EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2013
EMA/CHMP/661174/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Invented name XGEVA

Procedure No. EMEA/H/C/002173/II/0011

Marketing authorisation holder (MAH): Amgen Europe B.V.

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 15 June 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 proposed an extension of indication to add treatment of castration-resistant prostate cancer at high risk of developing bone metastases as determined by assessment of prostate-specific antigen (PSA). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC were proposed to be updated and the Package Leaflet was proposed to be updated accordingly.

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

Rapporteur: Kristina Dunder

Co-Rapporteur: Jan Müller-Berghaus

1.2. Steps taken for the assessment

Submission date:	15 June 2012
Start of procedure:	24 June 2012
Rapporteur's preliminary assessment report circulated on:	15 August 2012
Co-Rapporteur's preliminary assessment report circulated on:	6 September 2013
Rapporteur's updated assessment report circulated on:	14 September 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 September 2012
MAH's responses submitted to the CHMP on:	16 November 2012
Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	28 December 2012
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	17 January 2013
MAH's 2nd responses submitted to the CHMP on:	26 April 2013
Rapporteurs' preliminary assessment report on the MAH's 2nd responses circulated on:	10 June 2013

Rapporteur's updated assessment report on the MAH's 2nd responses circulated on:	19 June 2013
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	27 June 2013
MAH's 3rd responses submitted to the CHMP on:	23 September 2013
PRAC Rapporteur's RMP AR	3 October 2013
Rapporteur's preliminary assessment report on the MAH's 3rd responses circulated on:	8 October 2013
PRAC adoption of the PRAC Rapporteur's RMP AR:	10 October 2013
CHMP opinion:	24 October 2013

2. Scientific discussion

2.1. Introduction

XGEVA (denosumab) is a fully human monoclonal IgG2 antibody to RANK Ligand which was approved in the European Union for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours on 13 July 2011.

As part of the current procedure, the MAH initially applied for an extension of indication to add "treatment of castration-resistant prostate cancer at high risk of developing bone metastases as determined by assessment of prostate-specific antigen (PSA). XGEVA prolongs bone-metastasis-free survival by preventing bone metastases".

During the procedure, as part of the response to the 2nd CHMP Request for Supplementary Information (RSI), the applicant revised the proposed indication to:

"Delay of bone metastases in men with castration-resistant prostate cancer at high risk of developing bone metastases based on prostate-specific antigen (PSA) doubling time of 6 months or less".

In view of an outstanding major objection regarding clinical efficacy raised by the CHMP during the evaluation (see below), the MAH informed the Committee on 27 August 2013 of their decision not to pursue the claimed extension of the indication for XGEVA applied for under the present procedure, but proposed nevertheless to pursue with the application to enable implementation of the safety-related changes to the SmPC and Package Leaflet, and the changes to the risk management plan (RMP) that had been agreed during the CHMP review.

The CHMP endorsed the MAH's proposed way forward at its September 2013 CHMP meeting. Thus, the final scope of the application was revised as follows:

"Type II variation to delete the ADR cellulitis and text describing "skin infections (predominantly cellulitis) leading to hospitalisation" from section 4.8 of the SmPC and to delete the associated warning in SmPC section 4.4. Further, section 4.8 of the SmPC has been updated with a change in frequency of the ADR drug hypersensitivity from uncommon to rare, and with the addition of text describing symptoms of hypocalcaemia observed in clinical studies. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes to the SmPC and Package Leaflet and to update the contact details in the list of local representatives in the Package Leaflet."

2.2. Clinical Pharmacology aspects

Clinical pharmacokinetic (PK) data for denosumab were included and assessed as part of the original marketing authorisation application for Xgeva. Some PK data were also collected in study 20050147, which is pivotal clinical study included in the present application (see below).

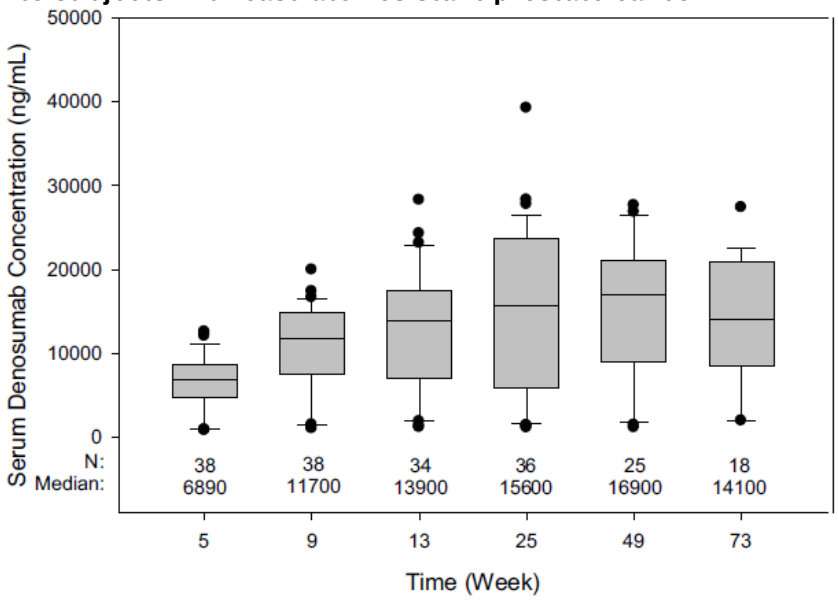
Concerning biopharmaceutical aspects, the marketed denosumab drug product preparation is a 70 mg/mL vial (1.7 mL deliverable volume for a total dose of 120 mg) and the product used in the pivotal study for the current application, Study 20050147, consisted of two 1.0-mL SC injections of a 60 mg/mL formulation to deliver a 120-mg dose of denosumab. Study 20060446 compared the pharmacokinetic profile of a single 120-mg SC dose of denosumab when administered as the above mentioned presentations. The results demonstrated that denosumab administered as one 120-mg injection (supplied from a single vial of 70 mg/mL denosumab) is bioequivalent to denosumab administered as two 60-mg injections (supplied from two vials of 60 mg/mL denosumab).

In study 20050147, blood samples for the measurement of serum denosumab concentrations were obtained from a subset of approximately 150 subjects before administration of investigational product on study day 1, then at weeks 5, 9, 13, 25, 49, 73, and at the end-of-study visit for the blinded treatment phase.

One hundred three subjects were enrolled in the substudy, of which 46 subjects received denosumab and 57 subjects placebo. Of the 46 subjects who received denosumab, 40 had serum denosumab concentrations assessed at baseline, 1 of whom (2.5%) had a quantifiable denosumab concentration for unknown reasons (30.137 ng/mL).

Trough serum denosumab concentrations (i.e. from samples obtained at the end of the SC dosing interval) are summarized in the figure below. The median trough serum denosumab concentration at the 1-month (week 5) visit was 6890 ng/mL. Exposures, based on trough serum concentrations, increased as anticipated, with approximately 2- to 2.5-fold higher median serum concentrations (15600 ng/mL) observed at month 6 (week 25). Median trough serum denosumab concentrations obtained at weeks 49 to 73 were similar (range 16900 to 14100 ng/mL).

Box plots for trough serum denosumab concentrations after SC administration of 120 mg denosumab Q4W to subjects with castrate-resistant prostate cancer



Solid line indicates median values, boxes indicate 25th to 75th percentiles, whiskers indicate 10th and 90th percentiles and circles represent outliers.

For the initially proposed extended indication, the proposed posology for XGEVA was the same as the currently approved posology. The PK data provided in study 20050147 is mainly descriptive and no formal population PK analysis has been made. However, the results obtained are consistent with results obtained in other indications and no relevant differences are expected. In the original CHMP assessment report for the initial XGEVA marketing authorisation application, it was concluded that disease status (i.e. breast cancer, prostate cancer, other solid tumours) does not markedly affect the pharmacokinetic profile of denosumab.

Concerning the use of different formulations/presentations for commercial use and in the clinical pivotal study, study 20060446 showed bioequivalence between the 60 and 70 mg/mL formulations when administered as a 120-mg dose. This study was also included in the original XGEVA marketing authorisation application and assessed in the corresponding CHMP assessment report and will therefore not be further discussed here.

In conclusion, the CHMP was of the view that the pharmacokinetic data provided are sufficient.

2.3. Clinical Efficacy aspects

Men with non-metastatic Castration Resistant Prostate Cancer (CRPC) will eventually develop clinically apparent metastatic disease, particularly to bone. Previous studies of bone-targeted agents in men with non-metastatic CRPC have failed to demonstrate significant improvement in delaying bone metastasis. These studies investigated clodronate (in hormone-sensitive prostate cancer) and zoledronic acid (in CRPC), as well as the endothelin receptor antagonist atrasentan (in CRPC). A study with another endothelin receptor antagonist, zibotentan, in patients with CRPC without bone metastases was recently terminated for lack of efficacy in 2011.

Denosumab is a fully human monoclonal IgG2 antibody to RANKL and binds with high affinity (Kd 3 x 10^{-12} M) and specificity to the soluble and cell membrane-bound forms of human RANKL. Binding to RANKL prevents RANK activation and inhibits the formation, activation, and survival of osteoclasts. As a result, denosumab is effective for prevention of “skeletal related events” in men with metastatic CRPC.

Pivotal study

Study 20050147

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center (319), international, Phase 3 Study of Denosumab on Prolonging Bone Metastasis-Free Survival in Men with Hormone-Refractory Prostate Cancer.

Study period; 03 February 2006 (date that the first subject was enrolled) to 30 July 2010 (primary analysis data cut-off date).

2.3.1. Methods – analysis of data submitted

Diagnosis and Main Criteria for Eligibility: Histologically-confirmed, CRPC who were chemically or surgically castrated and had a total serum testosterone level of < 50 ng/dl, a high risk for development of bone metastasis (PSA value ≥8.0 ng/mL no more than 3 months before randomization OR PSA doubling time ≤10 months), an ECOG performance status of 0 or 1, adequate organ function, no metastases to bone or other organs (except lymph nodes) (central confirmation), and no prior exposure to intravenous bisphosphonates.

Subjects were randomized (IVRS) in a 1:1 ratio to receive 120 mg denosumab or placebo subcutaneously once every 4 weeks.

The randomization scheme was stratified based on PSA criteria (PSA level ≥8.0 ng/mL AND PSA doubling time ≤10.0 months [yes/no]) and previous or current chemotherapy for prostate cancer (yes/no).

Number of Subjects Enrolled: A total of 1435 subjects were enrolled in the study. Of these subjects, 718 were randomized to receive denosumab.

Prior to unblinding, the decision was made to exclude subjects from all analyses when institutional review board (IRB) review activities and oversight were not ensured. Two subjects randomized to denosumab and 1 subject randomized to placebo met this criterion

Blinding: To maintain the integrity of the blind, the following parameters were concealed from investigators and sponsor personnel involved in conducting the study and managing the database: alkaline phosphatase, bone turnover markers, serum denosumab concentrations, and antidenosumab antibody levels.

It was strongly recommended that subjects take oral supplements of calcium and vitamin D throughout the study.

Primary endpoint: Bone metastasis free survival.

Full body radio-isotope bone scan were required every 16 weeks. Newly-occurring bone metastases were assessed as follows:

- If the central reader identified any change from baseline on a radioisotope bone scan, an x-ray, CT, or MRI scan of the area in question was obtained. Bone scan changes alone were not acceptable as sole evidence for scoring newly developed bone metastasis.
- If only an x-ray was performed and was inconclusive as to the cause of the change, additional radiological information was required. This additional information could be initiated by the investigator or requested by the central reader and consisted of either a CT or an MRI scan.
- If the central reader confirmed bone metastasis, the subject was not to receive any additional doses of investigational product.

The subject completed end of study visit assessments within 4 weeks of confirmation of bone metastasis and the subject entered the follow-up phase.

The objective to delay the occurrence of bone metastases in patients considered to be at high risk is clinically appropriate, the relevance obviously pending on the magnitude of the treatment effect.

In relation to an 'other concern' raised by the CHMP during the procedure, it was discussed whether the treatment effect as estimated by isotope scan or CT, is a measure of occurrence of metastases or a measure of the effects of metastases on osteoblast activation (isotope scan) or bone lesions (osteoclasts).

A delay in evolution of bone metastases would be expected to result in some degree of inhibition of PSA evolution. This, however, is not the case. As inhibition of osteoclast activation by blockade of RANKL is likely also to result in inhibition of osteblast activation, it is concluded that the primary endpoint is a measure of delay in detection of bone metastases.

Secondary Efficacy:

- Time to first bone metastasis (either symptomatic or asymptomatic) excluding death;
- Overall survival time.

Key Exploratory Efficacy:

- time to overall prostate cancer disease progression, prostate cancer progression-free survival;
- subject incidence of symptomatic bone metastasis;
- PSA (recorded value, percent change, and change from baseline);
- subject incidence of vertebral fracture;
- times to first non-vertebral fracture, first clinical fracture, first any fracture;
- bone turnover markers (recorded value, percent change, and change from baseline).

PRO and Healthcare Resource Utilization:

- BPI-SF (worst pain, pain severity, and pain interference scales), FACT-P (total score,
- FACT-G total score, and TOI), and EQ-5D health index and VAS;
- analgesic use;
- healthcare resource utilization.

Pharmacokinetic:

- denosumab serum concentration levels.

The external DMC convened approximately twice yearly to monitor unblinded safety and efficacy data.

It was recognized that the DMC may have felt ethically compelled to recommend early stopping in the event of overwhelming efficacy.

The rules for stopping the study were defined as follows:

For the formal interim analysis conducted when approximately 330 subjects developed bone metastasis or died, the critical p-values for rejecting the null hypothesis ($p<0.00135$) and rejecting the alternative hypothesis ($p>0.295$), as determined by Lan-DeMets spending function with an O'Brien-Fleming approach.

At other interim evaluations, the DMC focused on safety and only reviewed efficacy data to balance the risk:benefit assessment. At these analyses, the DMC should have considered recommending study termination due to overwhelming evidence of efficacy only if the p-value for the primary efficacy analysis was < 0.0005.

The study was allowed to continue to its planned final efficacy analysis and the DMC did not recommend any changes to the conduct of the study.

The original protocol was approved on 22 November 2005 and was subsequently amended 3 times. None of these amendments threatened the integrity of the study. The final SAP was dated 02 November 2010.

Of note, denosumab is currently licensed for the treatment of patients with prostate cancer and bone metastases. Denosumab (and placebo), however, was stopped when bone metastasis was diagnosed.

This might be questioned from a clinical perspective as a meaningful clinical question would be if early treatment of patients at risk is favourable from a benefit-risk perspective compared with initiation of treatment at time of diagnosis of bone metastasis. When the study was initiated (2006), however, XGEVA was not licensed (authorised in 2011); thus conventional treatment with bisphosphonates was initiated as clinically warranted.

The overall design of the study is thus considered acceptable.

2.3.2. Results

Reasons for study discontinuation

	Placebo n (%)	Denosumab 120 mg Q4W n (%)	All n (%)
Randomized	716	716	1432
On study through primary data analysis cutoff date	164 (22.9)	174 (24.3)	338 (23.6)
Discontinued prior to primary data analysis cutoff date	552 (77.1)	542 (75.7)	1094 (76.4)
Protocol-specified criteria[a]	297 (41.5)	247 (34.5)	544 (38.0)
Consent withdrawn	92 (12.8)	100 (14.0)	192 (13.4)
Death	53 (7.4)	56 (7.8)	109 (7.6)
Adverse event	25 (3.5)	36 (5.0)	61 (4.3)
Disease progression[b]	22 (3.1)	36 (5.0)	58 (4.1)
Other	24 (3.4)	32 (4.5)	56 (3.9)
Administrative decision	20 (2.8)	20 (2.8)	40 (2.8)
Noncompliance	8 (1.1)	6 (0.8)	14 (1.0)
Lost to follow-up	9 (1.3)	4 (0.6)	13 (0.9)
Protocol deviation	1 (0.1)	3 (0.4)	4 (0.3)
Ineligibility determined	1 (0.1)	2 (0.3)	3 (0.2)

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Percentages based on number of subjects randomized
[a] Protocol specified criteria includes bone metastasis confirmed by central reader
[b] Disease progression excluding bone metastasis

A rather high proportion of patients discontinued the study due to “consent withdrawn” prior to cut-off date. However, there are no major imbalances between study arms. It is not clear to what extent patients were followed for bone metastasis after study medication was stopped.

Censoring: In the subgroup of primary interest, i.e. those with PSA doubling time (DT) < 6 months, 36% on denosumab vs. 26% on placebo discontinued the study prior to the primary data analysis cut-off.

Sensitivity analyses using a model-based multiple imputation method were conducted to explore the potential effect of these early discontinuations on the primary analysis results in this subgroup.

If it is conservatively assumed that patients discontinuing the study had an increased risk of bone metastases of HR 1.2 and would have had a smaller benefit if continued on therapy, HR 1.0, then the HR in the subgroup of patients with PSA doubling time of <6 months would be 0.83 (p=0.03).

Baseline Demographics

	Placebo (N = 716)	Denosumab 120 mg Q4W (N = 716)	All (N = 1432)
Sex - n (%)			
Male	716 (100.0)	716 (100.0)	1432 (100.0)
Ethnic group / race - n (%)			
White or Caucasian	604 (84.4)	606 (84.6)	1210 (84.5)
Black or African American	35 (4.9)	41 (5.7)	76 (5.3)
Hispanic or Latino	37 (5.2)	32 (4.5)	69 (4.8)
Asian	18 (2.5)	17 (2.4)	35 (2.4)
Japanese	2 (0.3)	0 (0.0)	2 (0.1)
American Indian or Alaska Native	2 (0.3)	0 (0.0)	2 (0.1)
Native Hawaiian or Other Pacific Islander	1 (0.1)	0 (0.0)	1 (<0.1)
Other	17 (2.4)	18 (2.5)	35 (2.4)
Unknown	0 (0.0)	2 (0.3)	2 (0.1)
Age (years)			
N	716	716	1432
Mean	73.2	73.2	73.2
SD	8.3	8.8	8.6
Median	74.0	74.0	74.0
Q1, Q3	67.5, 80.0	67.0, 80.0	67.0, 80.0
Min, Max	49, 94	44, 97	44, 97
Geriatric age group - n (%)			
≥ 65 years	600 (83.8)	598 (83.5)	1198 (83.7)
≥ 75 years	324 (45.3)	332 (46.4)	656 (45.8)

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N = Number of subjects randomized

White/Caucasians dominated the study population.

Baseline Characteristics

	Placebo (N = 716)	Denosumab 120 mg Q4W (N = 716)	All (N = 1432)
ECOG performance status at study entry - n (%)			
0	514 (71.8)	505 (70.5)	1019 (71.2)
1	199 (27.8)	210 (29.3)	409 (28.6)
2	3 (0.4)	1 (0.1)	4 (0.3)
Primary tumor at diagnosis - n (%)			
T0 or T1 - T2a	132 (18.4)	122 (17.0)	254 (17.7)
T2 or T2b - T2c	217 (30.3)	231 (32.3)	448 (31.3)
T3 or T3a	217 (30.3)	214 (29.9)	431 (30.1)
T3b - T4	85 (11.9)	98 (13.7)	183 (12.8)
Tx	65 (9.1)	51 (7.1)	116 (8.1)
Regional lymph node at diagnosis - n (%)			
N0	331 (46.2)	331 (46.2)	662 (46.2)
N1	68 (9.5)	87 (12.2)	155 (10.8)
Nx	317 (44.3)	298 (41.6)	615 (42.9)
Presence of distant metastasis at diagnosis - n (%)			
M0	570 (79.6)	566 (79.1)	1136 (79.3)
M1	4 (0.6)	5 (0.7)	9 (0.6)
Mx	142 (19.8)	145 (20.3)	287 (20.0)
Gleason score at diagnosis - n (%)			
2-7	432 (60.3)	404 (56.4)	836 (58.4)
8-10	214 (29.9)	237 (33.1)	451 (31.5)
Missing	70 (9.8)	75 (10.5)	145 (10.1)
Current lymphatic metastasis - n (%)			
Yes	88 (12.3)	93 (13.0)	181 (12.6)
No	628 (87.7)	623 (87.0)	1251 (87.4)

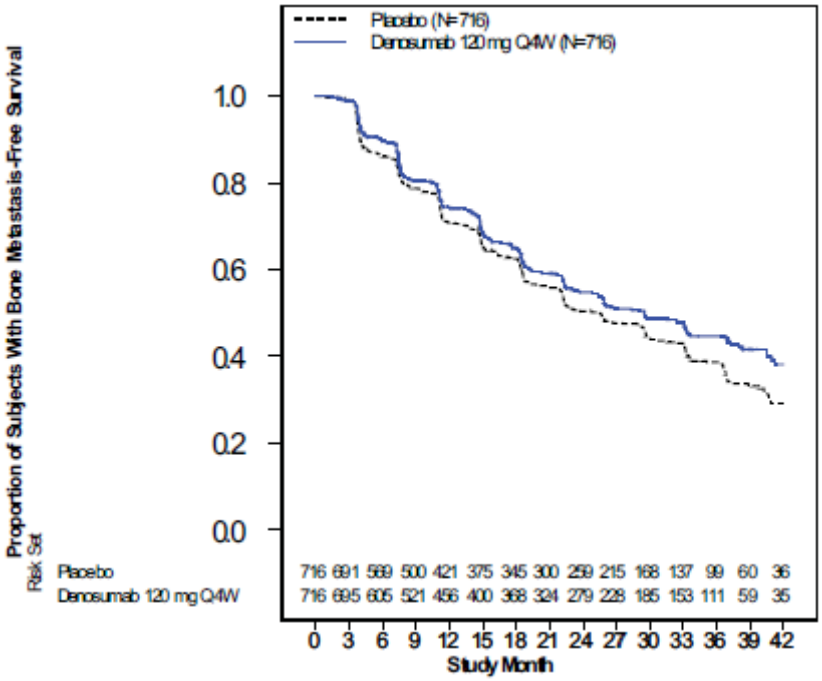
	Placebo (N = 716)	Denosumab 120 mg Q4W (N = 716)	All (N = 1432)
PSA doubling time (months)			
25th percentile	2.79	2.88	2.85
Median	5.05	5.15	5.11
75th percentile	8.63	8.53	8.57
PSA doubling time (months) - n(%)			
<= 10	580 (81.0)	574 (80.2)	1154 (80.6)
> 10	136 (19.0)	142 (19.8)	278 (19.4)
PSA value ≥ 8.0 ng/mL within 3 months prior to randomization - n (%)			
Yes	471 (65.8)	473 (66.1)	944 (65.9)
No	245 (34.2)	243 (33.9)	488 (34.1)
Prior chemotherapy regimens - n (%)			
Yes	54 (7.5)	63 (8.8)	117 (8.2)
No	662 (92.5)	653 (91.2)	1315 (91.8)

The study population appears representative of patients with castration resistant prostate cancer. There are no imbalances between study arms likely to be of any relevance.

Primary Endpoint, Bone Metastases-free Survival

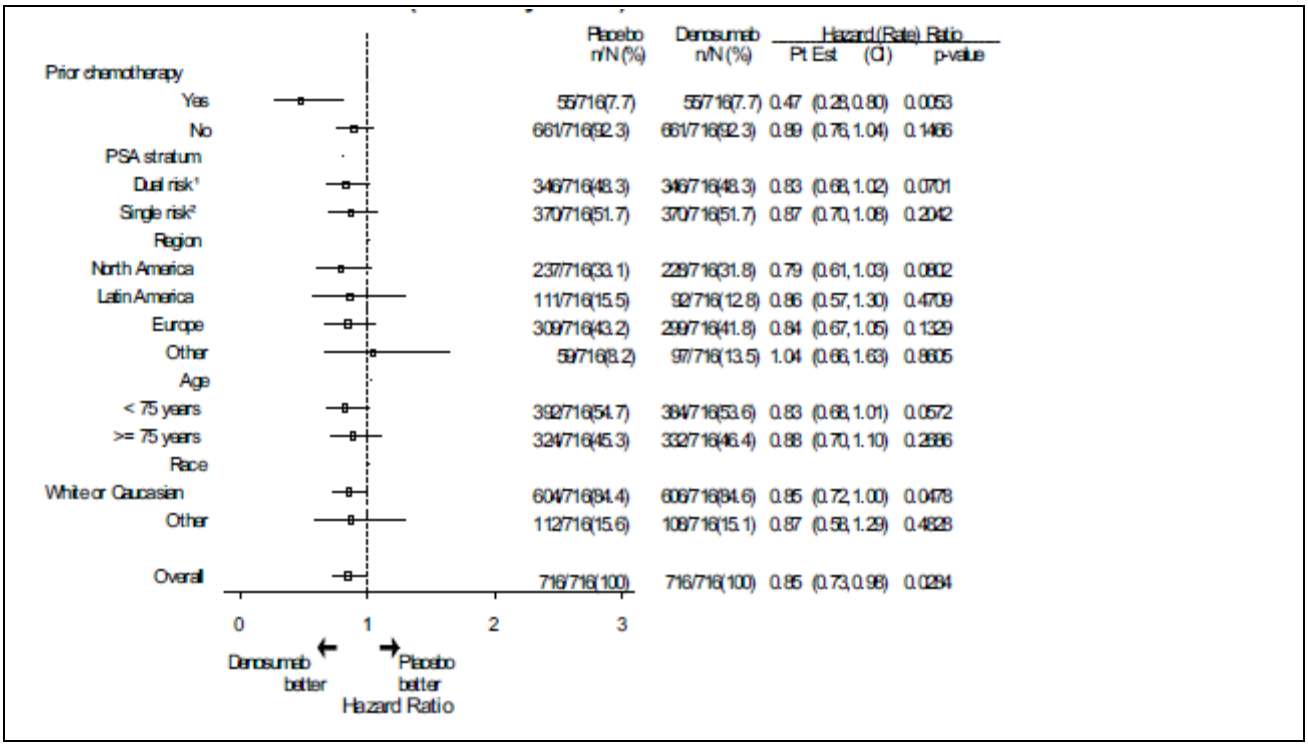
	Crude Incidence	KM Estimate of 25%-tile (Days)[a]		KM Estimate of Median (Days)[a]		Hazard Ratio[b]		
	n (%)	Pt Est	(95% CI)	Pt Est	(95% CI)	Pt Est	(95% CI)	p-value
Placebo (N = 716)	370 (51.7)	338.0	(289.00, 346.00)	768.0	(675.00, 897.00)			
Denosumab 120 mg Q4W (N = 716)	335 (46.8)	344.0	(334.00, 448.00)	897.0	(773.00, 1014.00)	0.85	(0.73, 0.98)	0.0284

N = Number of subjects randomized
[a] Kaplan-Meier estimate
[b] Based on the Cox proportional hazards model stratified by the randomized stratification factors; hazard ratio < 1 favors denosumab



At an event rate of about 50%, the HR is 0.85 at a p-value of 0.03, i.e. borderline. The median difference, about 4 months, observed after about 2 years of treatment appears to overestimate the treatment effect.

Subgroup analyses



The treatment effect appears reasonably consistent in most sufficiently large subgroups and appears better in those administered prior chemotherapy.

"Dual risk" refers to PSA level ≥8.0 ng/mL AND PSA doubling time ≤10.0 months PSA. Note that the HRs are rather similar comparing dual vs. single risk.

Prior chemotherapy and "dual risk" were stratification factors. Note that the treatment effect was no longer statistically significant if patients (about 8%) with prior chemotherapy are excluded.

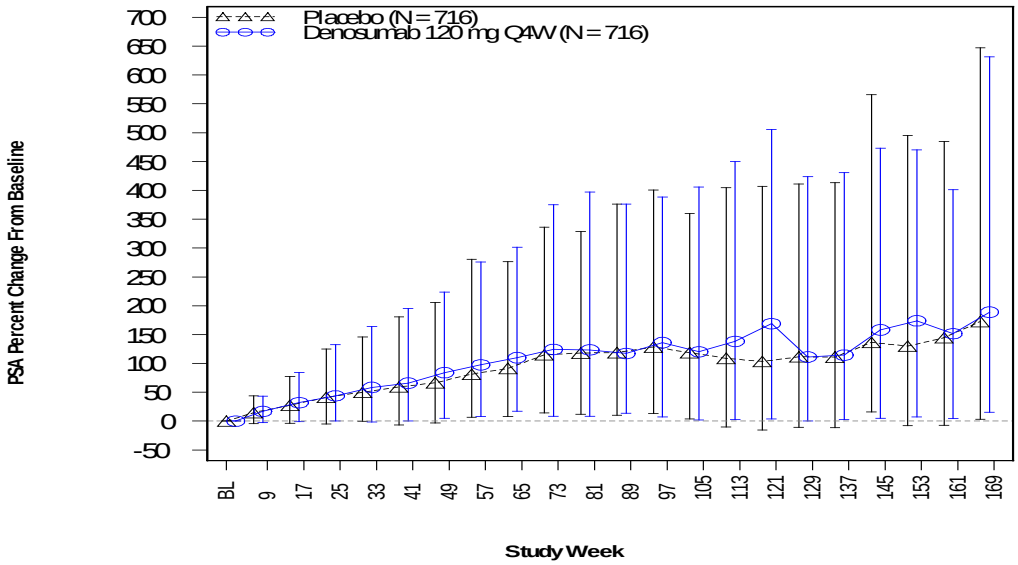
Secondary and Exploratory Endpoints

	Incidence	Median difference (m)	HR	p-value
Time to first bone metastasis (either symptomatic or asymptomatic), excluding deaths				
Placebo (N = 716)	319 (44.6%)			
Denosumab (N = 716)	286 (39.9%)	3.7	0.84 (0.71, 0.98)	0.0317
Overall survival				
Placebo (N = 716)	250 (34.9%)			
Denosumab (N = 716)	251 (35.1%)	-1.0	1.01 (0.85, 1.20)	0.9125
Time to symptomatic bone metastasis				
Placebo (N = 716)	96 (13.4%)			
Denosumab (N=716)	69 (9.6%)	NE	0.67 (0.49, 0.92)	0.0127
Prostate cancer progression-free survival				
Placebo (N = 716)	437 (61.0%)			
Denosumab (N = 716)	419 (58.5%)	2.5	0.89 (0.78, 1.02)	0.0931

The relative treatment effect appears larger in terms of time to symptomatic metastases, but the crude incidences are low. Of note, osteoclast inhibition by bisphosphonates is known to reduce pain in patients with overt bone metastases. Thus improved activity is expected in terms of time to symptomatic metastasis compared with time to detection of metastasis.

There are no trends in either direction in terms of survival.

PSA Percent Change From Baseline by Visit Median and Interquartiles (FAS)



N = Number of subjects randomized
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Output: g14-04_001_503_ah_psa_sum_psa_pctchg.cgm (Date Generated: 04FEB2011:14:49:33)
Source Data: adam.aslinfo, adam.albsaf

PSA change from baseline appears similar in both treatment groups. PSA would have been expected to increase prior to diagnosis of bone metastasis, i.e. opening for showing a difference between treatment arms even though patients were not followed after detection of bone metastasis. The treatment effect, however, is small in terms of bone metastasis free survival and variability might obscure differences.

Time to 25%, 50%, and 100% Increases in PSA (Full Analysis Set)

	Crude Incidence	Hazard Ratio[b]		
	n (%)	Pt Est	(95% CI)	p-value
Placebo (N = 685)	600 (87.6)			
Denosumab 120 mg Q4W (N = 692)	627 (90.6)	1.01	(0.90, 1.13)	0.8557
Time to 50% increase in PSA				
Placebo (N = 685)	560 (81.8)			
Denosumab 120 mg Q4W (N = 692)	590 (85.3)	1.02	(0.91, 1.15)	0.7217
Time to 100% increase in PSA				
Placebo (N = 685)	492 (71.8)			
Denosumab 120 mg Q4W (N = 692)	516 (74.6)	1.01	(0.89, 1.15)	0.8470

Based on the Cox proportional hazards model stratified by the randomized stratification factors; hazard ratio < 1 favours denosumab.

At time of diagnosis of bone metastasis PSA levels were also similar.

Fracture Endpoints

- Time to clinical fracture: hazard ratio [95% CI] of 0.80 [0.58, 1.11]; p = 0.1840
- Time to any fracture: hazard ratio [95% CI] of 0.85 [0.65, 1.11]; p = 0.2463

Ad hoc: Subject incidence of first major osteoporotic fracture (i.e. a clinical vertebral, hip, forearm, or humerus fracture not associated with a metastatic fracture, regardless of trauma severity) was 1.1% (denosumab) and 2.8% (placebo) groups, hazard ratio [95% CI] of 0.38 [0.17, 0.86]; p-value = 0.0202.

There was no statistically significant treatment effect in predefined fracture endpoints, but HRs are similar to bone metastasis free survival.

On-study anti-neoplastic therapy

	Placebo (N=716) n(%)	Denosumab 120 mg Q4W (N=716) n(%)
Number of subjects reporting use of on-study cancer chemotherapy and hormonal therapy (including bilateral orchiectomy)	715 (99.9)	715 (99.9)
Chemotherapy/biologicals	176 (24.6)	198 (27.7)
Docetaxel	74 (10.3)	87 (12.2)
Hormonal therapy excluding ADT and excluding bilateral Ox	302 (42.2)	275 (38.4)

ADT= androgen deprivation therapy, OX=orchextomy

There are no imbalances of likely importance in the use of on-study anti-cancer therapy.

Overrunning patients

After the primary analysis data cut-off date, subjects continued to receive double-blind treatment until the completion of the efficacy and safety analyses.

Three hundred sixty-two subjects (50.6%) who received denosumab and 388 subjects (54.2%) who received placebo developed a bone metastasis or died by the end of the extended blinded treatment phase. At time of the primary analysis, corresponding figures were 46.8% and 51.7%, respectively.

The hazard ratio (95% CI) for bone metastasis free survival was 0.88 (0.76, 1.01; p = 0.0704).

With respect to time to first bone metastasis, the hazard ratio (95% CI) was 0.86 (0.73, 1.00; p = 0.0517).

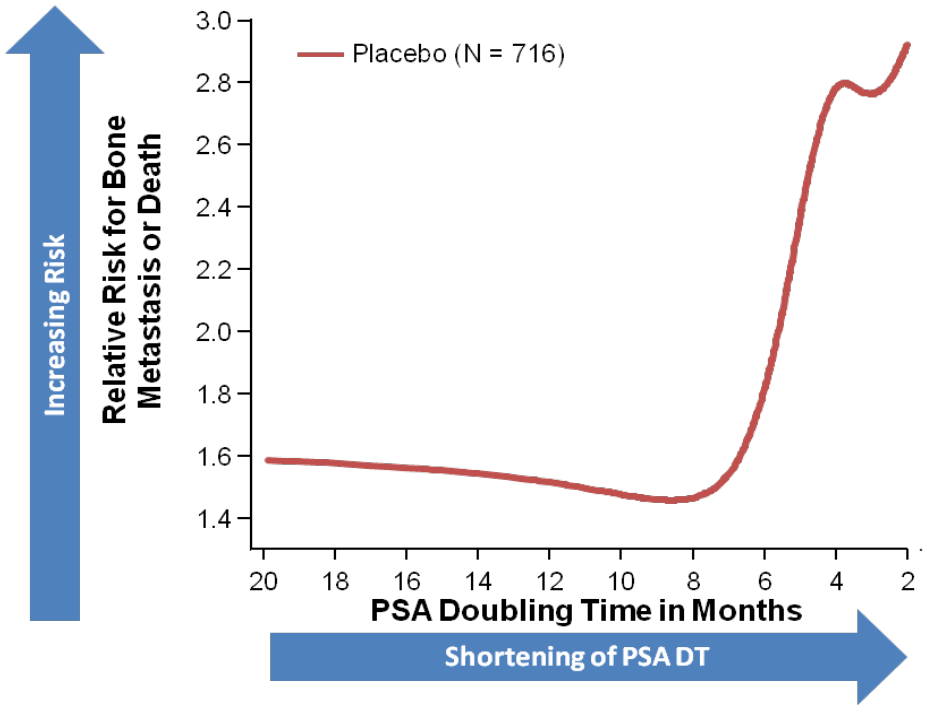
Seventy-three subjects (10.2%) who received denosumab and 98 subjects (13.7%) who received placebo developed a symptomatic bone metastasis. The hazard ratio (95% CI) for symptomatic bone metastasis was 0.70 (0.52, 0.95; p = 0.0207).

Of note, when overrunning patients are included, the difference in terms of the primary endpoint is no longer statistically significant at the 5% level.

Additional Post Hoc Efficacy Analyses for Study 20050147

The availability of baseline PSA kinetics afforded an opportunity to further investigate the relationship between PSA kinetics and efficacy parameters.

Relative Risk for Bone Metastasis-free Survival Over Prostate-specific Antigen Doubling Time in Placebo Group (Study 20050147 Full Analysis Set)



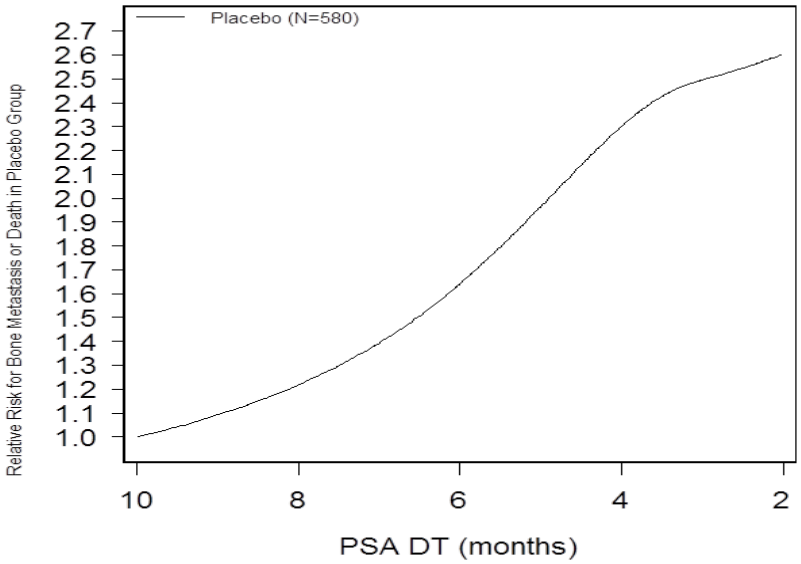
N = Number of subjects randomized
The curve was generated based on a Cox proportional model with a natural cubic spline of 6 degrees of freedom for the inverse of PSA doubling time

A relationship between PSA doubling time and risk of progression is expected and has repeatedly been reported previously.

When the analysis is restricted to subjects in Study 20050147 who were at risk based solely on PSA doubling time (i.e. excluding patients solely enrolled based on PSA value ≥8.0 ng/mL), the increase in the slope of the risk curve is less pronounced.

Because the subjects in Study 20050147 with PSA doubling times > 10 months were still at high risk for bone metastasis based on absolute PSA, the risk curve did not further decrease for longer PSA doubling times.

Figure 2. Risk for Bone Metastasis-free Survival Over PSA Doubling Time in Placebo Group (Subjects With Doubling Time ≤ 10 Months in Full Analysis Set)



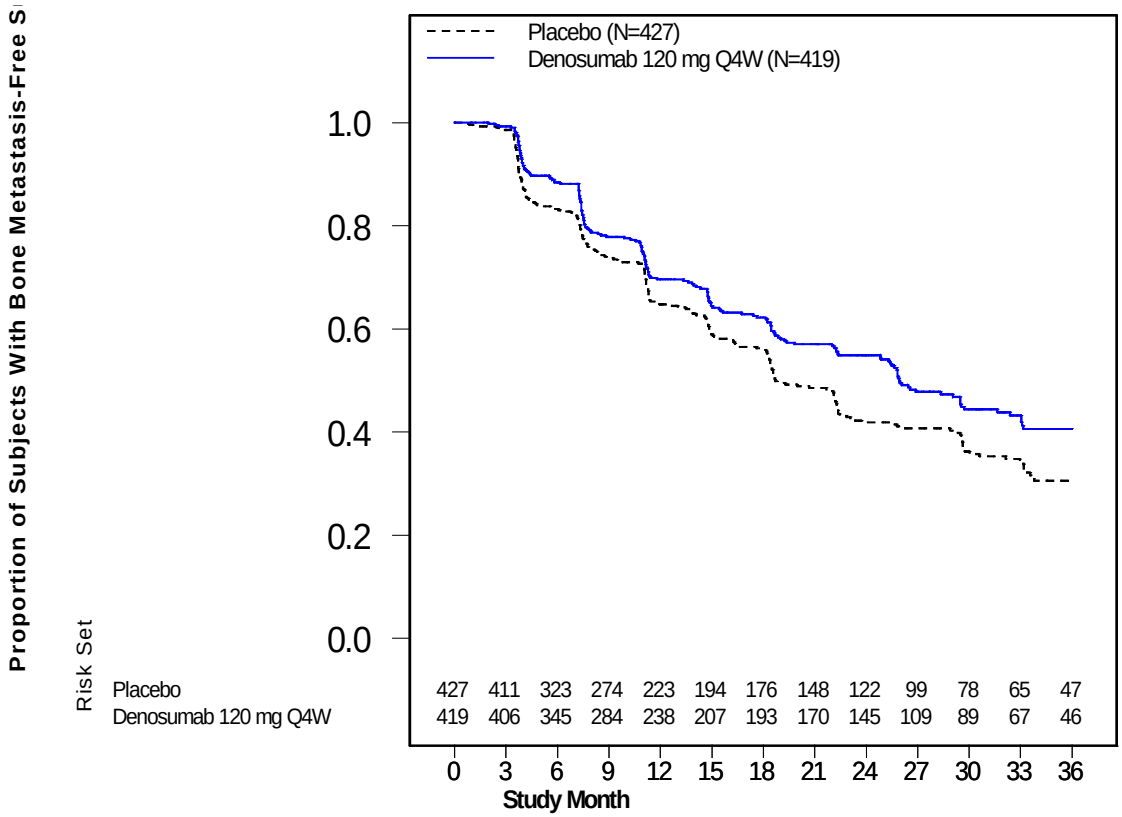
N = Number of subjects randomized
The curve was generated based on a Cox proportional model with a natural cubic spline of 3 degrees of freedom for the inverse of PSA doubling time

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/graphs/program/g-bmfs-psa-psadt10.sas
Output: g04-02-001-001-bmfs-psa-psadt10-l.cgm (Date Generated: 05JAN2012:15:13:09)
Source Data: adam.asleff, adam.aslbase

The selection of the PSA doubling time cut-off >< 6months is supported by data external to the study.

Approximately 60% of the entire study population had a PSA doubling time ≤ 6 months (N = 846). There were no likely relevant differences between treatment groups in baseline factors between treatment arms in this subpopulation.

Bone Metastasis-free Survival (Kaplan-Meier Curves) for Subjects With Prostate-specific Antigen Doubling Time ≤ 6 Months (Study 20050147 Subset of Full Analysis Set)



N = Number of subjects randomized

Program: /stat/amg162/b_mets/20050147/analysis/bla_2011pcprev_reg_prep/graphs/program/g-bm-time-si.sas
Output: g04-01-003-019-bm-surv-si-psa6-l.cgm (Date Generated: 29OCT2011:19:33:35)
Source Data: adam.asleff, adam.aslbase

	PSA doubling time ≤ 6 months				
	Crude Incidence	KM Estimate of Median (Months)[a]	Difference in Median Time to Event[b] (Months)	Denosumab vs Placebo (Hazard Ratio)[c]	
Endpoint	n (%)	Pt Est (95% CI)		Pt Est (95% CI)	p-value
Bone metastasis-free survival time					
Placebo (N = 427)	242 (56.7)	18.7 (18.23, 22.31)			
Denosumab 120 mg Q4W (N = 419)	197 (47.0)	25.9 (22.34, 31.64)	7.2	0.77 (0.64, 0.93)	0.0064
Time to first bone metastasis					
Placebo (N = 427)	212 (49.6)	22.1 (18.46, 25.79)			
Denosumab 120 mg Q4W (N = 419)	176 (42.0)	26.5 (25.40, 33.08)	4.4	0.80 (0.65, 0.97)	0.0257
Overall survival					
Placebo (N = 427)	165 (38.6)	40.7 (35.91, 45.77)			
Denosumab 120 mg Q4W (N = 419)	153 (36.5)	42.0 (36.21, NE)	1.3	0.99 (0.79, 1.23)	0.8947
Time to symptomatic bone metastasis					
Placebo (N = 427)	66 (15.5)	NE (NE, NE)			
Denosumab 120 mg Q4W (N = 419)	42 (10.0)	44.6 (NE, NE)	NE	0.62 (0.42, 0.91)	0.0144
Prostate cancer progression-free survival time[d]					
Placebo (N = 427)	286 (67.0)	15.3 (13.83, 18.40)			
Denosumab 120 mg Q4W (N = 419)	261 (62.3)	18.4 (14.78, 21.75)	3.1	0.84 (0.71, 0.99)	0.0378

All analyses presented are post hoc.

CI = confidence interval; NE = not estimable; Pt Est = point estimate; PSA = prostate-specific antigen

[a] Kaplan-Meier estimate

[b] denosumab median time – placebo median time

[c] Hazard ratio or rate ratio < 1 favors denosumab.

[d] p-values are adjusted for covariates.

The absolute treatment effect appears larger in this post hoc subgroup analysis due to at least two factors: the increased risk of bone metastases and an apparently increased relative activity of denosumab. In the FAS the medians for bone metastasis free survival were about 26 months (placebo) and 30 months (denosumab), vs. about 19 and 26 in this subpopulation.

If the efficacy analyses are focused on patients with PSA doubling time ≤ 10 Months, i.e. excluding patients enrolled only due to PSA ≥8.0 ng/mL, the bone metastases-free survival is **0.77** (95% CI 0.64; 0.93) in patients with PSA doubling time ≤6 months and **1.13** (95% CI 0.81; 1.57) in those with PSA doubling time >6 months.

To some degree, the apparent increase in relative activity in patients with short PSA doubling time is related to competing risks, however, the difference is considered too large to be explained by this. There are no external data supporting the notion that denosumab is more active in patients with short PSA doubling time. The credibility of this finding is thus strongly questioned.

Patient-reported Outcome

At study entry, pain severity was low and HRQOL assessments indicated high levels of HRQOL. During the study, increases in pain were relatively modest and generally similar between the denosumab and placebo groups. As expected no significant differences were observed between the treatment groups in

endpoints related to pain worsening or improvement. The use of analgesics was similar between the treatment groups.

2.3.3. Discussion

Design: Even though it is fully understood why study therapy was stopped when bone metastases were detected, and the study design is accepted, it is nevertheless of clinical importance to know whether early therapy in "the long run" is favourable to the initiation of therapy at the time of clinically overt bone metastasis.

Another issue is whether progression on therapy signifies some degree of resistance to denosumab, i.e. whether osteoclast activation is achieved through other means than RANKL. Alternative mechanisms to RANKL activation of osteoclasts do exist and thus it would be of interest to undertake a study designed to address this issue, e.g. through a randomised cross-over to a bisphosphonate vs. maintained denosumab in patients with progression on denosumab.

Statistical robustness: "Early treatment" of patients with prostate cancer at risk of bone metastases is not a simple case of extrapolation as there are failed trials with bisphosphonates. Thus p-values considerably lower than 5% in a single pivotal trial would normally be required to support the proposed new indication. In this case the p-value was 0.03 at the primary analyses; when overrunning patients were included 0.07. Furthermore, if patients pre-treated with chemotherapy (about 8%) are excluded, the treatment effect is no longer statistically significant.

During the procedure, the MAH has restricted the proposed indication to patients with PSA doubling time ≤6 months. Therefore the robustness and the validity of the subgroup results are of key importance, not the results in the FAS population.

Magnitude of the treatment effect, FAS: After more than 2 years of treatment, the incidence of bone metastasis is reduced with less than 5% at an overall level of about 45% corresponding to a HR of 0.85 in terms of bone metastasis free survival. This must be regarded as a modest treatment effect.

Subgroup analysis: Patients with PSA doubling time ≤6 months were identified post hoc as patients deriving more benefit. The MAH has reviewed and reported the results of other CRPC studies and also reported the use of PSA >=<6 months as a stratification factor in current studies and based on this data it is cautiously concluded that there is sufficient external support for this cut-off defining a subgroup at increased risk.

Magnitude of the treatment effect in patients with PSA doubling time ≤6 months: The reported bone metastasis-free HR is 0.77 (p=0.006) corresponding to a crude difference of about 10% (57% vs. 47%) after a median treatment time of about 1½ years. This, however, most likely constitutes an overestimate of the treatment effect.

In the complementary group of patients, i.e. those with a PSA doubling time of >6 months and less than 10 months, the bone metastasis-free HR is 1.13 (95% CI 0.81; 1.57). This per se is not considered to be a likely outcome and is therefore considered an indication of an overestimation of the treatment effect in the target population.

Whilst increased relative activity in patients with short PSA doubling time certainly is a possibility, there is no external data related to denosumab supporting this notion.

In addition, more patients in the denosumab arm withdrew prior to meeting the endpoint, 36% vs. 26%. If it is conservatively assumed that patients discontinuing the study had an increased risk of bone metastases of HR 1.2 and would have had smaller benefit if continued on therapy, HR 1.0, then the HR in the subgroup of patients with PSA doubling time of <6 months would be 0.83 (p=0.03).

Interaction between denosumab and bone scanning: Bone scans do not detect cancer lesions, but osteoblast activation. Bone metastases leads to a vicious circle of osteclast and osteoblast activation where denosumab inhibits osteoclast activation. Hypothetically, inhibition of osteoclast activation might lead to reduced osteoblast activation, thereby delaying positive findings on bone scans.

Due to the small treatment effect (HR 0.85, bone metastases free survival) none of the experiments undertaken can address this issue.

In conclusion, this submission for an extended indication to encompass patients with CRPC is based on a single pivotal trial. In the ITT population, the treatment effect is small and the results are not considered robustly documented from a statistical perspective.

Post hoc a subgroup of patients was identified with apparent increased benefit of therapy. Most likely, however, the benefit of therapy is overestimated and thus a proper benefit – risk assessment cannot be undertaken.

2.4. Clinical Safety aspects

- **Drug exposure**

Number of Subjects Receiving Denosumab and Duration of Cumulative Exposure in Advanced Cancer Studies

	Denosumab					
	≥ 1 Dose	≥ 1 Month	≥ 6 Months	≥ 1 Year	≥ 2 Years	≥ 3 Years
Overall total exposure	4043	4011	3122	2252	884	141
Phase 1 studies[a]	62	62	0	0	0	0
Phase 2 supportive studies[b]	288	283	247	181	9	4
Phase 3 advanced cancer SRE studies[c]	2841	2814	2151	1542	574	18
Phase 2 studies in other indications[d]	132	132	62	25	0	0
Study 20050147	720	720	662	504	301	119

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[a]Includes studies 20010123 and 20040176
[b]Includes studies 20040113 and 20040114
[c]Includes studies 20050136, 20050244 and 20050103 up to the end of study date or the entire blinded treatment cut-off date, whichever occurred first
[d]Includes studies 20050134 and 20040215

Also long-term experience with denosumab in patients with cancer is now extensive.

2.4.1. Methods – analysis of data submitted

Drug exposure Pivotal trial

	Study 20050147	
	Placebo	Denosumab 120 mg Q4W
Number of Subjects Randomized	716	716
Median number of months on study [a] (Q1, Q3)	19.01 (9.23, 30.44)	20.17 (10.15, 31.34)
Number of subjects receiving ≥ 1 dose of investigational product	709	716
Median cumulative investigational product exposure (months)[b] (Q1, Q3)	18.37 (8.51, 30.39)	19.33 (9.31, 30.37)
% of subjects who received investigational product		
≥ 1 year	63.8	67.2
≥ 1.5 years	51.2	53.8

The now submitted pivotal trial provides important safety data as it is placebo controlled and as patients had less advanced cancer.

As shown in the tables below, the number of patients >75 years of age is substantial, but the number with estimated creatinine clearance < 30 ml/min is low.

Exposure by Age Group and Gender (Study 20050147 Safety Analysis Set)

	Placebo (N=705)		Denosumab 120 mg Q4W (N=720)	
	Number of Subjects	Total Subj-yr	Number of Subjects	Total Subj-yr
Age Group	Male	Male	Male	Male
< 65 years	113	191.7	120	226.4
≥ 65 years	592	1014.7	600	1045.5
< 75 years	385	663.0	388	702.0
≥ 75 years	320	543.4	332	569.8

N = Number of subjects who received ≥ 1 active dose of investigational product
Subj-yr = Subject-years of follow-up, including the time period from the first active dose of investigational product to the end of study date or the primary data cut-off date, whichever comes first.

Exposure by Baseline Renal Impairment Status (Study 20050147 Safety Analysis Set)

Baseline Creatinine Clearance	Placebo (N=705)		Denosumab 120 mg Q4W (N=720)	
	Number of Subjects	Total Subj-yr	Number of Subjects	Total Subj-yr
< 15 mL/min	0	-	1	1.5
15 - < 30 mL/min	10	17.0	7	6.8
30 - < 60 mL/min	172	262.4	175	271.1
60 - < 90 mL/min	291	505.7	299	549.4
≥ 90 mL/min	228	416.3	233	435.5
Missing	4	5.0	5	7.6

2.4.2. Results

Summary of Adverse Events

	Study 20050147	
	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)
All	655 (92.9)	676 (93.9)
Serious	323 (45.8)	329 (45.7)
Fatal	67 (9.5)	73 (10.1)
Leading to study discontinuation	67 (9.5)	79 (11.0)
Leading to investigational product discontinuation	74 (10.5)	90 (12.5)
CTCAE Grade 3, 4, or 5	353 (50.1)	381 (52.9)
Adverse events related to investigational product[a]		
All	161 (22.8)	190 (26.4)
Serious	11 (1.6)	33 (4.6)
Fatal	1 (0.1)	0 (0.0)
Leading to study discontinuation	2 (0.3)	13 (1.8)
Leading to investigational product discontinuation	6 (0.9)	23 (3.2)
CTCAE Grade 3, 4, or 5	17 (2.4)	38 (5.3)

The absolute differences between placebo and denosumab are rather small, whether an event is considered related to study medication or not. The differences seen for “related” events refer to osteonecrosis of the jaw (ONJ).

Adverse events by preferred term > 5% in any treatment group

The MAH has tabulated altogether 23 adverse event categories with an incidence >5% comparing studies 20050147 (pivotal in this application), 20050103 (n=945 + 943) and studies 20050136/20050244/20050103 combined (n=2836 + 2841, all zoledronic acid comparative). A consistently higher incidence (0.8% and higher) of non-listed AEs was seen in the denosumab arms for:

Muscle spasm:	6.1 vs. 4.0% (0147)	5.4 vs. 2.9% (0103),	4.3 vs. 3.4% (0136/0244/0103)
Bronchitis:	5.6 vs. 4.5%	4.6 vs. 3.6%	4.4 vs. 3.6%
Influenza:	6.5 vs. 5.4%	4.2 vs. 2.5%	4.2 vs. 3.4%

Muscle spasm might be related to hypocalcaemia and "infections" are events of special interest. Please also refer to "Infections" below.

'Muscle spasm' will be included in the revised SmPC, section 4.8.

Adverse events leading to withdrawal of investigational product.

In Study 20050147, investigational product withdrawal due to adverse events was reported for 12.5% of subjects in the denosumab group and 10.5% of subjects in the placebo group.

Only osteonecrosis of the jaw (ONJ) and related terms stand out.

Fatal Adverse Events by Preferred Term in Descending Order of Frequency (> 1 Subject in Either Treatment Group) (Study 20050147, Safety Analysis Set)

Preferred Term	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)
Number of subjects with fatal adverse events	67 (9.5)	73 (10.1)
Prostate cancer	11 (1.6)	8 (1.1)
Renal failure	**2 (0.3)**	**6 (0.8)**
Myocardial infarction	**1 (0.1)**	**6 (0.8)**
Sepsis	3 (0.4)	4 (0.6)
Death	4 (0.6)	3 (0.4)
Metastases to lymph nodes	2 (0.3)	3 (0.4)
Metastases to bone	1 (0.1)	3 (0.4)
Cardiopulmonary failure	0 (0.0)	3 (0.4)
Cerebrovascular accident	2 (0.3)	2 (0.3)
Multi-organ failure	2 (0.3)	2 (0.3)
Prostate cancer metastatic	1 (0.1)	2 (0.3)
Cardiac failure	0 (0.0)	2 (0.3)
Renal failure acute	3 (0.4)	1 (0.1)
Metastases to liver	2 (0.3)	1 (0.1)
Pneumonia	5 (0.7)	0 (0.0)
Cachexia	2 (0.3)	0 (0.0)
Respiratory failure	2 (0.3)	0 (0.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects with fatal adverse events
Includes only treatment-emergent adverse events
Preferred terms are sorted by descending order of frequency in the denosumab group.
Coded using MedDRA version 13.1

Renal failure and MI should be noted.

Unlisted Serious Adverse Events with a higher incidence in the denosumab group, study 20050147 compared with prior studies (denosumab vs. placebo)

	20050147	20050103	20050136/0244/0103
Urinary retention:	7.5 vs. 4.4%	3.4 vs. 3.7%,	1.3 vs. 1.6%
Myocardial ischemia:	0.6 vs. 0	0.5 vs. 0.6	0.2 vs. 0.3

There appears to be no between study consistency as regards these signals.

"Urinary retention": based on available data and further analyses, it is concluded that there is no need to revise the SmPC in this regard.

"Cardiovascular disorder": based on available data there is no need to amend the SmPC, section 4.8 in this regard.

Adverse events of special interest

Hypocalcaemia: The event rate was, as expected, lower in the pivotal study for this submission, about 1.5% vs. about 10% in patients with bone metastatic disease.

Osteonecrosis of the jaw: Adverse events considered as potential cases of ONJ were identified using a broad search strategy and sent for adjudication by independent experts blinded to treatment allocation. Baseline oral/dental condition was assessed for each subject before enrolment and recorded in the case report form. A visual examination of the oral cavity was conducted every 6 months.

Number of adjudicated cases of ONJ: Placebo: 0

Denosumab: 33 (4.6%)

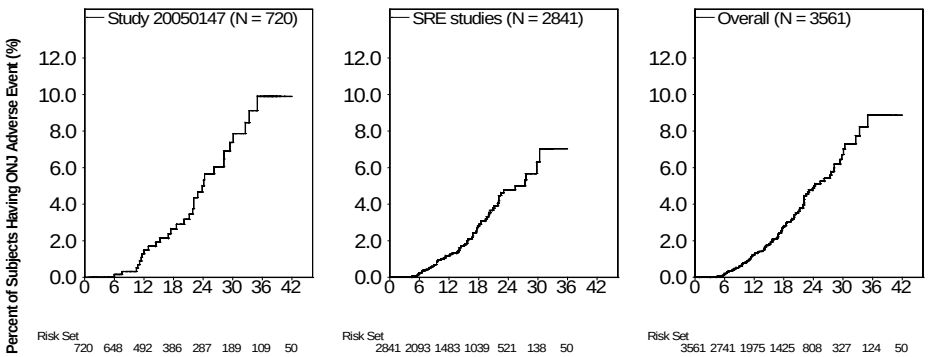
When adjusted for exposure, the rates of ONJ were similar across studies (0147, 0103 and 0136/0244/0103 combined).

Cumulative 1-year data (1.3, 1.4, 1.0 events per 100 subject-years, respectively)

Cumulative 2-year data (2.0, 2.2, 1.8 events per 100 subject-years, respectively)

Cumulative 3-year data (2.4, 2.1, 1.9 events per 100 subject-years, respectively)

Time to Adjudicated Positive Osteonecrosis of the Jaw Adverse Events for Denosumab



N = Number of subjects who received >= 1 dose of investigational product
Program: /userdata/stat/amg162/meta/bla_2011pcprev/analysis/req_quest/graphs/program/g-km-onj.sas
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Source Data: d09css.aae, d09css.aslinfo, paadam.aae, paadam.aslinfo

At about three years the incidence of ONJ is about 10-12%, ONJ grade 3 and above about 2-3% and finally 4-6% non-resolved events and there are no signs of reaching a plateau yet.

Although the incidence of ONJ is considerable it is in line with what would have been expected from previous trials. Of the 33 ONJ cases, no subjects presented with grade 4 or 5 events, 10 with grade 3 events, 16 with grade 2 events, and 7 with grade 1 events. Ten of these events required no surgical treatments; 21 required surgical treatments limited in nature (i.e. sequestrectomy, debridement, and curettage); and 2 subjects had bone resection. No notable impact of ONJ on subject-reported pain or HRQOL has been reported. By end of data capture resolution of ONJ has been documented for 13 (39%) subjects.

Infections: Due to putatively relevant inhibition of monocytes and antigen presenting cells, infectious events are of special interest.

Serious Adverse Events, Infections and Infestations

	Study 20050147		Study 20050103		Study 20050136/20050244/20050103 Combined	
SYSTEM ORGAN CLASS High Level Term Preferred Term	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
INFECTIONS AND INFESTATIONS	58 (8.2)	65 (9.0)	108 (11.4)	130 (13.8)	309 (10.9)	329 (11.6)

In all studies there seems to be a slightly higher incidence in the denosumab arms. With respect to opportunistic infections, no pattern indicative of increased risk was identified, but the number of cases is low. With respect to tuberculosis, e.g. there was only one single case (denosumab arm).

Adverse Events, Infections and Infestations

SYSTEM ORGAN CLASS High Level Term Preferred Term	Study 20050147 Placebo (N=705) n (%)	Study 20050147 Denosumab 120 mg Q4W (N=720) n (%)	Study 20050103 Zoledronic Acid 4 mg Q4W (N=945) n (%)	Study 20050103 Denosumab 120 mg Q4W (N=943) n (%)	Study 20050136/20050244/20050103 Combined Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Study 20050136/20050244/20050103 Combined Denosumab 120 mg Q4W (N=2841) n (%)
INFECTIONS AND INFESTATIONS	316 (44.8)	360 (50.0)	375 (39.7)	402 (42.6)	1218 (42.9)	1233 (43.4)
Sinusitis	17 (2.4)	25 (3.5)	5 (0.5)	16 (1.7)	50 (1.8)	70 (2.5)

Also here there appears to be a slightly higher overall incidence in denosumab arms. Apart from bronchitis and influenza as discussed previously, consistency between studies is seen (at a low level) only for sinusitis. Due to type of infections and obvious multiplicity issues, no further action is considered indicated at this point in time.

Skin infections: In the currently approved SmPC the following is stated in section 4.4:

"Skin infections (predominantly cellulitis) leading to hospitalisation

In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, skin infections leading to hospitalisation (predominantly cellulitis) were reported more frequently in patients receiving XGEVA (0.9%) compared with zoledronic acid (0.7%).

In postmenopausal women with osteoporosis, skin infections leading to hospitalisation were reported for 0.4% women receiving Prolia (denosumab 60 mg every 6 months) and for 0.1% women receiving placebo (see section 4.4). "

The MAH proposed to delete this paragraph from the SmPC as well as "Cellulites" in 4.8 where it is reported in the frequency category "uncommon". Given the totality of the data this is acceptable.

Serious Adverse Events of Skin Infections

SYSTEM ORGAN CLASS High Level Term Preferred Term	Study 20050147 Placebo (N=705) n (%)	Study 20050147 Denosumab 120 mg Q4W (N=720) n (%)	Study 20050103 Zoledronic Acid 4 mg Q4W (N=945) n (%)	Study 20050103 Denosumab 120 mg Q4W (N=943) n (%)	Study 20050136/20050244/20050103 Combined Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Study 20050136/20050244/20050103 Combined Denosumab 120 mg Q4W (N=2841) n (%)
Cellulitis	4 (0.6)	5 (0.7)	4 (0.4)	6 (0.6)	12 (0.4)	18 (0.6)
Erysipelas	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	2 (<0.1)	5 (0.2)
Skin infection	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (<0.1)	2 (<0.1)
Wound infection	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (<0.1)
Postoperative wound infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (<0.1)	1 (<0.1)

Adverse Events of Skin Infections

SYSTEM ORGAN CLASS High Level Term Preferred Term	Study 20050147 Placebo (N=705) n (%)	Study 20050147 Denosumab 120 mg Q4W (N=720) n (%)	Study 20050103 Zoledronic Acid 4 mg Q4W (N=945) n (%)	Study 20050103 Denosumab 120 mg Q4W (N=943) n (%)	Study 20050136/20050244/20050103 Combined Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Study 20050136/20050244/20050103 Combined Denosumab 120 mg Q4W (N=2841) n (%)
Cellulitis	9 (1.3)	16 (2.2)	15 (1.6)	17 (1.8)	47 (1.7)	51 (1.8)
Wound infection	2 (0.3)	5 (0.7)	3 (0.3)	3 (0.3)	4 (0.1)	10 (0.4)
Subcutaneous abscess	0 (0.0)	2 (0.3)	1 (0.1)	4 (0.4)	4 (0.1)	8 (0.3)
Fungal skin infection	4 (0.6)	3 (0.4)	2 (0.2)	2 (0.2)	10 (0.4)	6 (0.2)
Furuncle	2 (0.3)	3 (0.4)	3 (0.3)	2 (0.2)	6 (0.2)	6 (0.2)
Infected skin ulcer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	2 (<0.1)	3 (0.1)
Postoperative wound infection	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.1)	5 (0.2)

Altogether, the totality of data does not indicate that there is an increased risk in denusomab treated patients.

Malignancies: For the same reasons, malignancies are of special interest.

SYSTEM ORGAN CLASS Preferred Term	Study 20050147 Placebo (N=705) n (%)	Study 20050147 Denosumab 120 mg Q4W (N=720) n (%)	Study 20050103 Zoledronic Acid 4 mg Q4W (N=945) n (%)	Study 20050103 Denosumab 120 mg Q4W (N=943) n (%)	Study 20050136/20050244/20050103 Combined Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Study 20050136/20050244/20050103 Combined Denosumab 120 mg Q4W (N=2841) n (%)
Number of subjects reporting serious adverse events	323 (45.8)	329 (45.7)	568 (60.1)	594 (63.0)	1620 (57.1)	1599 (56.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	69 (9.8)	65 (9.0)	118 (12.5)	114 (12.1)	456 (16.1)	447 (15.7)

There is no overall increase and with respect to individual tumours no pattern of significance was noticed.

Hypersensitivity reactions: In the current SmPC “drug hypersensitivity” is reported as “uncommon”, a category proposed to be changed to “rare”.

Serious Adverse Events

SYSTEM ORGAN CLASS High Level Term Preferred Term	Study 20050147 Placebo (N=705) n (%)	Study 20050147 Denosumab 120 mg Q4W (N=720) n (%)	Study 20050103 Zoledronic Acid 4 mg Q4W (N=945) n (%)	Study 20050103 Denosumab 120 mg Q4W (N=943) n (%)	Study 20050136/20050244/20050103 Combined Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Study 20050136/20050244/20050103 Combined Denosumab 120 mg Q4W (N=2841) n (%)
MMUNE SYSTEM DISORDERS (Cont'd)						
Drug hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	3 (0.1)
Anaphylactic reaction	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	1 (<0.1)
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Anaphylactic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

Adverse Events

SYSTEM ORGAN CLASS High Level Term Preferred Term	Study 20050147 Placebo (N=705) n (%)	Study 20050147 Denosumab 120 mg Q4W (N=720) n (%)	Study 20050103 Zoledronic Acid 4 mg Q4W (N=945) n (%)	Study 20050103 Denosumab 120 mg Q4W (N=943) n (%)	Study 20050136/20050244/20050103 Combined Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Study 20050136/20050244/20050103 Combined Denosumab 120 mg Q4W (N=2841) n (%)
IMMUNE SYSTEM DISORDERS	11 (1.6)	8 (1.1)	8 (0.8)	12 (1.3)	51 (1.8)	61 (2.1)
Allergic conditions	11 (1.6)	8 (1.1)	7 (0.7)	12 (1.3)	47 (1.7)	60 (2.1)
Hypersensitivity	3 (0.4)	2 (0.3)	6 (0.6)	3 (0.3)	19 (0.7)	26 (0.9)
Drug hypersensitivity	3 (0.4)	2 (0.3)	1 (0.1)	7 (0.7)	10 (0.4)	25 (0.9)
Anaphylactic reaction	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)	2 (<0.1)
Allergic oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)
Anaphylactic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)	0 (0.0)

In the current study, fourteen (3.3%) subjects in the denosumab group and 10 (2.4%) subjects in the placebo group had adverse events potentially associated with hypersensitivity. The most common adverse events potentially associated with hypersensitivity reported for subjects in either group were urticaria (5 [1.2%] denosumab, 1 [0.2%] placebo), drug hypersensitivity (1 [0.2%], 3 [0.7%]), face oedema (2 [0.5%], 0), hypersensitivity (1 [0.2%], 1 [0.2%]), swelling face (1 [0.2%], 1 [0.2%]), anaphylactic reaction (1 [0.2%], 1 [0.2%]), and eye swelling (1 [0.2%], 2 [0.5%]).

For the 4 subjects (1 denosumab and 3 placebo) with an adverse event with the preferred term of drug hypersensitivity, the corresponding verbatim term indicated that the event was associated with other drugs (i.e., chemotherapy and antibiotics (cephalexin and clindamycin)).

An individualised causality assessment undertaken indicates that a change from uncommon to rare is justified.

Cardiovascular Events:

Subject Incidences of Cardiac Adverse Events (≥ 5 Subjects in Either Treatment Group in Study 20050147) and Serious Cardiac Adverse Events (≥ 5 Subjects in Either Treatment Group in Study 20050147) (Safety Analysis Set, Study 20050147 and Study 20050103)

	Study 20050147		Study 20050103	
	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)
Cardiac Disorders	82 (11.6)	105 (14.6)	160 (16.9)	151 (16.0)
Atrial fibrillation	19 (2.7)	16 (2.2)	20 (2.1)	24 (2.5)
Myocardial infarction	9 (1.3)	14 (1.9)	13 (1.4)	9 (1.0)
Angina pectoris	7 (1.0)	10 (1.4)	8 (0.8)	4 (0.4)
Myocardial ischemia	3 (0.4)	10 (1.4)	10 (1.1)	8 (0.8)
Congestive cardiac failure	9 (1.3)	9 (1.3)	9 (1.0)	13 (1.4)
Bradycardia	5 (0.7)	8 (1.1)	3 (0.3)	1 (0.1)
Tachycardia	5 (0.7)	8 (1.1)	19 (2.0)	21 (2.2)
Cardiac failure	6 (0.9)	6 (0.8)	33 (3.5)	27 (2.9)
Arrhythmia	10 (1.4)	5 (0.7)	11 (1.2)	15 (1.6)
Palpitations	0 (0.0)	5 (0.7)	4 (0.4)	3 (0.3)
Pericardial effusion	0 (0.0)	5 (0.7)	1 (0.1)	3 (0.3)
Coronary artery disease	5 (0.7)	3 (0.4)	1 (0.1)	5 (0.5)
Serious Cardiac Disorders	49 (7.0)	56 (7.8)	97 (10.3)	90 (9.5)
Myocardial infarction	8 (1.1)	12 (1.7)	13 (1.4)	9 (1.0)
Atrial fibrillation	12 (1.7)	6 (0.8)	8 (0.8)	10 (1.1)
Congestive cardiac failure	7 (1.0)	6 (0.8)	7 (0.7)	8 (0.8)
Myocardial ischemia	0 (0.0)	6 (0.8)	6 (0.6)	5 (0.5)
Angina pectoris	3 (0.4)	5 (0.7)	5 (0.5)	1 (0.1)

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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 denosumab group in Study 20050147 and coded using MedDRA Version 13.1.

Due to the apparent increase in events of cardiac ischemia, independent adjudication was also undertaken.

Autoimmune Disorders: This group of disorders has not been categorized as being of special interest by the MAH. A thorough assessment of all possible entries has not been undertaken, but thyroid disorder, mainly thyroiditis (hypo-, hyper-), might serve screening purposes as thyroiditis is frequently reported e.g. in relation to alpha interferon treatment.

	Study 20050147		Study 20050103		Study 20050136/20050244/20050103 Combined	
SYSTEM ORGAN CLASS High Level Term Preferred Term	Placebo (N=705) n (%)	Denosumab 120 mg Q4W (N=720) n (%)	Zoledronic Acid 4 mg Q4W (N=945) n (%)	Denosumab 120 mg Q4W (N=943) n (%)	Zoledronic Acid 4 mg Q4W (N=2836) n (%)	Denosumab 120 mg Q4W (N=2841) n (%)
ENDOCRINE DISORDERS	7 (1.0)	9 (1.3)	5 (0.5)	15 (1.6)	24 (0.8)	56 (2.0)
Thyroid gland disorders	6 (0.9)	9 (1.3)	2 (0.2)	5 (0.5)	10 (0.4)	29 (1.0)
Hypothyroidism	4 (0.6)	6 (0.8)	1 (0.1)	2 (0.2)	7 (0.2)	17 (0.6)
Goitre	0 (0.0)	2 (0.3)	1 (0.1)	1 (0.1)	3 (0.1)	5 (0.2)
Hyperthyroidism	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	5 (0.2)
Thyroid cyst	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (<0.1)
Thyroid disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Thyroid mass	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

It is concluded that there is currently no strong evidence to support that denosumab acts as an immune modulating agent in adult animals or humans. It is also agreed that that the number of events of hyper- or hypothyroidism is low and in some cases confounded. It is concluded that "high dose" denosumab might be associated with an increased event rate of thyroid disorders.

Safety in patients with PSA doubling time ≤ 6 months

Overall, the safety profile in this subpopulation was similar to the FAS.

2.4.3. Discussion

The safety profile of denosumab remains essentially stable and the overall differences in incidences of adverse events between the denosumab and placebo arm are small.

However, of the AEs considered by investigators related to study medication, serious AEs and AEs leading to study discontinuation occurred more frequently with denosumab. To a large extent this refers to ONJ and at about three years the incidence is about 10-12%, grade 3 and above about 2-3 % and there are no signs of reaching a plateau yet. Of the 33 ONJ cases no subjects presented with grade 4 or 5 events, 10 (30.3%) with grade 3 events, 16 (48.5%) with grade 2 events, and 7 (21.2%) with grade 1 events. Ten (30%) of these events required no surgical treatments; 21 (64%) required surgical treatments limited in nature; and 2 subjects had bone resection. No notable impact of ONJ on subject-reported pain or HRQOL has been reported. By end of data capture resolution of ONJ has been documented for 13 (39%) subjects.

Quantitatively, and as expected, events of hypocalcaemia were fewer in patients at risk for bone metastasis compared with those with established bone involvement.

The SmPC and Package Leaflet will be updated to include 'muscle spasm'.

There are signals as regards thyroiditis and the RMP has been updated accordingly.

The MAH requested removal of skin infections/cellulitis from sections 4.4 and 4.8, which is acceptable given the totality of data available.

There is currently no clear signal as regards CV events. However in Study 20050147 there was a clear imbalance in myocardial ischemia (6 subjects who received denosumab, no subjects who received placebo). The totality of data, however, does not indicate that 4.8 should be revised at present.

2.5. Risk management plan

The identified risk of skin infection leading to hospitalisation has been deleted, whilst infection remains as potential risk.

Thyroid function disorders have been added on request from CHMP.

Overall, there are only minor amendments to the latest agreed version of the RMP as a consequence of variation II/11 and the safety-related changes implemented in the SmPC and package Leaflet. These changes are considered non-controversial and can thus be agreed.

2.6. Changes to the Product Information

In view of an outstanding major objection raised by the CHMP during the evaluation, the MAH informed the CHMP on 27 August 2013 of their decision not to pursue the claimed extension of the indication for XGEVA applied for under the present procedure, but proposed nevertheless to pursue with the application

to enable implementation of the safety-related changes to the SmPC and Package Leaflet, and the changes to the risk management plan (RMP) that had been agreed during the CHMP review.

The CHMP endorsed the MAH's proposed way forward at its September 2013 CHMP meeting. Thus, the final scope of the application was revised as follows:

"Type II variation to delete the ADR cellulitis and text describing "skin infections (predominantly cellulitis) leading to hospitalisation" from section 4.8 of the SmPC and to delete the associated warning in SmPC section 4.4. Further, section 4.8 of the SmPC has been updated with a change in frequency of the ADR drug hypersensitivity from uncommon to rare, and with the addition of text describing symptoms of hypocalcaemia observed in clinical studies. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes to the SmPC and Package Leaflet and to update the contact details in the list of local representatives in the Package Leaflet."

These following changes to the product information were agreed as part of the present variation application:

Summary of Product Characteristics (SmPC)

Section 4.4:

~~Skin infections leading to hospitalisation (predominantly cellulitis)~~

~~In clinical trials in patients with advanced malignancies involving bone, skin infections leading to hospitalisation (predominantly cellulitis) were reported (see section 4.8). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.~~

Section 4.8:

Table 1 Adverse reactions reported in patients with advanced malignancies involving bone

MedDRA system organ class	Frequency category	Adverse reactions
~~Infections and infestations~~	~~Uncommon~~	~~Cellulitis[1]~~

MedDRA system organ class	Frequency category	Adverse reactions
Immune system disorder	Rare~~Uncommon~~	Drug hypersensitivity
	Rare	Anaphylactic reaction[1]

……

Hypocalcaemia

In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, hypocalcaemia was reported in 9.6% of patients treated with XGEVA and 5.0% of patients treated with zoledronic acid.

A grade 3 decrease in serum calcium levels was experienced in 2.5% of patients treated with XGEVA and 1.2% of patients treated with zoledronic acid. A grade 4 decrease in serum calcium levels was experienced in 0.6% of patients treated with XGEVA and 0.2% of patients treated with zoledronic acid (see section 4.4).

Symptoms of hypocalcaemia in clinical studies included paresthesias or muscle stiffness, twitching, spasms and muscle cramps.

……..

~~*Skin infections (predominantly cellulitis) leading to hospitalisation*~~

~~In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, skin infections leading to hospitalisation (predominantly cellulitis) were reported more frequently in patients receiving XGEVA (0.9%) compared with zoledronic acid (0.7%).~~

~~In postmenopausal women with osteoporosis, skin infections leading to hospitalisation were reported for 0.4% women receiving Prolia (denosumab 60 mg every 6 months) and for 0.1% women receiving placebo (see section 4.4).~~

Package Leaflet

The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity make editorial changes to the SmPC and Package Leaflet and to update the contact details in the list of local representatives in the Package Leaflet, which is acceptable.

All the changes above were agreed by the CHMP.

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

Patients with castration resistant prostate cancer (CRPC) eventually develop bone metastases and skeletal complications. Denosumab is currently licensed for the prevention of skeletal related events (SRE) in patients with solid tumours and known bone metastases.

As part of the current procedure, the MAH initially applied for an extension of indication to add "treatment of castration-resistant prostate cancer at high risk of developing bone metastases as determined by assessment of prostate-specific antigen (PSA). XGEVA prolongs bone-metastasis-free survival by preventing bone metastases".

During the procedure, as part of the response to the 2nd CHMP Request for Supplementary Information (RSI), the applicant revised the proposed indication to:

"Delay of bone metastases in men with castration-resistant prostate cancer at high risk of developing bone metastases based on prostate-specific antigen (PSA) doubling time of 6 months or less".

Pivotal for this application is a placebo controlled study conducted in patients with CRPC at increased risk for bone metastases based PSA levels ≥8.0 ng/ml or PSA doubling time ≤10 months. As the study was initiated prior to the authorisation of XGEVA for prevention of SRE, study therapy was stopped at the time of diagnosis of bone metastasis. Thus, the benefit of early therapy vs. initiation of therapy at the time of overt bone metastasis cannot not be assessed. The primary endpoint was bone metastasis free survival.

Benefit

After a median duration of therapy of more than 2 years the absolute benefit in terms of patients free of metastasis was about 5% at an overall level of about 45%. In terms of HR the point estimate was 0.85. The median difference was about 4 months.

Standard subgroup analyses show essentially the same treatment effect, including the stratification factor PSA ≥8.0 ng/ml AND PSA doubling time ≤10 months (yes/no). In patients with prior chemotherapy (stratification factor) results look more promising.

In a *post hoc* defined subgroup of patients encompassing about 60% of patients enrolled with a PSA doubling time of ≤6 months, the HR was 0.77 and the difference in crude incidence of bone metastasis

was about 10% at an overall incidence of about 50% after about median 1½ year of therapy. The median difference appears to overestimate the treatment effect, but was about 7 months.

No benefit in terms of survival (HR 1.0) or symptoms based on PRO was demonstrated, but time to symptomatic bone metastasis was improved HR 0.67 in the FAS, crude incidence 13.4% vs. 9.6%. This possibly relates to the pain reducing effect of osteoclast inhibition.

Uncertainties

"Early treatment" of patients with prostate cancer at high risk for bone metastasis is not a simple case of extrapolation based on documented efficacy in patients with overt bone metastases as there are failed trials with bisphosphonates. A p-value clearly lower than 5%, if derived from a single pivotal trial, would thus be required to support the proposed new indication from a biostatistical perspective. In this case, the p-value was 0.03 at the primary analyses and when overrunning patients were included, 0.07. In addition, the results were no longer statistically significant when the small group of patients (8%) with prior chemotherapy was excluded.

It is acknowledged that the apparent treatment effect is better (HR 0.77, at a p-value of 0.006) in patients with a PSA doubling time of ≤6 months, but it represents the results of *post hoc* analyses. The cut off for PSA doubling-time was defined in retrospect and the risk curve for bone metastases derived from the current study shows a steep increase around this cut-off. While a relationship between PSA doubling time and risk is expected, the very steep increase is unexpected and in need of external support to be considered credible.

The cut-off ><6 months is cautiously considered sufficiently supported by external data. There is, however, no external support for the notion that denosumab shows higher activity in patients with more aggressive disease; HR 0.77 vs. 1.13, <6 months vs. >6 months. It was also noticed that the censoring rate was clearly higher in the denosumab arm in this sub-group (36% vs. 26%). Altogether, available data indicate that the reported treatment effect (HR 0.77) is overestimated.

Risk

Denosumab is well tolerated in the vast majority of patients.

Osteonecrosis of the jaw (ONJ), however, is a concern. In the current study about 5% of the patients in the denosumab arm were affected, i.e. essentially the same incidence per year of therapy as in other cancer studies. Also the severity of the events appears to be the same. Of the 33 subjects with positively adjudicated ONJ in the current study, no subjects presented with CTCAE grade 4 or 5 events, 10 subjects presented with grade 3 events (interfering with daily life), 16 subjects with grade 2 events, and 7 subjects with grade 1 events (asymptomatic). As in other studies, no impact on scheduled assessment of pain (BPI-SF) was observed.

From a clinical practice viewpoint, at about three years the incidence of ONJ is about 10-12%, grade 3 and above about 2-3 % and there are no signs of reaching a plateau yet.

In the current population, cases of hypocalcaemia were fewer than in patients with overt bone metastasis, about 1.5% vs. about 10%.

Uncertainties

Due to the mechanism of action some event types are followed more closely including infections and malignancies. In this submission a possible increase in thyroid disorder was noticed and may be related to activation of autoimmune disorders. The RMP has been updated accordingly.

Benefit – Risk conclusion

In the full study population, the treatment effect in terms of bone metastasis-free survival has not been convincingly documented statistically. Furthermore, the apparent treatment effect is modest. Thus available data make attempts to undertake a thorough benefit – risk assessment futile in the full study population.

In the *post hoc* identified subgroup where the apparent benefit of treatment is improved without signs of increased treatment related risks, the lack of external data supporting the notion that the activity of denosumab is increased, constitutes a major concern.

In conclusion, altogether the benefit – risk balance in the proposed new indication has not been shown to be favourable. Therefore, following the assessment of all available data the CHMP adopted the following major objection to be addressed by the MAH in writing and at an oral explanation:

"This submission for an extended indication to encompass patients with CRPC is based on a single pivotal trial. In the ITT population, the treatment effect is small and the results are not considered robustly documented from a statistical perspective.

Post hoc a subgroup of patients was identified with apparent increased benefit of therapy. Most likely, however, the benefit of therapy is overestimated and may not outweigh the risk of ONJ and thus a proper benefit – risk assessment cannot be undertaken."

In view of the outstanding major objection above, the MAH informed the CHMP on 27 August 2013 of their decision not to pursue the claimed extension of the indication for XGEVA applied for under the present procedure, but proposed nevertheless to pursue with the application to enable implementation of the safety-related changes to the SmPC and Package Leaflet, and the consequential changes to the risk management plan (RMP) that had been agreed during the CHMP review.

The CHMP endorsed the MAH's proposed way forward at its September 2013 CHMP meeting. Thus, the final scope of the application was revised as follows:

"Type II variation to delete the ADR cellulitis and text describing "skin infections (predominantly cellulitis) leading to hospitalisation" from section 4.8 of the SmPC and to delete the associated warning in SmPC section 4.4. Further, section 4.8 of the SmPC has been updated with a change in frequency of the ADR drug hypersensitivity from uncommon to rare, and with the addition of text describing symptoms of hypocalcaemia observed in clinical studies. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes to the SmPC and Package Leaflet and to update the contact details in the list of local representatives in the Package Leaflet."

Following the final revision of the scope of the application, the CHMP concluded that the proposed safety-related changes to the SmPC, Package Leaflet and RMP can be agreed. The benefit/risk balance for XGEVA remains positive in the already approved indication:

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

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

Update of section 4.8 of the SmPC to delete the ADR cellulitis and the text describing "skin infections (predominantly cellulitis) leading to hospitalisation" and to delete the associated warning in SmPC section 4.4. Further, section 4.8 of the SmPC has been updated with a change in frequency of the ADR drug hypersensitivity from uncommon to rare, and with the addition of text describing symptoms of hypocalcaemia observed in clinical studies. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make editorial changes to the SmPC and Package Leaflet and to update the contact details in the list of local representatives in the Package Leaflet.

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

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.