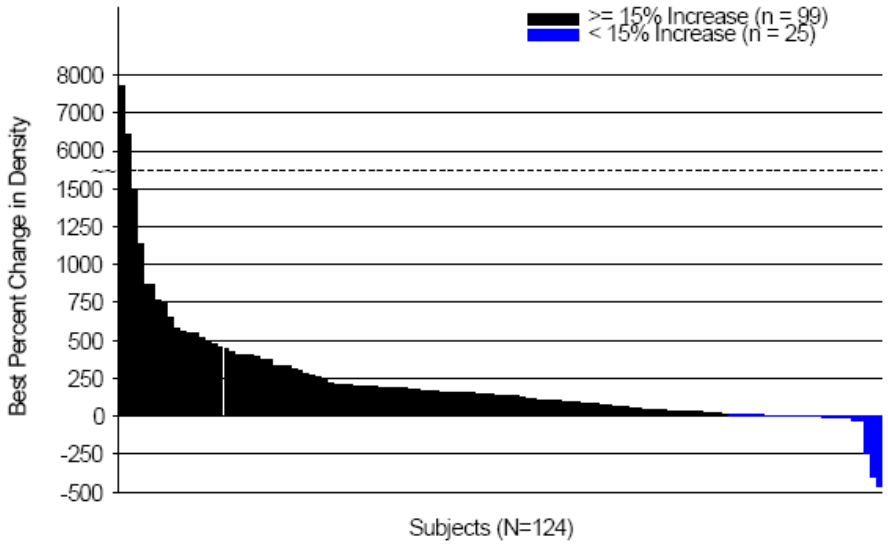


Table 12. Proportion of Subjects with an Objective Tumor Response by Lesion Type (Subjects with at Least One Evaluable Time Point Assessment) (Efficacy Analysis Set)

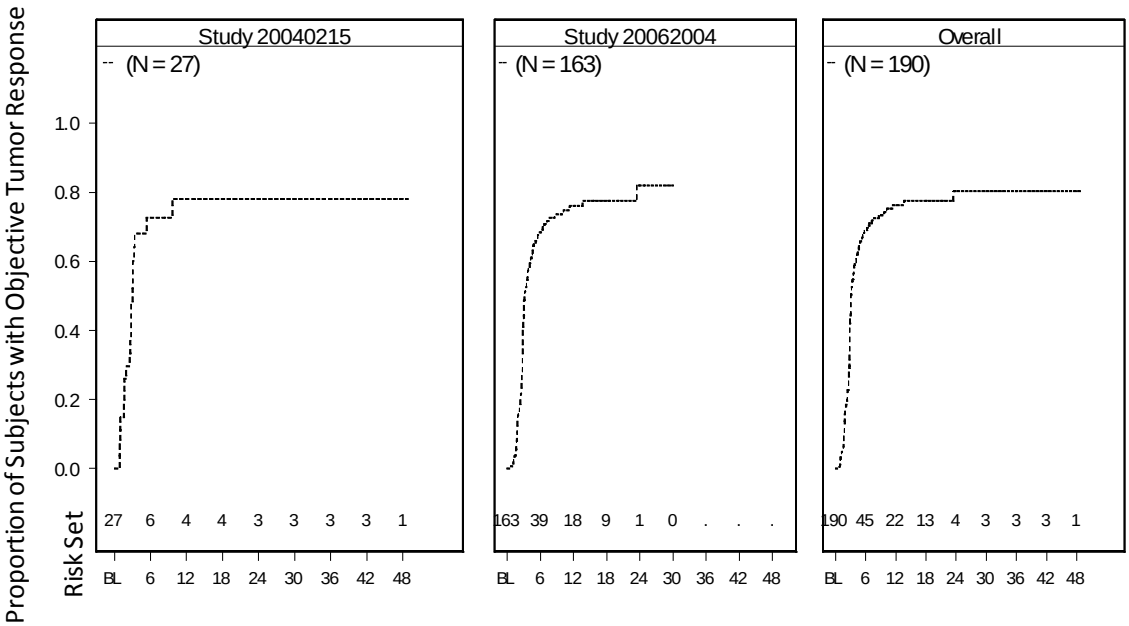
	Soft Tissue Lesion or Lesion With Soft Tissue Component		Bone Lesion		Bone and Soft Tissue Containing Lesions	
	n/N1 (%)	95% CI[a]	n/N1 (%)	95% CI[a]	n/N1 (%)	95% CI[a]
Proportion of subjects with an objective tumor response (CR, PR)						
Based on best response	46/49 (93.9)	(83.1, 98.7)	89/126 (70.6)	(61.9, 78.4)	1/2 (50.0)	(1.3, 98.7)
RECIST 1.1	28/49 (57.1)	(42.2, 71.2)	19/123 (15.4)	(9.6, 23.1)	0/2 (0.0)	(0.0, 84.2)
EORTC	4/4 (100.0)	(39.8, 100.0)	21/21 (100.0)	(83.9, 100.0)	0/1 (0.0)	(0.0, 97.5)
Density/size	46/48 (95.8)	(85.7, 99.5)	87/125 (69.6)	(60.7, 77.5)	1/2 (50.0)	(1.3, 98.7)

n = number of subjects with a response
N1 = number of subjects with at least one evaluable time point assessment with the respective lesion type using the respective tumor response criteria.
[a] Exact confidence interval.
Source: Table tiae4.4.501; results by individual study are provided in source table.

A statistically significant moderate correlation was observed between RECIST and density/size evaluations: 27.2% of subjects had a response by both criteria (Phi correlation coefficient = 0.35; p-value < 0.001). RECIST response was only weakly correlated with EORTC (Phi correlation coefficient = 0.09; p-value = 1.00). A moderate correlation was also observed between density/size and EORTC, although the relationship was not statistically significant (Phi correlation coefficient: 0.55; p-value = 0.115).

The median time (95% CI) to objective tumour response among responders was 2.8 months (2.76, 2.89) based on best response using any tumour response criteria. The median time (95% CI) to objective tumour response after the first dose of denosumab for all evaluable subjects was 3.1 months (2.89, 3.65) based on the best response using any tumour response criteria. The figure below shows the Kaplan-Meier curve for the time to objective tumour response based on best response using any tumour response criteria for all evaluable subjects.

Time to First Objective Tumor Response Based on Best Response Kaplan-Meier Curve (Subjects With At Least One Evaluable Time Point Assessment) (Efficacy Analysis Set)



N = number of subjects who were eligible for the study, received at least 1 dose of denosumab, and had at least 1 evaluable time point assessment.

Source: Figure tiae4.1.2.1 (21June2012:14:53:39)

Based on the clinical data, eleven of the 190 subjects (5.8%) in the objective tumor response analysis set had radiologic evidence of disease progression at any time using any of the 3 evaluation criteria, as determined by the independent radiographic analysis. For these 11 subjects, the radiological determinations of disease progression were made 0.2 to 21.9 months (median 3.68 months) after the first dose of denosumab.

Table 2. Summary of Time to Disease Progression Using Any Tumor Response Criteria (Subjects With Disease Progression) (Efficacy Analysis Set)

	n	Mean	SD	Min	Q1	Median	Q3	Max
Time to disease progression (months)								
Study 20040215 (N = 27)	3	8.16	9.88	1.9	1.87	3.06	19.55	19.5
Study 20062004								
Cohort 1 (N = 114)	6	8.02	8.04	0.2	3.68	4.63	13.11	21.9
Cohort 2 (N = 49)	2	2.22	0.81	1.6	1.64	2.22	2.79	2.8
Cohorts 1 and 2 (N = 163)	8	6.57	7.31	0.2	2.22	3.70	9.33	21.9
Overall (N = 190)	11	7.00	7.58	0.2	1.87	3.68	13.11	21.9

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N = number of enrolled subjects who were eligible for the study, received at least one dose of denosumab, and had at least one evaluable time point assessment
n = number of subjects with disease progression

Table 13. Proportion of Subjects With Sustained Objective Tumor Response (Efficacy Analysis Set)

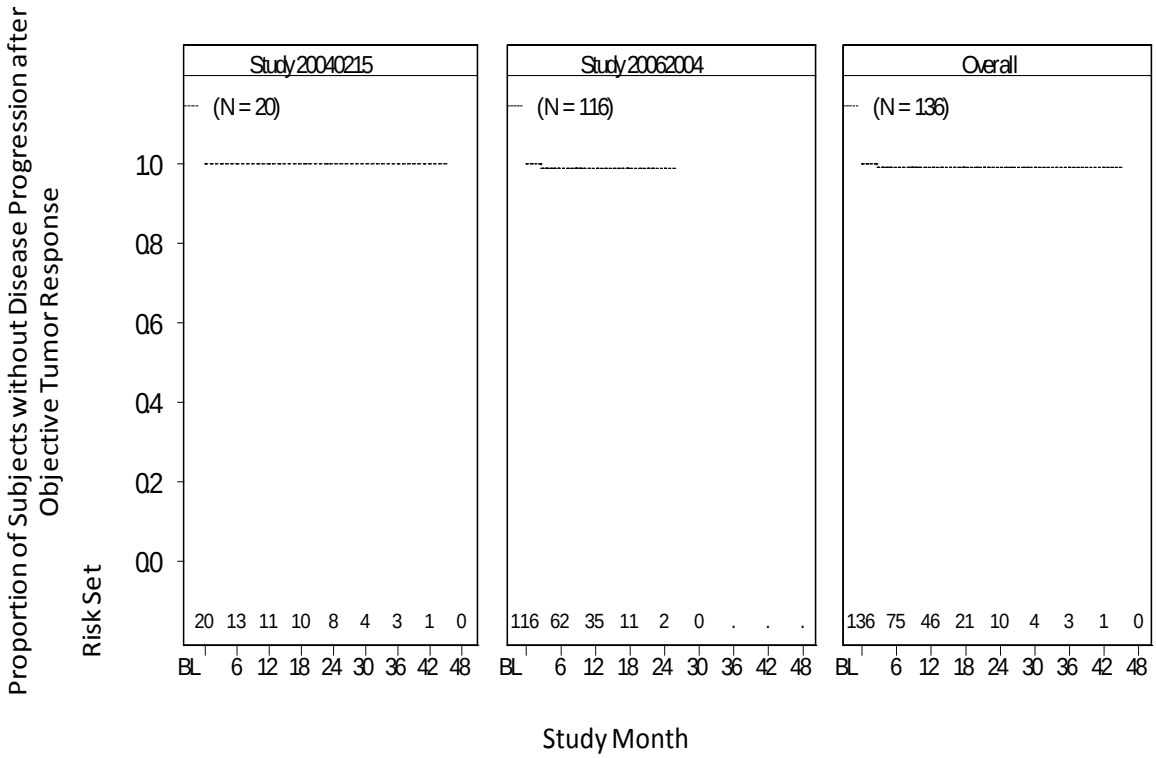
	n	N1	Percent	95% CI[a]
Sustained for at least 4 weeks				
Based on best response	102	153	66.7	(58.6, 74.1)
RECIST 1.1	32	150	21.3	(15.1, 28.8)
EORTC	18	20	90.0	(68.3, 98.8)
Density/size	101	143	70.6	(62.4, 77.9)
Sustained for at least 8 weeks				
Based on best response	99	147	67.3	(59.1, 74.8)
RECIST 1.1	32	144	22.2	(15.7, 29.9)
EORTC	17	18	94.4	(72.7, 99.9)
Density/size	99	138	71.7	(63.5, 79.1)
Sustained for at least 12 weeks				
Based on best response	98	144	68.1	(59.8, 75.6)
RECIST 1.1	32	141	22.7	(16.1, 30.5)
EORTC	16	17	94.1	(71.3, 99.9)
Density/size	97	135	71.9	(63.5, 79.2)
Sustained for at least 24 weeks				
Based on best response	76	111	68.5	(59.0, 77.0)
RECIST 1.1	26	109	23.9	(16.2, 33.0)
EORTC	11	12	91.7	(61.5, 99.8)
Density/size	76	102	74.5	(64.9, 82.6)

n = number of subjects with a response

N1 = number of subjects with at least 2 evaluable time point assessments that were at least 4, 8, 12, or 24 weeks apart using the respective tumor response criteria.

[a] Exact confidence interval.

Duration of Objective Tumor Response Based on Best Response (Subjects with an Objective Tumor Response) (Efficacy Analysis Set)



N = number of enrolled subjects who were eligible for the study, received at least 1 dose of denosumab, and had an objective tumor response

Source: Figure tiae4.1.1.1 (21June2012:14:53:39)

Based on clinical outcome measures of treatment response as assessed by the investigator in the individual clinical studies (ie, time to disease progression, proportion of subjects without surgery at month 6, and disease status for Study 20062004), clinical outcomes for evaluable subjects and those without imaging data were similar.

Subgroup analyses

The adolescent population was included in the independent evaluation of objective tumour response and 6 had at least 1 evaluable time point assessment. As of the data cut-off all 6 remained on study and were receiving denosumab; they had unresectable GCTB. The median time on-study was 6.3 months, the median number of denosumab doses received was 9.5, and the maximum number 21. Based on best response using any tumour response criteria, 66.7% (4 of 6) had an objective tumour response; 33.3% (2 of 6) had an objective tumour response based on modified RECIST and 66.7% (4 of 6) based on density / size. No adolescent was evaluable by modified EORTC criteria.

2.7. Overall conclusions on clinical efficacy

Discussion on clinical efficacy

The majority of the patients included in the GCTB studies are inoperable or have disease where surgery would lead to severe morbidity. As indicated in the interims analysis in study 20062004 about 10% had received previous chemotherapy, 20% had previous radiotherapy, 60% had previous surgery.

The data provided demonstrate that denosumab has a number of pharmacological effects expected from the mode of action i.e. that activation of osteoclast-like giant cells is inhibited. The histopathological results obtained in study 20040215 provide support for this conclusion and it is supported by the reduced metabolic activity evident from the PET-data. The histopathology results in study 20062004 and study 20040215 relate to the reduction of the number of giant cells, which is consistently seen in most evaluable subjects. The applicant also describes a reduction of the neoplastic stromal cell area relative to the total tumour area compared to baseline and an increase in the extracellular matrix composed of collagen and osteoid and woven bone.

The efficacy endpoints were based on investigators assessments, in the interims analyses of inoperable patients (cohort 1) only 6 of 169 enrolled patients had disease progression, and at the data snap-shot, two years later, 21 of the 258 enrolled patients had progressive disease based on investigator assessment. For patients where surgery would lead to severe morbidity (cohort 2) at the interims analysis two of 100 patients had progressive disease and at the data snap-shot 10/228 had progressive disease.

A retrospective independent review of imaging data was performed for patients enrolled in study 20040215 and 20062004. About half of the patients enrolled were included in the retrospective analyses; there were no obvious differences between subjects included/not included in the retrospective analyses. The majority of patients (72%) had a response in the retrospective analyse, however the vast part was defined by density/length (modified inverse Choi) or metabolic activity (EORTC/^{18}FDG-PET), only 25% had a response as defined by RECIST.

Support for a clinically meaningful effect of denosumab is provided by the reported reduction in both frequency and severity of surgery. At the interims analysis 90% (64/71) of the enrolled patients in cohort 2 had not had surgery by month 6. The applicant has provided a blinded independent evaluation of surgery required supporting the investigators assessments. This was consistent with data from the data snap-shot where 92% (209/228) had not undergone surgery by month 6.

Although per inclusion subjects in cohort 1 were inoperable, 34 subjects became eligible to have surgery.

In cohort 2 109 had no GCTB surgery performed over the entire study and 84 underwent a less morbid surgical procedure compared to planned at base line. Twenty six of 225 (11.7%) subjects underwent their originally planned surgery.

In total two patients in cohort 1, and ten patients in cohort 2 had a complete resection by the time of the interims analysis. At the update data snap-shot about 20 % of the patients in the whole study had complete resections 13 (4.9%) in cohort 1 and 91 (39.2%) in cohort 2.

Six subjects of 34 subjects with GCTB surgery in Cohort 1 (17.6%) had disease progression or recurrence after GCTB surgery, and 18 subjects of 127 subjects with GCTB surgery in Cohort 2 (14.2%) had disease progression or recurrence after GCTB surgery.

There was a reported investigator-judged beneficial effect and reduction in pain, however most patients did not have a severe analgesic use at start of the study.

The single-arm design and the lack of historical controls for the two studies reduce the certainty with which conclusions can be drawn from the data. Furthermore, the objective efficacy variables in study 20062004 were not systematically collected. The observation time, also including the last update, is limited to about 200 patients that are treated beyond two years and 100 beyond three years in the context of the time to recurrence rate with two years as the duration frequently cited in the literature study data is still limited.

The number of adolescents is also very limited n=10 in the original safety set, n=15 at the August 2012 up-date, and n= 18 in the data snap-shot.

The duration of treatment has in the studies been to progression or complete resection, there is no data on shorter treatment duration than until progression, but from the very limited data there are no indications on a rebound effect after denosumab was discontinued.

2.7.1. Conclusions on the clinical efficacy

There are several lines of evidence that support that denosumab has the intended biological effect and also a clinically meaningful effect. Although the main effect seems to be stabilising the disease, a few patients has become operable and a larger number has undergone less morbid surgery than initially planned. There is also data on a clinical benefit and pain reduction, however with regards to the nature of the disease and the non-controlled study these results are hard to fully evaluate. The duration of treatment is, except continuation until progression, not exhaustively evaluated and this has been addressed in the SmPC. The long-term effects need to be further addressed as proposed in the final analysis of 20062004 and proposed study 20140114.

2.8. Clinical Safety aspects

2.8.1. Patient exposure

The denosumab clinical development program as of the 25 March 2011 data cutoff date for the GCTB indication includes two phase 2 studies including 304 subjects: Study 20040215 a, which enrolled 37 subjects, and Study 20062004, an ongoing study with safety data for 281 subjects (including 14 patients who previously participated in Study 20040215). Ten patients were below 18 years.

Additional safety data was collected for study 20062004 through 31 Aug 2012. In total data for 472 subjects who had received at least 1 dose of denosumab, including 251 subjects in Cohort 1, 209 subjects in Cohort 2, and 12 subjects in Cohort 3. The median time on study 15.54 months (0.1, 46.3) months.

As a response to the second RSI a further update including 501 patients in study 20062004 was provided (see below).

Denosumab 120 mg SC Q4W has been approved for preventing or reducing the risk of skeletal-related events (SREs) in patients with bone metastases from solid tumors. Three pivotal international, phase 3, randomized, double blind, active controlled clinical studies provided the primary support for the denosumab XGEVA Advanced Cancer (SRE) marketing application. The primary safety evaluations for this program included data from 2841 subjects administered denosumab. A summary of the exposure data for GCTB and SRE treatment based on the March 2011 read-out are shown in the table below.

Number of patients receiving denosumab by duration of cumulative exposure and study type in advanced cancer and GCTB programs

	Denosumab					
	≥ 1 Dose	≥ 1 Month	≥ 6 Months	≥ 1 Year	≥ 2 Years	≥ 3 Years
Overall total exposure	4310	4270	3323	2391	930	189
Phase 1 studies[a]	62	62	0	0	0	0
Phase 2 supportive studies[b]	383	378	284	198	9	4
Phase 3 advanced cancer studies[c]	3561	3534	2813	2046	875	170
Giant cell tumor studies[d]	304	296	226	147	46	15

[a] Includes studies 20010123 and 20040176
[b] Includes studies 20040113, 20040114 and 20050134
[c] Includes studies 20050136, 20050244, 20050103 and 20050147
[d] Includes studies 20040215 and 20062004
Source: Table tias5-1.2

147 patients were treated with denosumab in GCTB indication >1 year, 46 >2 years, 15> 3 years.

The median duration on study was 19.4 months in Study 20040215 and 10.4 months in Study 20062004.

	Study 20040215 Denosumab 120 mg Q4W	Study 20062004 Denosumab 120 mg Q4W	Overall[b] Denosumab 120 mg Q4W
Number of subjects enrolled	37	282	305
Number of months on study[a]			
N	37	282	305
Mean	22.13	11.50	13.42
SD	16.28	7.57	10.71
Median	19.38	10.40	11.17
Q1, Q3	7.69, 38.90	5.32, 16.72	5.36, 18.23
Min, Max	2.0, 48.9	0.0, 29.1	0.0, 54.1
Number of subjects receiving ≥1 dose of investigational product	37	281	304
Number of doses received			

	Study 20040215 Denosumab 120 mg Q4W	Study 20062004 Denosumab 120 mg Q4W	Overall[b] Denosumab 120 mg Q4W
N	37	281	304
Mean	24.3	14.3	16.2
SD	17.0	7.9	10.9
Median	21.0	13.0	14.0
Q1, Q3	9.0, 42.0	7.0, 20.0	8.0, 21.5
Min, Max	4, 54	1, 33	1, 60

In the safety update of 31 Aug 2012, 486 patients enrolled in Cohort 1 and Cohort 2. Out of those 400 had a study duration of > 12 months and 209 had a study duration of >24 months (59% in Cohort 1 and 25% in Cohort 2). The median exposure of denosumab was 23 doses and the longest exposure 64 doses.

2.8.2. Adverse events

	Study 20040215 Denosumab 120 mg Q4W (N=37) n (%)	Study 20062004 Denosumab 120 mg Q4W (N=281) n (%)	Overall[b] Denosumab 120 mg Q4W (N=304) n (%)
Adverse events regardless of relationship			
All	33 (89.2)	236 (84.0)	259 (85.2)
Serious	9 (24.3)	25 (8.9)	34 (11.2)
Fatal	1 (2.7)	1 (0.4)	2 (0.7)
Leading to study discontinuation	2 (5.4)	13 (4.6)	15 (4.9)
Leading to investigational product discontinuation	2 (5.4)	14 (5.0)	16 (5.3)
CTCAE Grade 3, 4, or 5	10 (27.0)	50 (17.8)	59 (19.4)
Adverse events related to investigational product[a]			
All	12 (32.4)	140 (49.8)	149 (49.0)
Serious	0 (0.0)	3 (1.1)	3 (1.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)
Leading to study discontinuation	1 (2.7)	2 (0.7)	3 (1.0)
Leading to investigational product discontinuation	1 (2.7)	2 (0.7)	3 (1.0)
CTCAE Grade 3, 4, or 5	1 (2.7)	15 (5.3)	16 (5.3)

The most common AEs observed are summarised below.

Adverse events by preferred term in overall descending order of frequency (≥5% subject incidence in either study) safety subjects, treatment analysis phase, integrated analysis of safety.

Preferred Term	Study 20040215 Denosumab 120 mg Q4W (N=37) n (%)	Study 20062004 Denosumab 120 mg Q4W (N=281) n (%)	Overall[b] Denosumab 120 mg Q4W (N=304) n (%)
Number of subjects reporting adverse events[a]	33 (89.2)	236 (84.0)	259 (85.2)
Arthralgia	11 (29.7)	55 (19.6)	64 (21.1)
Headache	6 (16.2)	51 (18.1)	56 (18.4)
Nausea	7 (18.9)	48 (17.1)	54 (17.8)
Back pain	11 (29.7)	42 (14.9)	53 (17.4)
Fatigue	6 (16.2)	45 (16.0)	51 (16.8)
Pain in extremity	9 (24.3)	41 (14.6)	49 (16.1)
Vomiting	3 (8.1)	25 (8.9)	28 (9.2)
Musculoskeletal pain	5 (13.5)	21 (7.5)	26 (8.6)
Nasopharyngitis	4 (10.8)	20 (7.1)	24 (7.9)
Oedema peripheral	0 (0.0)	24 (8.5)	24 (7.9)
Upper respiratory tract infection	4 (10.8)	19 (6.8)	23 (7.6)
Constipation	6 (16.2)	16 (5.7)	22 (7.2)
Diarrhoea	3 (8.1)	19 (6.8)	21 (6.9)
Cough	6 (16.2)	14 (5.0)	19 (6.3)
Weight increased	1 (2.7)	18 (6.4)	19 (6.3)
Muscle spasms	4 (10.8)	13 (4.6)	17 (5.6)
Hypophosphataemia	0 (0.0)	17 (6.0)	17 (5.6)
Toothache	0 (0.0)	17 (6.0)	17 (5.6)
Non-cardiac chest pain	4 (10.8)	12 (4.3)	16 (5.3)
Abdominal pain	2 (5.4)	14 (5.0)	16 (5.3)
Paraesthesia	2 (5.4)	14 (5.0)	16 (5.3)
Bone pain	1 (2.7)	15 (5.3)	16 (5.3)
Insomnia	1 (2.7)	15 (5.3)	16 (5.3)
Myalgia	0 (0.0)	16 (5.7)	16 (5.3)
Dizziness	2 (5.4)	13 (4.6)	15 (4.9)
Neck pain	2 (5.4)	13 (4.6)	15 (4.9)
Rash	2 (5.4)	13 (4.6)	15 (4.9)
Pyrexia	2 (5.4)	12 (4.3)	14 (4.6)
Anaemia	3 (8.1)	9 (3.2)	12 (3.9)
Asthenia	2 (5.4)	11 (3.9)	12 (3.9)
Dyspnoea	4 (10.8)	7 (2.5)	11 (3.6)
Decreased appetite	3 (8.1)	8 (2.8)	11 (3.6)

Urinary tract infection	2 (5.4)	9 (3.2)	11 (3.6)
Hypoaesthesia	2 (5.4)	8 (2.8)	10 (3.3)
Vertigo	2 (5.4)	8 (2.8)	10 (3.3)
Influenza	3 (8.1)	6 (2.1)	9 (3.0)
Anxiety	2 (5.4)	6 (2.1)	8 (2.6)
Dyspepsia	2 (5.4)	6 (2.1)	8 (2.6)
Sinusitis	2 (5.4)	5 (1.8)	7 (2.3)
Muscular weakness	4 (10.8)	2 (0.7)	6 (2.0)
Hyperglycaemia	3 (8.1)	2 (0.7)	5 (1.6)
Bronchitis	2 (5.4)	3 (1.1)	5 (1.6)
Lower respiratory tract infection	2 (5.4)	1 (0.4)	3 (1.0)
Metastases to lung	2 (5.4)	1 (0.4)	3 (1.0)

N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 14.1.
[a] Includes all adverse events, not only those occurring with ≥ 5% frequency
[b] Subjects who rolled over from 20040215 to 20062004 or who discontinued 20040215 and re-entered 20062004 are counted only once in the overall column and their analysis period for the overall column will start from study 20040215 and end at study 20062004.
Source: Table tias6-5.1.1

Adverse events of interest:

Events of interest include hypocalcemia, ONJ, adverse events potentially associated with hypersensitivity, infections, malignancies, and cardiovascular adverse events.

Information was updated with data up to 31 Aug 2012.

Summary of adverse events of interest in studies 20040215 and 20062004 (up to March 2011 and study 20062004 safety follow-up period (up to 31 Aug 2012).

Event of Interest	Denosumab 120 mg Q4W Studies 20040215 and 20062004 up to 25 March 2011 (N = 304) n (%)	Denosumab 120 mg Q4W Study 20062004 During the Reporting Period (26 March 2011 to 31 August 2012) (N = 438)[a] n (%)	Denosumab 120 mg Q4W Study 20062004 Cumulatively up to 31 August 2012 (N = 472) n (%)
Hypocalcaemia			
Adverse events	15 (4.9)	13 (3.0)	25 (5.3)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)
Adjudicated positive ONJ	4 (1.3)	3 (0.7)	6 (1.3)[b]
Adverse events potentially associated with hypersensitivity			
Adverse events	30 (9.9)	37 (8.4)	63 (13.3)
Serious adverse events	0 (0.0)	1 (0.2)	1 (0.2)
Infection			
Adverse events	109 (35.9)	112 (25.6)	169 (35.8)
Serious adverse events	9 (3.0)	14 (3.2)	19 (4.0)
Malignancy			
Adverse events	3 (1.0)	2 (0.5)	5 (1.1)
Cardiac disorders			
Adverse events	12 (3.9)	10 (2.3)	18 (3.8)
Serious adverse events	0 (0.0)	2 (0.5)	2 (0.4)
Vascular disorders			
Adverse events	18 (5.9)	17 (3.9)	30 (6.4)
Serious adverse events	0 (0.0)	1 (0.2)	1 (0.2)

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[a] N = Number of subjects who received ≥ 1 dose of denosumab and remained on study after March 26, 2011

[b] Represents the cumulative incidence in Study 20062004. One additional case was reported from Study 20040215.

n = Number of subjects reporting ≥ 1 event

Includes only treatment-emergent adverse events and serious adverse events

Coded using MedDRA version 14.1 (25 March 2011) and 15.1 (26 March 2011 to 31 August 2012) by preferred term search strategy or Standardized MedDRA Query.

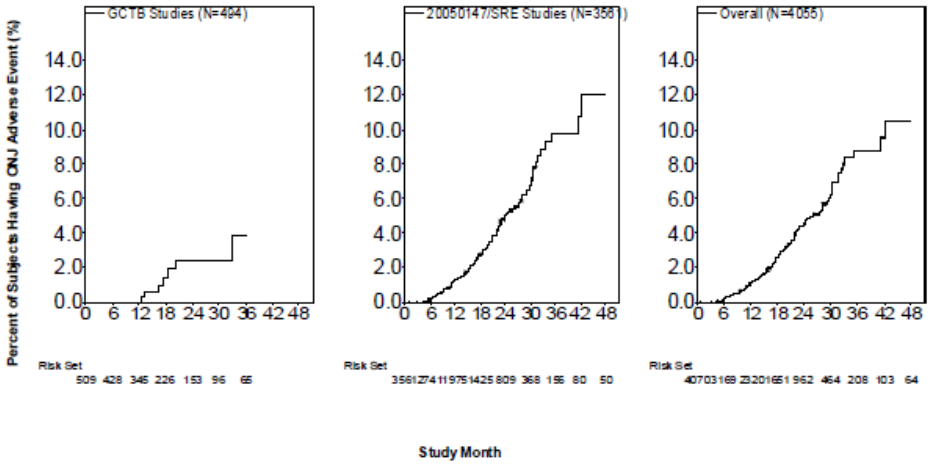
ONJ

At the interim analysis (median time on study 11.2 months), the overall subject incidence of ONJ positively adjudicated by the external adjudication committee was 1.3% (4 subjects): 2.7% (1 subject) in Study 20040215 (median time on study 19.4 months) and 1.1% (3 subjects) in Study 20062004 (median time on study 10.4 months). Two of the 4 subjects had a tooth extraction prior to the ONJ event. One subject received oral antibiotic rinses for treatment of ONJ, and 2 subjects received antibiotics and limited dental procedures. The last subject underwent open dissection of the sinuses, osteotomy of the upper jaw, oral-antral fistula closure, and extraction of 4 teeth.

At the update (Aug 2012), further 3 cases were reported.

Of the seven cases in total 2 had resolved and 5 were reported ongoing.

Figure 1. Time to Adjudicated Positive Osteonecrosis of the Jaw Adverse Events for Denosumab-treated Subjects in GCTB Studies and Study 20050147 and SRE Studies Pooled Kaplan-Meier Curves



Malignancies

No malignancies were reported in Study 20040215. Three malignancies were reported in Study 20062004, 2 bone sarcomas and 1 thyroid cancer; none of these was considered to be related to denosumab by the investigators. The 2 bone sarcomas were serious adverse events resulting in denosumab discontinuation and discontinuation from the study.

In addition, 5 subjects discontinued the studies due to disease progression (2 subjects discontinued Study 20040215 and 3 subjects discontinued Study 20062004). Two additional subjects were diagnosed with osteosarcoma following discontinuation from Study 20040215.

Overall, there were 9 subjects with either bone malignancy or disease progression: 5 subjects with disease progression, 2 subjects with osteosarcoma following discontinuation, and 2 subjects with bone malignancy. Based on information available for each case, 4 of these subjects appeared to have malignant transformation of GCTB, with 1 of these cases being associated with prior radiotherapy. Three subjects had either prior history of osteosarcoma or sarcoma present at baseline, and 2 subjects appeared to have sarcoma that was misdiagnosed as GCTB.

At the update further two subjects reported malignancies one case of sarcoma and one case of giant cell bone tumour.

2.8.3. Serious adverse events and deaths

At the interim analysis thirty-four subjects (11.2%) had experienced serious adverse events and 3 subjects (1.0%) experienced serious adverse events considered related to investigational product. There were two cases each of osteonecrosis of the jaw and osteomyelitis and there was one each of the remaining SAEs. By MedDRA the rates were highest in investigations in infections and infestations (3.0%) injury, poisoning and procedural complications (3.0%); musculoskeletal and connective tissue disorders (2.0%); neoplasms benign, malignant and unspecified (1.6%); and nervous system disorders (1.6%)

One subject in each study (0.7% overall) died, in study 200415 “neoplasm malignant” and in study 20062004, respiratory failure. Both patients had pulmonary metastases.

In the update (Aug 2012) Serious adverse events were reported for 47 subjects (10.7%) during the reporting interval from last update. Back pain were reported for five patients, four with bone giant cell tumour, three with ONJ, two patients each had appendicitis, cellulitis, subcutaneous abcess and anemia reported. All other events were reported for one patient.

Four patients died, the reported events were bone giant cell tumour, sarcoma, complete suicide and respiratory failure.

Two cases of hyperparathyroidism were reported; increased levels of PTH were reported.

2.8.4. Laboratory findings

Denosumab administration was associated with mild, transient decreases in serum calcium in studies 20040215 and 20062004. Subject incidence of grade 2 calcium decreases was 8/304 (2.6%).

Denosumab administration was associated with decreases in serum phosphorus in studies 20040215 and 20062004. CTCAE grade 3 low phosphorus values were observed for 3 subjects (8.1%) in Study 20040215 and 26 subjects (9.3%) in study 20062004.

Hypocalcemia as well as hypophosphatemia are included as ADRs in the SmPC.

No other clinically significant changes in laboratory variables are reported from the two studies in GCTB populations.

The laboratory findings were in line with previously observed changes.

2.8.5. Safety in special populations

The pharmacokinetics, safety, and tolerability of denosumab were evaluated in a phase 1 study in healthy volunteers and subjects with impaired renal function (Study 20040245). Overall, the results of this study indicate that no dose adjustments of denosumab are required when administered to patients with renal impairment. In this study, the potential for hypocalcemia in subjects with severe renal impairment or subjects with end-stage renal disease receiving dialysis appeared greater compared with subjects who had mild or moderate renal impairment and with subjects who had normal renal function. This is addressed in an ongoing type II variation.

Denosumab has not been evaluated in subjects with impaired liver function.

The lack of studies in patients with impaired liver function is acceptable on the basis of the pharmacokinetics of denosumab and its effects on liver CYP-enzymes.

Paediatric population: In total ten patients above the age of 12 with giant cell tumour of the bone were included in study 20062004. In the update (Aug 2012) in total 15 adolescents were treated, and in the data snap-shot (Aug 2013) in total 18 adolescents were treated.

2.8.6. Immunological events

No subjects tested positive for binding antidenosumab antibodies during Studies 20040215 or 20062004, consistent with the low incidence of binding antibodies observed throughout the denosumab clinical development program (< 1 of over 3000 denosumab-treated subjects in the studies included in the denosumab Advanced Cancer marketing application). No neutralizing antibodies have been reported in any denosumab clinical study to date.

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

No drug-drug interaction studies have been made.

This is acceptable on the basis of the pharmacokinetics of denosumab and it's effects on liver CYP-enzymes.

2.8.8. Discontinuation due to AES

A summary of the discontinuation AEs is provided in the table below.

Adverse Events Leading to Investigational Product Discontinuation by Preferred Term in Descending Order of Frequency (Safety Subjects, Treatment Analysis Phase, Integrated Analysis of Safety)

Preferred Term	Study 20040215 Denosumab 120 mg Q4W (N=37) n (%)	Study 20062004 Denosumab 120 mg Q4W (N=281) n (%)	Overall[a] Denosumab 120 mg Q4W (N=304) n (%)
Number of subjects reporting adverse events leading to investigational product discontinuation	2 (5.4)	14 (5.0)	16 (5.3)
Osteonecrosis of jaw	1 (2.7)	1 (0.4)	2 (0.7)
Pathological fracture	1 (2.7)	0 (0.0)	1 (0.3)
Anaemia	0 (0.0)	1 (0.4)	1 (0.3)
Arthralgia	0 (0.0)	1 (0.4)	1 (0.3)
Bone neoplasm	0 (0.0)	1 (0.4)	1 (0.3)
Metastases to lung	0 (0.0)	1 (0.4)	1 (0.3)
Neoplasm progression	0 (0.0)	1 (0.4)	1 (0.3)
Pain in extremity	0 (0.0)	1 (0.4)	1 (0.3)
Post procedural infection	0 (0.0)	1 (0.4)	1 (0.3)
Respiratory failure	0 (0.0)	1 (0.4)	1 (0.3)
Sarcoma	0 (0.0)	1 (0.4)	1 (0.3)
Spindle cell sarcoma	0 (0.0)	1 (0.4)	1 (0.3)
Tooth abscess	0 (0.0)	1 (0.4)	1 (0.3)
Tooth infection	0 (0.0)	1 (0.4)	1 (0.3)
Tumour haemorrhage	0 (0.0)	1 (0.4)	1 (0.3)

N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the overall denosumab group and coded using MedDRA Version 14.1.
[a] Subjects who rolled over from 20040215 to 20062004 or who discontinued 20040215 and re-entered 20062004 are counted only once in the overall column and their analysis period for the overall column will start from study 20040215 and end at study 20062004.
Source: Table tias6-15.2

Most discontinuation AEs are related to either to ONJ or malignancies emphasising the need for long term data to assess the risks associated with long-term treatment.

Updated safety in response to second RSI:

501 patients in all three cohorts that received ≥1 dose of denusumab were included in the data snap-shot.

Table1. Summary of On-Study Duration (Safety Subjects Cohort 1 and 2) (Study 20062004 EU Snapshot, Cutoff of 30 August 2013)

Duration On-study	Study 20062004 Cohort 1 (N = 257) n (%)	Study 20062004 Cohort 2 (N = 229) n (%)	Study 20062004 Cohorts 1 and 2 (N = 486) n (%)
> 6 months	249 (96.9)	225 (98.3)	474 (97.5)
> 12 months	226 (87.9)	174 (76.0)	400 (82.3)
> 18 months	185 (72.0)	88 (38.4)	273 (56.2)
> 24 months	151 (58.8)	58 (25.3)	209 (43.0)

18 skeletally mature adolescents were enrolled and treated with denuosumab for 25.5 (9.5-46.6) months.

A total of 186 patients were included in the follow up phase (45 patients >1 year and 6 patients >18 months).

Table 4. Summary of Subject Incidence of Adverse Events (Safety Analysis Set) (Study 20062004 EU Snapshot, Cutoff of 30 August 2013)

	All (N=501) n (%)
Adverse events regardless of relationship	
All	461 (92.0)
Serious	88 (17.6)
Fatal	5 (1.0)
Leading to study discontinuation	25 (5.0)
Leading to investigational product discontinuation	25 (5.0)
CTCAE Grade 3, 4, or 5	122 (24.4)
Adverse events related to investigational product[a]	
All	282 (56.3)
Serious	18 (3.6)
Fatal	1 (0.2)
Leading to study discontinuation	9 (1.8)
Leading to investigational product discontinuation	8 (1.6)
CTCAE Grade 3, 4, or 5	37 (7.4)

Page 1 of 1

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

The most common adverse events were consistent with previous reported events (arthralgia, fatigue, headache, pain in extremity, back pain and nausea). Adverse events of grade 3-5 were reported for 24%.

In total 18% of the subjects experienced serious adverse events the most common events were ONJ (7 subjects 1.4%), back pain (5 subjects 1.0%, bone giant cell tumour out of one was a malignant transformation (5 subjects 1.0 %), anemia (4 subjects 0.8%), appendicitis (4 subjects, 0.8%) and gastroenteritsis (3 subjects, 0.6%).

In total 5 patients had died during the treatment phase, the reported fatal adverse events were disease progression, suicide, two respiratory failures, transformation to high-grade sarcoma.

The only events that lead to discontinuation of study in more than one patient wee ONJ in 4 subjects and sarcoma in 2 subjects.

Table 5. Summary of Clinically Significant Adverse Events (Safety Analysis Set) (Study 20062004 EU Snapshot, Cutoff of 30 August 2013)

Event of Interest	All (N=501) n (%)
Subjects with adverse events of hypocalcaemia	30 (6.0)
Subjects with serious adverse events of hypocalcaemia	0 (0.0)
Subjects having adjudicated positive ONJ adverse events	10 (2.0)
Subjects with adverse events potentially associated with hypersensitivity	77 (15.4)
Subjects with serious adverse events potentially associated with hypersensitivity	1 (0.2)
Subjects with adverse events of infection	218 (43.5)
Subjects with serious adverse events of infection	25 (5.0)
Subjects with adverse events of skin infection	14 (2.8)
Subjects with serious adverse events of skin infection	2 (0.4)
Subjects with adverse events of new primary malignancy	11 (2.2)

ONJ = osteonecrosis of the jaw
N = Number of subjects who received ≥ 1 dose of denosumab
n = Number of subjects reporting ≥ 1 adverse event
Includes only treatment-emergent adverse events and serious adverse events
Coded using MedDRA version 16.0 by preferred term search strategy or SMQ.

ONJ

Ten patients had positively adjucate ONJs during the treatment phase and one during follow-up phase (the event started 117 days after discontinuation of denosumab, five had resolved and 6 were ongoing at time of the data snap-shot.

New primary malignancies: Eleven cases were reported during the treatment period; two sarcomas, two cases of breast cancer, one of each of bone giant cell tumour, bone sarcoma, neoplasm progression, papillary thyroid cancer, spindle cell sarcoma, soft tissue neoplasm and one case of tumour pain.

GCTB malignancy (cases of primary malignant GCTB (PMGCTB), secondary malignant GCTB (SMGCTB) and sarcomatuos transformation (ST); Ten cases were reported during treatment period. Of these two were reported as secondary malignant GCTB, three subjects had sarcomatous transformation that were reported as new primary malignancies.

Pregnancies

Thirteen subjects became pregnant, 6 had elective or spontaneious abortions, three withdrew from study and had full-term infants without complications and the rest the outcome is unknown.

There were 11 paternal exposures.

Follow-up phase

Fifteen **SAEs** were reported; 2 subjects each of anemia, asthenia, death, metastases to lung and nausea, all other events in one case each.

Fatal events were reported in 8 cases (progression in six cases and unknown in two cases).

ONJ, Malignancies

One case of positively adjudicated ONJ and one case of PMGCTB were reported, three patients had new malignancies (one PMGCTB, one adenocarcinoma of the colon and one bronchioalveolar carcinoma).

2.8.9. Post marketing experience

Not applicable for GTCB.

2.9. Overall conclusions on clinical safety

Discussion on clinical safety

The major safety results seem consistent with data from previous studies, no new major safety concerns has emerged. However, further follow-up is needed to exclude effects related to long-term treatment.

Almost all patients experienced adverse events, about 5% led to treatment (or study) discontinuations. About 20 % experienced serious adverse events at the date of the data snap-shot. The most common SAEs were ONJ (7 subjects, 1.4%), back pain (5 subjects) and bone giant cell tumour of the bone (5 subjects). In total five patients had fatal events.

The main safety concerns are: ONJ, which is an established adverse effect, and a potential impact on malignant transformation, which is part of the natural course of GCTB. In total 10 subjects had positively adjudicated ONJ during the treatment phase but also one case was reported in the follow-up phase 3 months post-treatment. Six of the ONJs were ongoing at the time for the data snap-shot.

There were six cases reported of malignant transformation, two cases of secondary malignancy of giant cell tumour of the bone and four cases of sarcomatous transformation (two of which transformation to malignant lung lesions) as per the data snap-shot. Three of those had had previous radiotherapy.

Both for ONJ and malignant transformation there were cases reported post-treatment.

A difficulty in the evaluation of safety profile of denosumab is the uncontrolled study design. The subjects in this indication are younger and will be exposed for a longer duration than in previously approved indication, also the rarity of important events such as ONJ and malignant transformation indicate the need for follow-up both during treatment and follow-up including sufficient number of patients.

Finally, the number of adolescents studied is small and does not allow any clear safety conclusions for this group per se. An acceptance of this patient group based on the present safety data has to rely on assumptions about similarities with adult subjects and not on the experience with the adolescent subjects.

Conclusions on clinical safety

The safety profile so far is consistent with the known safety profile of denosumab. However as the exposure in the current indication is longer than for previous indications; further safety follow-up is needed to allow more adequate assessments of safety, as proposed with the study 20140114 which is part of the agreed RMP.

2.10. Risk management plan

PRAC advice

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

This advice is based on the following content of the Risk Management Plan version 10.0 of 11 July 2014:

Safety concerns

Table: Summary of safety concerns

Important identified risks	hypocalcemia, ONJ, hypersensitivity reactions, atypical femoral fracture, musculoskeletal pain
Important potential risks	infection, cardiovascular events, malignancy, osteonecrosis outside the jaw, immunogenicity, cataracts in men with prostate cancer undergoing ADT, thyroid function disorder, **delay in diagnosis of PMGCTB**
Missing information	risks during pregnancy and lactation, pediatric patients, patients with multiple myeloma, patients with renal impairment, 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 GCTB, off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity

Pharmacovigilance plans

Table: Ongoing and Planned Studies in the Pharmacovigilance Plan

Only studies specifically concerning GCBT included below.

Study / Activity Type, Title, and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
20062004 An open-label, multicenter phase 2 study of denosumab in subjects with GCTB Category 3	• Evaluate the safety profile of denosumab in subjects with GCTB • Evaluate time to disease progression in subjects with unsalvageable GCTB treated with denosumab (cohort 1) • Evaluate the proportion of subjects who do not require surgery in denosumab-treated subjects with salvageable GCTB (cohort 2) • Evaluate denosumab pharmacokinetics (PK) in adolescent and adult subjects with GCTB (PK subset)	Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with GCTB	Ongoing	Primary analysis report anticipated 2019 Final report anticipated 2019
20080560 Controlled clinical study A double-blind, placebo-controlled study to evaluate new or worsening lens opacifications in subjects with nonmetastatic prostate cancer receiving denosumab for bone loss due to androgen deprivation therapy Category 3	• To assess the effect of denosumab on cataract event development or progression by month 12 based on a change of ≥ 1.0 in posterior subcapsular, ≥ 1.0 in cortical, or ≥ 0.7 in nuclear opalescence using the LOCS III score • To assess the effect of denosumab on cataract event development or progression by month 12 based on a change of ≥ 1.5 in posterior subcapsular, ≥ 1.5 in cortical, or ≥ 1.5 in nuclear opalescence using the LOCS III score • To assess the effect of denosumab on cataract event development or progression by month 6 based on LOCS III scores • To assess the effect of denosumab on confirmed cataract event development or progression by month 12 based on LOCS III scores • To assess the effect of denosumab on the incidence of decreased best corrected visual acuity from the baseline best corrected visual acuity on the “Early Treatment Diabetic Retinopathy Study” charts • To assess the effect of denosumab on change in refraction needed to achieve best corrected visual acuity • To describe the safety of denosumab administration as measured by adverse events and safety laboratory parameters	Cataract in men with prostate cancer receiving ADT	Ongoing	Final report anticipated Q1 2017
20101102 Postmarketing case registry study Osteonecrosis of the jaw (ONJ) case registry Category 3	• Estimate the rate and describe the time course of resolution of ONJ • Describe the clinical features of ONJ including severity and staging at registry enrollment • Characterize the frequency of risk factors for incident ONJ such as a history of inflammatory dental disease (periodontal and dental abscesses), dentoalveolar procedures, smoking, use of anti-angiogenic agents, and duration/dosing regimens of antiresorptive agents prior to the development of ONJ • Characterize subsequent treatment patterns for ONJ including antimicrobial rinses, antibiotics, and surgery • Characterize treatment patterns of antiresorptive therapy subsequent to incident ONJ such as the proportion of subjects who continue to be treated with antiresorptive agents by specific agents and ONJ severity and stage	ONJ, prior IV bisphosphonate treatment	Ongoing	Final report anticipated Q4 2021
20101335 Postmarketing	• To estimate the proportion of XGEVA prescriptions that are for off-label	Pediatric patients,	Ongoing	Final report anticipated Q2

observational study Postmarketing utilization study to estimate off-label use of XGEVA (denosumab 120 mg) in selected European countries using multiple observational databases Category 3		indications • To estimate the proportion of patients receiving XGEVA off-label • To describe the distribution of types of XGEVA off-label use at the prescription level and the patient level • To describe the distribution of XGEVA off-label prescriptions by provider specialty	patients with multiple myeloma		2014
20101363 Postmarketing observational study A noninterventional pharmacovigilance study of osteonecrosis of the jaw and infection leading to hospitalization among patients with cancer treated with XGEVA or zoledronic acid in Sweden, Denmark, and Norway Category 3		• To estimate, by treatment cohort, the 1-, 2-, 3-, 4-, and 5-year incidence proportions and 95% CIs for medically confirmed ONJ among patients with cancer whose initial antiresorptive treatment is XGEVA or IV zoledronic acid • To estimate, by treatment cohort, the 1-, 2-, and 3-year incidence proportions and 95% CIs for infection leading to hospitalization for the XGEVA and zoledronic acid inception cohorts • To estimate the 1-, 2-, 3-, 4-, and 5-year incidence proportions and 95% CIs for medically confirmed ONJ in patients who start cancer-related antiresorptive treatment with any oral or IV bisphosphonate at the dose indicated for cancer patients and switch to XGEVA • To estimate the 1-, 2-, 3-, 4-, and 5-year incidence proportions and 95% CIs for medically confirmed ONJ for the XGEVA-switch cohort stratified by the number of prior cancer-related bisphosphonate treatments • To characterize the XGEVA inception, zoledronic acid inception, and the XGEVA-switch cohorts with respect to patient characteristics, cancer type, medical history, and number of cancer-related bisphosphonate or XGEVA treatments	ONJ, infection, prior IV bisphosphonate treatment	Ongoing	Final report anticipated Q4 2019
20110102 Survey study Survey of oncology practitioners prescribing XGEVA in Europe to evaluate their knowledge of XGEVA Summary of Product Characteristics pertaining to osteonecrosis of the jaw Category 3	To survey oncologists prescribing XGEVA in Europe to evaluate their knowledge of the XGEVA SmPC pertaining to ONJ		ONJ	Not yet started	Anticipated 2015
20140114 Long-term safety follow-up of subjects with giant cell tumor of bone treated with denosumab in Protocol 20062004 Category 3	Estimate incidence rates (annual and cumulative) of adverse events of interest during long-term safety follow-up of subjects with GCTB treated with denosumab in Study 20062004. Adverse events of interest include severe symptomatic hypocalcemia, ONJ, atypical femoral fracture malignancy in GCTB, and pregnancy.		Hypocalcemia ONJ Atypical femoral fracture Pregnancy Malignancy in GCTB Malignancy	Not yet started	Anticipated Q4 2023

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Identified Risks		
Hypocalcemia	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • What you need to know before you use XGEVA • Warnings and precautions • Possible side effects	Direct Healthcare Professional Communication (Dear Healthcare Professional Letter) was previously distributed to remind practitioners about the risk of severe symptomatic hypocalcemia associated with XGEVA and to inform about the risk of late onset of hypocalcemia. A further Direct Healthcare Professional Communication will be distributed following approval of the SmPC text in order to make healthcare providers aware of the extension for calcium monitoring within the XGEVA SmPC to include all patients, not just those with renal impairment.
ONJ	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.1, Pharmacodynamic properties Relevant text is provided in the following sections of the PIL: • What you need to know before you use XGEVA • Warnings and precautions • Possible side effects	Direct Healthcare Professional Communication (Dear Healthcare Professional Letter) will be distributed following approval of the updated SmPC text to remind practitioners about the risk of ONJ with XGEVA and that oral health should be monitored.

Hypersensitivity reactions	Relevant text is provided in the following sections of the SmPC: • Section 4.3, Contraindications • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • What you need to know before you use XGEVA • Possible side effects	None
Atypical femoral fracture	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • Warnings and precautions • Possible side effects, Rare side effects	None
Musculoskeletal pain	Relevant text is provided in the following sectionsections of the SmPC: • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • Possible side effects, Very common side effects	None
Potential Risks		
Infection	None	None
Cardiovascular events	None	None
Malignancy	Relevant text is provided in the following sections of the SmPC • Section 4.1, Therapeutic indications • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.1, Pharmacodynamic properties Relevant text is provided in the following sections of the PIL: • What XGEVA is and what it is used for • Children and adolescents How to use XGEVA	None
Osteonecrosis outside of the jaw	None	None
Immunogenicity	Relevant text is presented in the following section of the SmPC: Section 5.1, Pharmacodynamic properties	None
Cataracts in men with prostate cancer undergoing ADT	None	None
Thyroid function disorder	None	None
Missing Information		
Risks during	Relevant text is provided in the following sections of the SmPC:	None

pregnancy and lactation	• Section 4.6, Fertility, pregnancy, and lactation • Section 5.3, Preclinical safety data Relevant text is provided in the following section of the PIL: Pregnancy and breast-feeding	
Pediatric patients	Relevant text is provided in the following sections of the SmPC: • Section 4.8, Undesirable effects • Section 4.2, Posology and method of administration • Section 5.1, Pharmacodynamic properties • Section 5.2, Pharmacokinetic properties • Section 5.3, Preclinical safety data Relevant text is provided in the following section of the PIL: Children and adolescents	None
Multiple myeloma	Relevant text is provided in the following section of the SmPC: Section 5.1, Pharmacodynamic properties	None
Patients with hepatic impairment	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration Section 5.2, Pharmacokinetic properties	None
Patients with previous intravenous treatment bisphosphonate	Relevant text is presented in the following section of the SmPC: • Section 4.5, Interaction with other medicinal products and other forms of interaction • Section 5.1, Pharmacodynamic properties Relevant text is presented in the following section of the PIL: Other medicines and XGEVA	None
Safety with long-term treatment and with long-term follow-up after treatment in Adults and skeletally mature adolescents with GCTB	None	None
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity	None	None

The CHMP endorsed this advice without changes.

2.11. Changes to the Product Information

Summary of Product Characteristics

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

4.1 Therapeutic indications

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

Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

4.2 Posology and method of administration

Posology

Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present (see section 4.4).

Bone metastases from solid tumours
The recommended dose of XGEVA for the prevention of skeletal related events is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm.

~~Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present (see section 4.4).~~

Giant cell tumour of bone
The recommended dose of XGEVA for the treatment of giant cell tumour of bone 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.

Patients in the phase II study who underwent complete resection of giant cell tumour of bone did receive an additional 6 months of treatment following the surgery as per study protocol.

Patients with giant cell tumour of bone should be evaluated at regular intervals to determine whether they continue to benefit from treatment. In patients whose disease is controlled by XGEVA, the effect of interruption or cessation of treatment has not been evaluated, however limited data in these patients does not indicate a rebound effect upon cessation of treatment.

Patients with renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2). Experience in patients on dialysis or with severe renal impairment (creatinine clearance < 30 ml/min) is limited (see section 4.4 for recommendations relating to monitoring of calcium).

Patients with hepatic impairment
The safety and efficacy of denosumab have not been studied in patients with hepatic impairment (see section 5.2).

Elderly patients (age ≥ 65)
No dose adjustment is required in elderly patients (see section 5.2).

Paediatric population
Treatment of skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity: the posology is the same as in adults.

XGEVA is not recommended in paediatric patients (age < 18) other than skeletally mature adolescents with giant cell tumour of bone. ~~as the safety and efficacy of XGEVA in these patients have not been established.~~

The safety and efficacy of XGEVA have not been evaluated in paediatric patients (age < 18) other than skeletally mature adolescents with giant cell tumour of bone.

4.4 Special warnings and precautions for use

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Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has occurred in patients treated with XGEVA. In clinical trials, the incidence of ONJ was higher with longer duration of exposure (see section 4.8); ONJ has also been diagnosed after treatment with Xgeva with the majority of cases occurring within 5 months after the last dose.

Patients who developed ONJ in clinical studies generally had known risk factors for ONJ, including invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), poor oral hygiene or other pre-existing dental disease, ~~advanced malignancies~~, infections, or concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors, radiotherapy to the head and neck). A dental examination with appropriate preventive dentistry should be considered prior to treatment with XGEVA in patients with active dental and jaw conditions (as listed above). While on treatment, patients should avoid invasive dental procedures if possible.

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Malignancy in Giant Cell Tumour of Bone or progression to metastatic disease is an infrequent event and a known risk in patients with Giant Cell Tumour of Bone. Patients should be monitored for radiological signs of malignancy, new radiolucency or osteolysis. Available clinical data does not suggest an increased risk of malignancy in GCTB patients treated with XGEVA.

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4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of XGEVA in pregnant women. Reproductive toxicity was shown in a study of cynomolgus monkeys, dosed throughout pregnancy with denosumab at AUC exposures 12-fold higher than the human dose (see section 5.3).

XGEVA is not recommended for use in pregnant women and women of childbearing potential not using highly effective contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with XGEVA. Any effects of Xgeva are likely to be greater during the second and third trimesters of pregnancy since monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

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4.8 Undesirable effects

Summary of the safety profile
The safety of XGEVA was evaluated in:

- 5,931 patients with advanced malignancies involving bone ~~and is derived from~~ in active-controlled, clinical trials examining the efficacy and safety of XGEVA versus zoledronic acid in preventing the occurrence of skeletal related events.
- 523 patients with giant cell tumour of bone in single-arm, clinical trials examining the efficacy and safety of XGEVA.

The adverse reactions are presented in table 1.

Tabulated list of adverse reactions
The following convention has been used for the classification of the adverse reactions reported in three phase III and ~~one~~ two phase II clinical studies (see table 1): very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000). Within each frequency grouping and system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported in patients with advanced malignancies involving bone or with giant cell tumour of bone

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In two phase II single-arm clinical trials in patients with giant cell tumour of bone, hypocalcaemia was reported in 5.7% of patients. None of the adverse events was considered serious.

……

In two phase II single-arm clinical trials in patients with giant cell tumour of bone, ONJ occurred in 2.3% (12 of 523) of patients treated with XGEVA (median overall exposure of 20.3 months; range: 0 -83.4). The patient year adjusted incidence of ONJ was 0.2% during the first year of treatment and 1.7% in the second year. The median time to ONJ was 19.4 months (range: 11 - 40). Based on duration of exposure, there are insufficient data in GCTB patients to assess risk of ONJ beyond 2 years.

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Paediatric population
XGEVA was studied in an open label trial that enrolled 18 skeletally mature adolescents with giant cell tumour of bone. Based on these limited data, the adverse event profile appeared to be similar to adults.

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5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of bone diseases – other drugs affecting bone structure and mineralisation, ATC code: M05BX04

Mechanism of action
RANKL exists as a transmembrane or soluble protein. RANKL is essential for the formation, function and survival of osteoclasts, the sole cell type responsible for bone resorption. Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone destruction in metastatic bone disease and multiple myeloma. Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction.

Giant cell tumours of bone are characterized by neoplastic stromal cells expressing RANK ligand and osteoclast-like giant cells expressing RANK. In patients with giant cell tumour of bone, denosumab binds to RANK ligand, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and proliferative tumour stroma is replaced with non-proliferative, differentiated, densely woven new bone.

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Clinical efficacy in adults and skeletally mature adolescents with giant cell tumour of bone
The safety and efficacy of XGEVA was studied in two Phase II open-label, single arm trials (studies 4 and 5) that enrolled 529 patients with giant cell tumour of bone that was either unresectable or for which surgery would be associated with severe morbidity.

Study 4 enrolled 37 adult patients with histologically confirmed unresectable or recurrent giant cell tumour of bone. Response criteria included elimination of giant cells based on histopathology or lack of progression by radiography.

Of the 35 patients included in the efficacy analysis, 85.7% (95% CI: 69.7, 95.2) had a treatment response to XGEVA. All 20 patients (100%) with histology assessments responded. Of the remaining 15 patients, 10 (67%) radiographic measurements showed no progression of the target lesion.

Study 5 enrolled 507 adult or skeletally mature adolescents with giant cell tumour of bone and evidence of measurable active disease.

In Cohort 1 (patients with surgically unsalvageable disease), median time to disease progression was not reached, 21 of the 258 treated patients had disease progression. In Cohort 2 (patients with surgically salvageable disease whose planned surgery was associated with severe morbidity), 209 of the 228 evaluable patients treated with XGEVA had not undergone surgery by month 6. Overall of 225 patients for whom giant cell tumours of bone surgery (excluding lung metastases only) was planned, 109 had no surgery performed and 84 underwent a less morbid procedure than planned at baseline. The median time to surgery was 261 days**.**

Upon enrolment of 305 patients in studies 4 and 5 a retrospective independent review of radiographic imaging data was performed. One hundred and ninety had at least 1 evaluable time point response and were included in the analysis (table 3). Overall, XGEVA achieved objective tumour responses in 71.6% (95% CI 64.6, 77.9) of patients (table 3)) assessed by any of the modalities, with the majority of responses defined by a reduction in fluorodeoxyglucose PET activity or increase in density measured in CT/HU, only 25.1 % of the patients had a response per RECIST. The median time to response was 3.1 months (95% CI 2.89, 3.65). The median duration of response was not estimable (four patients experienced disease progressions following an objective response). In 190 subjects evaluable for objective tumour response, 55 subjects had GCTB surgery, out of which 40 subjects had complete resections.

Table 3: Objective treatment response in patients with giant cell tumour of bone

	Number of patients evaluable for response	**Number of patients with an objective response**	**Proportion (%) (95% CI)** [1]
Based on best response	190	136	71.6(64.6, 77.9)
RECIST 1.1[2]	187	47	25.1(19.1, 32.0)
EORTC[3]	26	25	96.2(80.4, 99.9)
Density/Size[4]	176	134	76.1(69.1, 82.2)

[1] CI= Exact Confidence Interval
[2] RECIST 1.1: Modified Response Evaluation Criteria in Solid Tumours to evaluate tumour burden based on computed tomography (CT)/magnetic resonance imaging (MRI)
[3] EORTC: Modified European Organisation for Research and Treatment of Cancer criteria to evaluate metabolic response using fluorodeoxyglucose positron emission tomography (FDG-PET)
[4] Density/Size: Modified Inverse Choi criteria to evaluate tumour size and density using Hounsfield units based on CT/MRI

Effect on pain
Upon enrolment of 282 patients, in Study 5 cohorts 1 and 2 combined, a clinically meaningful reduction in worst pain (i.e., ≥ 2 point decrease from baseline) was reported for 31.4% of patients at risk (i.e. those who had a worst pain score of ≥ 2 at baseline) within 1 week of treatment, and ≥ 50% at week 5. These pain improvements were maintained at all subsequent evaluations. Baseline pre-treatment analgesic use in cohort 1

and cohort 2 was graded on a seven point scale, where 74.8% of patients reported no or mild analgesic use (i.e. analgesic score ≤ 2) and 25.2 % of patients used strong opioids (i.e. analgesic score 3 to 7).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with XGEVA in all subsets of the paediatric population in the prevention of skeletal related events in patients with bone metastases and subsets of the paediatric population below the age of 12 in the treatment of giant cell tumour of bone (see section 4.2 for information on paediatric use).

In Study 5, XGEVA has been evaluated in a subset of 18 adolescent patients (aged 13-17 years) with giant cell tumour of bone who had reached skeletal maturity defined by at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus) and body weight ≥ 45 kg. An objective response was observed for four of six evaluable adolescent patients in an interim analysis of Study 5. An investigator assessment reported that all 18 adolescent patients had a best response of stable disease or better (complete response in 2 patients, partial response in 8 patients, and stable disease in 8 patients). The European Medicines Agency has deferred the obligation to submit the final results of this study.

5.2 Pharmacokinetic properties

Absorption
Following SC administration, bioavailability was 62%.

Biotransformation
Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination
In subjects with advanced cancer, who received ~~With~~ multiple doses of 120 mg every 4 weeks an approximate 2-fold accumulation in serum denosumab concentrations was observed and steady-state was achieved by 6 months, consistent with time-independent pharmacokinetics. In subjects with giant cell tumour of bone who received 120 mg every 4 weeks with a loading dose on days 8 and 15, steady-state levels were achieved within the first month of treatment. Between weeks 9 and 49, median trough levels varied by less than 9%. In subjects who discontinued 120 mg every 4 weeks, the mean half-life was 28 days (range 14 to 55 days).

Package Leaflet

The Package Leaflet has been updated in accordance with the SmPC.

In addition, the MAH took the opportunity to update the contact details for the local representative in Croatia, which is acceptable.

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

3.1. Benefits

3.1.1. Beneficial effects

The majority of patients included in GCTB studies (200420015 and 20062004) are inoperable or have disease where surgery would lead to severe morbidity. The proposed indication is restricted to these populations.

In study 20042015 a beneficial effect was shown by a decrease in both giant cells and neoplastic cells in all twenty patients who had biopsies pre and during treatment. In ten of the fifteen patients who were evaluated only radiologically a response (as defined by stable disease at week 25) was recorded. In study 200420015 also a reduction from baseline in bone turn-over markers was shown, however except for TRAP-5b they were within reference ranges at baseline.

Study 20062004, which was primarily a safety study, included two cohorts, Cohort 1 with primary unresectable tumours and Cohort 2, where surgery would lead to substantial morbidity. The efficacy endpoints where, for the cohorts respectively; time to disease progression and proportion of subjects without any surgery at month 6.

The median time to objective tumour response (Based on any tumour response criteria) was three months. At the interims analysis (March 2011) only 4 % (6/169) in cohort 1 had progressive disease and 90% in cohort 2 (64/71) had not undergone surgery by month 6. At the data “snap-shot” with cut-off date 20 Aug 2013 the corresponding numbers were 8.1% (21/258) and 92% (209/228) respectively. Almost 20 % of the patients had a complete resection over the study. The majority of which in cohort 2, only 5% had a complete resection in cohort 1 and 40% in cohort 2. A total of 34 (13%) of subjects in cohort 1 and 127 (56%) of subjects in cohort 2 had on-study surgery.

A retrospective independent radiographic review of tumour response was performed by a central imaging vendor including patients from both studies. CT, MRI and/or PET were provided for 190 (of 303) patients where imaging data were available. A response as defined by any of the modalities was recorded in 72 % (136/190) of the patients had a response however the majority of responses was seen in density or reduced metabolic activity and only 25% of the patients had a response as defined by RECIST.

There were indications of clinical benefits such as a reduction in pain, however at baseline the majority of patients did not have a strong opioid use, and investigator assessed clinical benefit.

3.1.2. Uncertainty in the knowledge about the beneficial effects

The GCTB is a rare disease which consequently limits the recruitment to the studies; however in this application the studies also are uncontrolled which adds to the uncertainty. With regards to the rarity of the disease also the validity of literature and historical comparisons is limited.

The impact of the “stabilisation of the disease” as reported could not be fully evaluated without a control group, as the natural course of the inoperable GCTB is not extensively documented and in addition most patients included in the current GCTB studies have no relevant treatment options.

With regards to histological findings only a part of the population in the study 200420015 was sampled, and it is impossible to make firm conclusions if the sample is fully representative for the population. The same

holds true for the populations evaluated by different radiological modalities. The independent review radiology assessments were only including 60% of the patients in the studies, analyzes have been made with regards to demographic factors and other criteria to confirm the validity of the sample, however if this is a biased selection or a representative population will never be fully elucidated.

There is an uncertainty if the observed “avoidance of” and “reduced extent of surgery” during the observation period is accompanied by a long-term benefit as the follow-up still is limited. Furthermore the endpoint “to perform a less morbid surgery” is depending on the investigators classification of surgery at inclusion, although this has partly been addressed by an independent review but still the initial definition is based on subjectivity.

In study 20062004 the efficacy was not up-front systematically evaluated, but only as per standard of care, obviously the decision to perform radiology could be influenced by different factors.

Although there is no indication on a rebound effect after discontinuation of denosumab the data is still limited and no firm conclusions can be made. After GCTB surgery 6/34 (17.6%) in cohort 1 and 18/127 (14.2%) in cohort 2 had disease progression or recurrence after surgery.

The clinical benefit as assessed by investigators and the reduction in pain is not possible to evaluate without a control group in this particular context i.e. inoperable patients with no obvious treatment alternative.

The number of adolescents is very limited and the results are consequently more uncertain in this population.

3.2. Risks

3.2.1. Unfavourable effects

The safety profile is consistent with the known safety profile of denosumab. However the population in this indication is younger than previous populations and the duration of treatment is longer which has to be taken into consideration.

Almost all patients experienced adverse events, about 5% led to treatment (or study) discontinuations.

There are two major safety problems of interest to denosumab in the GCTB population:

- ONJ, which is an established adverse effect, and

- a potential impact on malignant transformation, which is part of the natural course of GCTB.

In total 10 subjects had positively adjudicated ONJ during the treatment phase and one case was reported in the follow-up phase, three months post-treatment. Six of the ONJs were ongoing at the last up-date.

There were six cases reported of malignant transformation, two cases of secondary malignancy of giant cell tumour of the bone and four cases of sarcomatous transformation (two of which transformation to malignant lung lesions) as per the data snap-shot. Three of those had had previous radiotherapy which is a common feature in sarcomatous transformation. So far this seems fairly consistent with the rate in GCTB.

3.2.2. Uncertainty in the knowledge about the unfavourable effects

As denosumab treatment can be expected to be continued for several years in the GCTB indications, the follow-up, although more substantiated in the last update, is of vital importance to fully understand the cumulative incidence of clinically important AEs.

There are reports of ONJ both during and after discontinuation however as the follow-up is limited the knowledge on both long-term effects of treatment and after denosumab discontinuation is still uncertain.

Also with regards to the natural course with malignant transformation in GCTB the follow-up is still too limited to rule out an adverse effect, according to data presented malignant transformation occurs typically ≥ 1 year after diagnosis ranging 1-8 years in studies.

The consequences of a reduction in surgery i.e. if not the whole initial tumour containing area is removed is not evaluated in the studies however in these indications where the tumour is inoperable this is of less importance.

Also with regards to safety the number of adolescents is too limited to draw firm conclusions, information must be based also on adult data.

3.3. Balance

The populations in the GCTB indications have a disease that is inoperable either because of the location and size or by severe morbidity consequences by surgery. The positive effect as demonstrated by a stabilisation of the disease and reduction in surgery are with regards to the very limited, if any, treatment options and the subjectivity inherent in many parameters hard to fully evaluate. However there are complete resections reported which is of obvious clinical importance.

Denosumab treatment can be expected to be continued for several years in the GCTB indications, the follow-up, although more substantiated in the last up-date, is of importance to fully understand the effect and the cumulative adverse effects.

A severe adverse event is ONJ which is reported both during and after discontinuation of denosumab, however as the follow-up is limited the knowledge on long-term effects both on ONJ but also other events after denosumab discontinuation is still uncertain.

Also with regards to the natural course with malignant transformation in GCTB the follow-up is still too limited to rule out an adverse effect.

3.3.1. Importance of favourable and unfavourable effects

A complete resection has been performed in about 20% of the patients over the study which, is considered of clinical importance, so are the cases where a less morbid surgical procedure could be performed.

A stabilisation of the disease would also be of clinical importance however as there is no control population the true effect is hard to estimate. The tumour responses are mainly reported as density or reduction in activity, the radiological responses by RECIST are recorded in about 25% of the patients. The reduced activity/ increase in density is consistent with a pathologic response as described by a reduction of both giant cells and neoplastic stromal component but the true clinical value could not be estimated.

The major unfavourable effects are ONJ which is a serious concern as it has adverse impact on quality of life and has been described also after discontinuation, of the cases reported during the GCTB studies about half are ongoing.

An increase in malignant transformations would be of a negative importance if an increase compared to the natural course of GCTB would be detected.

3.3.2. Benefit-risk balance

In the populations described in the indication: giant cell tumour of the bone that is unresectable or where surgical resection is likely to result in severe morbidity the fairly limited effect in number of complete resections, but also reductions in surgical morbidity is of clinical importance.

The stabilising effect is more difficult to evaluate without a control-population. There are also other indications of effect as measured by density or activity in the lesions, or a reduction in giant cells or neoplastic stroma cells. The clinical value to the patients of these parameters remains uncertain. Also the validity of reduction in pain and clinical benefit assessed by investigator is uncertain.

The major concerns are ONJ during, and after, long-term treatment and an adverse effect on malignant progression during or after the study. So far these events are rare and the benefit currently out-weighs these concerns, however further follow-up is needed as proposed in the long-term follow-up study.

3.3.3. Conclusion

For the proposed indications with inoperable GCTB or GCTB where surgical resection is likely to result in severe morbidity the benefit/risk is considered favourable however with regards to the long duration of treatment further follow-up is needed as proposed in the study 20140014.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

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

Extension of indication to add treatment of giant cell tumour of bone in adults or skeletally mature adolescents. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, section 4.6 of the SmPC was updated with further guidance regarding pregnancy. In addition, the MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet and to update the contact details for the local representative in Croatia in the Package Leaflet.

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

Paediatric Data

No paediatric clinical studies were submitted as the only paediatric clinical study in the PIP is deferred (completion date December 2014).