RISK MANAGEMENT PLAN

for

Denosumab

Data lock point (DLP) for RMP: 31-Oct-2024

Version Number: 0.2

Dated: 16-Dec-2024

[redacted]

[redacted]

Risk Management Plan – Denosumab

Risk Management Plan for:	Denosumab
RMP Version number:	0.2
Data lock point for this RMP:	31-Oct-2024
Date of final sign off:	16-Dec-2024
Rationale for submitting an updated RMP:	In response to CHMP day 80 assessment the safety specifications have been revised to align with most recent version of originator RMP
Summary of significant changes in this RMP:	• Removed 'Infection' and 'Osteonecrosis Outside the Jaw Including External Auditory Canal' from important potential risk to be in line with the originator RMP. • Removed traceability under PART III: PHARMACOVIGILANCE PLAN • Updated information with respect to Study B1000-PMO-03-G-02, as this study is completed now.
Other RMP versions under evaluation • RMP version number • Submitted on • Procedure number	Not applicable
Details of the currently approved RMP • Version number • Approved with procedure • Date of approval (Opinion date)	Not applicable, this is the initial RMP
QPPV	Sanja Prpic [redacted]
Signature	[redacted]

Risk Management Plan for:	Denosumab
E-mail address of contact person	[redacted]

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List of Abbreviations

Term/Abbreviation	Explanation
AAC	Area Above the Curve
ADA	Anti-Drug Antibodies
AEs	Adverse events
AFF	Atypical femoral fracture
AIDS	Acquired Immune Deficiency Syndrome
ATC Code	Anatomical Therapeutic Chemical Classification System {ATC) Code
AUC	Area under the curve
AUC0-inf	Area Under the serum Concentration time curve from time 0 to the infinity
AUC0-t	Area Under the serum Concentration versus time curve from time 0 to the last sampling time at which concentrations were at or above the limit of quantification
AUCext	Percentage of AUCinf due to extrapolation from tt (time of last measurable concentration) to infinity
BBL	Biocon Biologics Limited
BMD	Bone Mineral Density
CIs	Confidence Interval
Cmax	Maximum observed serum Concentration
COX-2	Cyclooxygenase-2,
CRPC	castrate-resistant prostate cancer
CSR	Clinical Study Report
CV	cardiovascular
DIBD	Development International Birth Date
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EOS	End of Study
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GC	Glucocorticoid
GCTB	Giant Cell Tumor of Bone
GIOP	Glucocorticoid-induced osteoporosis
GLSMs	Geometric Least Squares Means
GVP	Good Pharmacovigilance Practices
HALT	Hormone ablation therapy

HIV	Human immunodeficiency virus
ICF	Informed Consent Form
lgG2	lmmunoglobulin G 2 Subclass
INN	International Nonproprietary Name
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NPM	New Primary Malignancy
OI	Osteogenesis Imperfecta
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
PI	Product information
PIL	Package Information Leaflet
PMO	Postmenopausal osteoporosis
PL	Package leaflet
PK	Pharmacokinetics
PMGCTB	primary malignant giant cell tumor of bone
PSUR	Periodic Safety Update Report
Q4w	Once every 4 Weeks
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RANKL	RANK ligand
RMP	Risk management plan
SC	Subcutaneous
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Queries
SREs	Skeletal-Related Event
SOC	System organ class
t1/2	Apparent terminal elimination half-life
TEAE	Treatment Emergent Adverse Event
tmax	Time to Maximum Observed Concentration
US	United States
WHO	World Health Organization

Part I: Product(s) Overview

Table 1: Product overview

Active substance (s) (INN or common name):	Denosumab
Pharmacotherapeutic group (s): (Anatomical Therapeutic Chemical Classification System (ATC) Code):	Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralisation: ATC code: M05BX04
Marketing Authorisation Applicant:	Biosimilar Collaborations Ireland Limited
Medicinal products to which this RMP refers	1
Invented name (s)in the European Economic Area (EEA)	Bmab 1000 (Denosumab)
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Denosumab is a fully human monoclonal antibody of the immunoglobulin G (IgG) 2 subclass
	Summary of mode of action: Bmab1000 has high affinity and specificity for the soluble and cell membrane-bound forms of human receptor activator of nuclear factor kappa-B (RANK} ligand (RANKL}
	Composition: Bmab1000 vial contains 120 mg of denosumab in 1.7 mL of solution (70 mg/mL). Important information about its composition: Denosumab is derived from the Xeno-mouse™ technology and produced in genetically engineered mammalian (Chinese hamster ovary} cells. List of excipients: Acetic acid, glacial Sodium acetate trihydrate Sodium hydroxide (for pH adjustment) Sorbitol Polysorbate 20 Water for injections

Hyperlink to the Product Information	Bmab1000 Product information (Module 1.3.1)
Indication (s) in the EEA	Current: Prevention of skeletal-related events (SREs} (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone} in adults with advanced malignancies involving bone. Treatment of adults and skeletally mature adolescents with giant cell tumor of bone (GCTB} that is unresectable or where surgical resection is likely to result in severe morbidity.
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended dose of Denosumab for prevention of SREs is 120 mg administered as a single subcutaneous (SC) injection once every 4 weeks (Q4W) into the thigh, abdomen, or upper arm. Patients must be adequately supplemented with calcium and vitamin D. The recommended dose of Bmab1000 for treatment of adults or skeletally mature adolescents with GCTB is 120 mg Q4W administered as an SC injection, with additional 120 mg SC injections on days 8 and 15 of treatment of the first month of therapy.
	Proposed: Not applicable.
Pharmaceutical form (s) and strengths	Current: Bmab1000 is supplied in vials as a sterile, preservative-free solution intended for SC injection. The vial presentation contains 120 mg of denosumab at 70 mg/ml.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the European Union (EU)?"	Yes

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable as this RMP pertains to a similar biologic. (Ref: In accordance with the Good Pharmacovigilance Practices (GVP) - Biological medicinal products[Error! Reference source not found.] "All parts of an RMP are required for a biosimilar, except for RMP part II, module SI "Epidemiology of the target population).

Part II: Module SII - Non-clinical part of the safety specification

No pharmacokinetic (PK), toxicokinetic (TK), Anti-Drug Antibody (ADA) evaluation and toxicology have been performed yet for Bmab 1000.

Based on appropriate Food and Drug Administration (FDA) and EMEA guidelines as well as the feedback received from FDA type 2 meeting (Reference ID:4813057) and European Medicines Agency (EMA) Scientific Advice (EMEA/H/SA/4398/1/2020/III) in vivo studies are deemed not necessary for the establishment of biosimilarity, as functional assays performed as a part of primary pharmacodynamics are highly sensitive in detecting differences between Bmab 1000, US-Licensed Xgeva® and EU-Approved Xgeva®.

The key safety findings from non-clinical studies reported for reference product Xgeva® and relevance to human use are summarized below[Error! Reference source not found.]:

Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity **Reproductive toxicity** Denosumab had no effect on female fertility or male reproductive organs in monkeys at exposures that were 9.5- to 16-fold higher, respectively, than the human exposure at 120 mg SC administered once Q4W. In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at area above the curve (AAC) exposures up to 10-fold higher than the human dose (120 mg Q4W), there was no evidence of maternal or fetal harm. In this study, fetal lymph nodes were not examined. In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AAC exposures 12-fold higher than the human dose (120 mg every 4-weeks), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced hematopoiesis, and tooth malalignment;	Denosumab is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with Denosumab. It is not known if denosumab is excreted in human milk. Because denosumab has the potential to cause adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP.

absence of peripheral lymph nodes; and decreased neonatal growth. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal.	
Developmental toxicity: Denosumab has been shown to be a potent inhibitor of bone resorption by inhibition of RANKL. Adolescent primates dosed with denosumab at 2.8 and 15 times (10 and 50 mg/kg dose) the clinical exposure based on AAC had abnormal growth plates. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced hematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery period from birth out to 6 months of age, the effects on bone largely returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. In neonatal rats, inhibition of RANKL (target of denosumab therapy) was associated with inhibition of bone growth, altered growth plates, and inhibited tooth eruption, and these changes were partially reversible upon cessation of RANKL inhibition.	The safety and efficacy of Bmab1000 have not been established in pediatric patients other than skeletally mature pediatric patients with GCTB. Treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. Bmab1000 is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with Bmab1000.
Safety pharmacology	Not applicable
Other toxicity-related information or data	Not applicable

Part II: Module SIII - Clinical trial exposure

The Clinical development is in accordance with the plan discussed with the CHMP during the EMA scientific advices (EMEA/H/SA/4398/1/2020/III, 2021EMA/SA/0000063174 and EMA/SA/0000091701) and United states Food and Drug Administration (USFDA) (FDA type 2 meeting Reference ID: 4813057 and Reference ID: 5128115). During the follow-up EMA advice (EMA/SA/0000063174), it was proposed by Biocon and endorsed by CHMP that the efficacy and safety (including immunogenicity) data collected up to Week 52 are sufficient for submission of the MA application whereas the addendum to the CSR (78-week data), once available, can be submitted later during the MA procedure.

During the CHMP EMA scientific advice (EMEA/H/SA/4398/1/2020/III), biosimilarity has been demonstrated in a fully analytical similarity exercise and extended functional characterization, and the Clinical trials phase 1 and Phase 3 (*B1000-NHV-01-G-01*, B1000-PMO-03-G-02) demonstrate 1. PK comparability II. Compatibility within an indication representative for both efficacy and safety (i.e in the planned indication of post-menopausal osteoporosis), extrapolation to all EU indications of Prolia and Xgeva® for BMab 1000-P and BMab 1000-X, respectively, is accepted.

Clinical trial development programme for Bmab 1000 consisted of the following two clinical trials (*B1000-NHV-01-G-01*, B1000-PMO-03-G-02) that aimed to establish biosimilarity of Bmab 1000 with the reference medicinal product, Prolia® in terms of pharmacokinetics, pharmacodynamics, safety and efficacy.

- Study **B1000-NHV-01-G-01**: A Phase 1, randomized, Double-blind, Two-arm, Single-dose, Parallel-Group Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Bmab 1000 and Prolia® in Normal Healthy Volunteers
- Study **B1000-PMO-03-G-02**: A Randomized, Double-Blind, Multicenter, Parallel-Arm Phase 3 Study to Compare the Efficacy, Pharmacodynamics, Safety, and Immunogenicity between Bmab 1000 and Prolia in Postmenopausal Women with Osteoporosis.

Overall, 479 patients in Phase 3 and 189 subjects (healthy volunteers) in Phase 1 trial have been enrolled into 2 clinical trials and 238 patients and 94 subjects have received Bmab 1000 since the DIBD (05 Feb 2022).

Study B1000-NHV-01-G-01 completed on 30 May 2024 and Study B1000-PMO-03-G-02 was completed on 29 Aug 2024.

Study B1000-NHV-01-G-01: (Status: Completed)

Study Design

This was a Phase 1, multi-center, randomized, double-blind, two-arm, single dose, parallel group study to establish PK similarity between Bmab 1000, US Prolia after a single 60 mg subcutaneous injection in healthy male and female subjects. Up to 190 subjects were to be enrolled to ensure that at least 176 subjects completed the study.

Potential subjects were screened to assess their eligibility to enter the study within 28 days prior to the dose administration. The study consisted of up to 4 weeks of screening period, 10 days of in-clinic stay, and 36 weeks of outpatient follow up period after dosing on Day (D) 1.

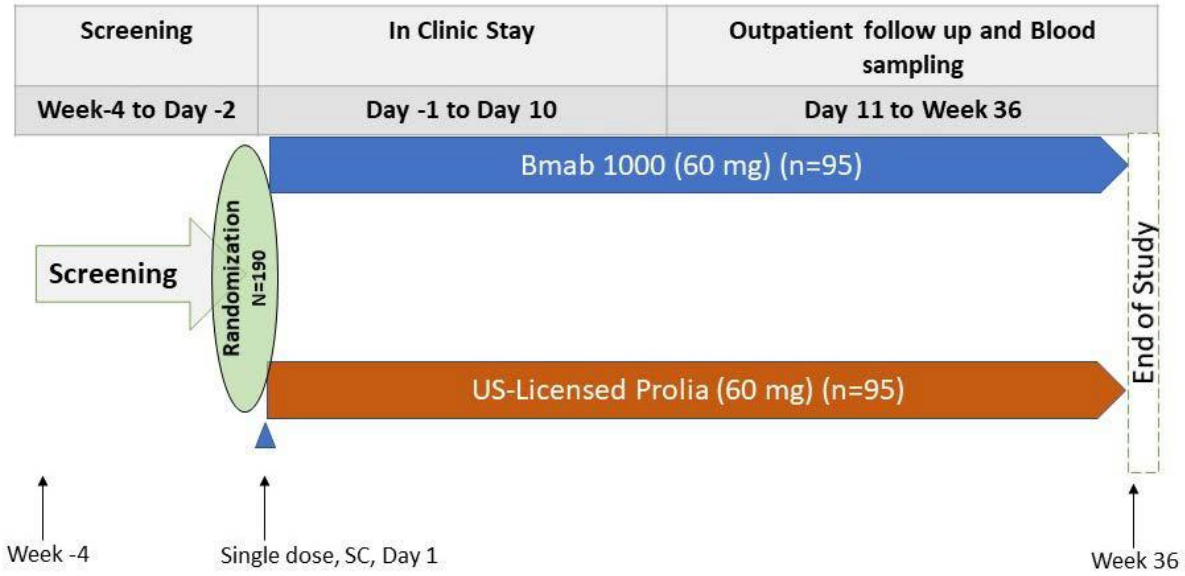
Subjects were randomized in a 1:1 ratio to receive a single dose of 60 mg study drug on Day 1 as either:

- US Prolia
- Bmab 1000.

The total duration of study participation for each subject (from screening through end-of-study [EOS] visit) was anticipated to be approximately 40 weeks.

The start of the study was defined as the date the first subject signed an Informed consent form (ICF). The point of enrolment occurred at the time of subject number allocation. The end of the study was defined as the date of the last subject's last assessment (scheduled or unscheduled).

A schematic of the study design is presented below.



Overall, 189 subjects were randomized and dosed in the study. Of them, 185 subjects (97.8%) completed the study in accordance with the protocol and protocol amendment. Four subjects did not complete the study; one subject who had received US Prolia withdrew consent from the study and three were withdrawn for other reasons, including lack of compliance with the protocol (received US Prolia), loss to follow-up (received Bmab1000), and personal relocation (leading to consent withdrawal) (received Bmab1000).

Subject disposition for the safety population is summarized in the table below.

	60 mg Bmab 1000 (N = 94)	**60 mg US Prolia (N = 95)**	**Overall (N = 189)**
Randomized	94	95	189
Dosed	94	95	189
Completed the Study	92 (97.87%)	93 (97.89%)	185 (97.8%)
Discontinued the Study	2 (2.12%)	2 (2.10%)	4 (2.11%)
Withdrawal by Subject	0	1 (1.06%)	1 (0.52%)
Other	1 (1.06%)	2 (2.10%)	3 (1.58%)
Population			
Safety	94 (100%)	95 (100%)	189 (100%)
Pharmacokinetic	91 (96.8%)	93 (97.9%)	184 (97.4%)

One-hundred and eighty-nine (100.0%) subjects received the study drug per planned dose. Overall, 94 subjects received a single dose of 60 mg Bmab 1000, 95 subjects received a single dose of 60 mg US Prolia on Day 1 as per the randomization schedule.

Pharmacokinetics Conclusions

- Following a single s.c. dose of 60 mg Bmab 1000 and Prolia®, the mean Cmax, AUC0-t and AUC0-inf, including the partial AUCs (AUC18-85days and AUC113-253days) were comparable between the two treatment groups.
- The tmax, Ct, and the t1/2 were comparable between the Bmab 1000 and Prolia® treatment groups. The AUCext(%) was less than 1% following administration of both study treatments reflecting that the PK sampling duration considered for the study was adequate for reliable estimation of the terminal phase.
- Statistical analysis demonstrated PK similarity between Bmab 1000 and Prolia® as the 90% CIs of GLSMs ratio for primary PK parameters (Cmax, AUC0-t and AUC0-inf), were entirely contained within the predefined bioequivalence range of 0.8000 and 1.2500.
- Statistical analysis of protein-adjusted primary PK parameters (Cmax/P, AUC0-t/P and AUC0-inf/P) supported PK similarity between Bmab 1000 and Prolia® as the 90% CIs of GLSMs ratio (Test/Reference) fell within the bioequivalence range of 0.8000 and 1.2500.

Immunogenicity

- The incidence of ADA in the Prolia® group and in the Bmab 1000 group closely matched throughout the study: the number of participants with ADA+ increased until D57 (91 [98.9%] participants in the Bmab 1000 group and 87 [93.5%] participants in the Prolia® group) and was stable until D85 91 [98.9%] participants in the Bmab 1000 group and 88 [94.6%] participants in the Prolia® group). The number of positive participants then decreased until the end of study (EOS) visit, when 5 (5.4%) participants in the Bmab 1000 group and 2 (2.2%) participants in the Prolia® group were positive.
- The evolution of ADA titers over time in both treatment groups also matched closely

Safety summary

- Overall, 99 (52.4%) participants experienced at least one treatment emergent AE (TEAE), and a total of 221 TEAEs were reported: 110 TEAEs in 47 (50.0%) participants in the Bmab 1000 group and 111 TEAEs in 52 (54.7%) participants in the Prolia® group.
- No grade 3 or higher TEAEs were reported.
- Most TEAEs were grade 1, with 38 participants (40.4%) experiencing grade 1 TEAEs in the Bmab 1000 group and 32 participants (33.7%) in the Prolia® group. Additionally, grade 2 TEAEs were reported and in 23 participants (24.5%) in the Bmab 1000 group and in 33 participants (34.7%) in the Prolia® group.
- The majority of the events were not related to the study drug. In the Bmab 1000 group, 85 out of 110 TEAEs, reported in 41 (43,6%) participants, were considered not related to treatment, and in the Prolia® group, 98 out of 111 TEAEs, reported in 50 (52,6%) participants, were considered not related to the study drug.
- Incidence of treatment related adverse events were nominally higher in the Bmab1000 group than in the Prolia® group; however the number of events in each PT was low. In the Bmab 1000 group, 25 out of 110 TEAEs, reported in 16 (17.0%) participants were considered related to treatment, and in the Prolia® group, 13 out of 111 TEAEs, in 9 (9.5%) participants, were considered related to treatment.

Conclusions

- Following a single s.c. dose of 60 mg Bmab 1000 and 60 mg Prolia, the concentration time profiles were comparable.
- Statistical analysis demonstrated PK similarity for PK parameters (AUC0-inf, AUC0-t, and Cmax) between Bmab 1000 and the Prolia as the 90% CIs of GLSMs ratio (Test/Reference)

fell within the predefined bioequivalence range of 0.8000 and 1.2500 (i.e., 80.00% and 125.00%).

- A single dose of 60 mg Bmab 1000/Prolia was safe and well tolerated in healthy subjects across the two treatment groups. The majority of the AEs were mild in severity and were considered not related to the study drugs. The incidence of ADA was observed to be similar between the two treatment arms.
- The results from this study complement the comparative physical and chemical characterization of Bmab 1000 and Prolia, confirming that the demonstrated analytical comparability translates into highly similar clinical exposure over time i.e. bioequivalence and highly similar pharmacodynamic behavior of Bmab 1000 and Prolia. Seen in context this study provides additional support for the contention that Bmab 1000 qualifies as a biosimilar to Prolia®.

Study B1000-PMO-03-G-02 (Status: Completed)

Study Design

This is a randomized, double-blind, multicenter, parallel-arm, Phase 3 study to compare the efficacy, PK, PD, safety, and immunogenicity of Bmab 1000 and Prolia in postmenopausal women with osteoporosis.

A total of 479 postmenopausal women aged ≥55 and <80 years with a Bone mineral Density (BMD) absolute value consistent with a T-score ≤−2.5 and ≥−4.0 at the lumbar spine were enrolled.

The study consisted of 3 study periods: Screening period; Part 1, double-blind active-controlled period; and Part 2, transition period.

Screening Period (from Day −28 to Day −1)

Screening evaluations will be completed within 28 days prior to the randomization.

Part 1, Double-Blind Active-Controlled Period (from Week 0 [Day 1] to Week 52 Pre-dose)

In the double-blind active-controlled period, eligible patients will be randomly assigned (1:1) to receive either Bmab 1000 (60 mg) or Prolia (60 mg) via SC injection on Day 1 (Week 0, the same date as randomization) and at Week 26. Patients will be followed up for 26 weeks after the second dose. The randomization will be stratified by geographical region (US, Europe), prior use of bisphosphonate treatment (Yes, No), and age of the patient (<65, ≥65 years). Efficacy, PK, PD, and safety including immunogenicity data will be collected as per Schedule of Events.

Part 2, Transition Period (from Week 52 to Week 78 [EoS Visit])

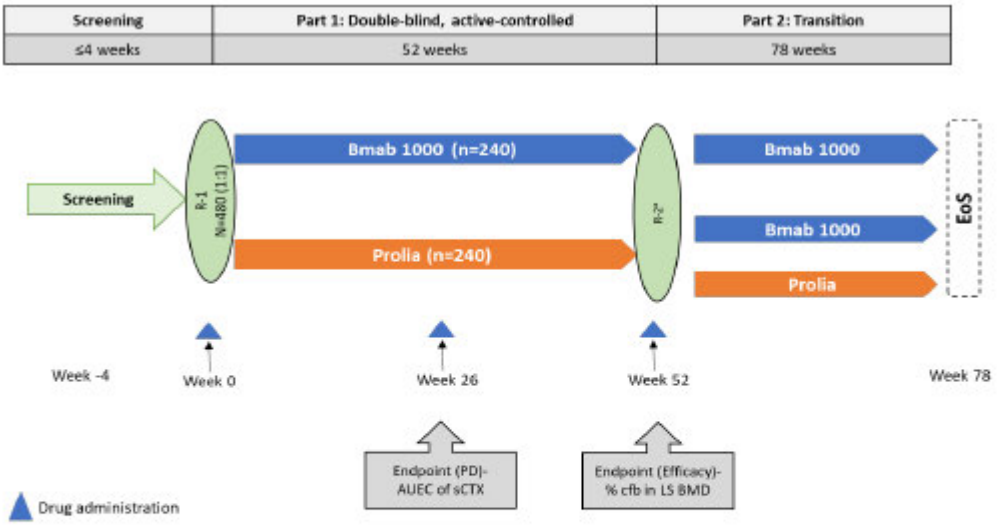
All patients who complete Part 1 will undergo the re-randomization process prior to the study treatment administration at Week 52. Prior to dosing at Week 52, patients in the Prolia arm will be randomly assigned in a 1:1 ratio to receive either Bmab 1000 or Prolia at Week 52. This is done to obtain data after a single switch in patients who have been treated with Prolia.

To maintain the study blinding, the patients in the original Bmab 1000 arm will also go through the re-randomization procedure; however, they will continue to receive Bmab 1000.

The re-randomization will take place within the original strata used for the randomization at baseline. All applicable assessments including efficacy, PK, PD, safety including immunogenicity will be performed as per the Schedule of Events.

The end-of-study visit will be at Week 78 post-randomization.

A schematic of the study design is presented below



Abbreviations: AUEC, area under the effect curve; BMD, bone mineral density; cfb, change from baseline; EoS, end-of-study; LS, lumbar spine; PD, pharmacodynamic; sCTX, serum C-terminal telopeptide of Type 1 collagen; R-1, first randomization; R-2, re-randomization

a. At Week 52, patients in the Prolia arm will be re-randomized in 1:1 ratio to receive Bmab 1000 or Prolia. To maintain the blinding, patients in Bmab 1000 arm will undergo re-randomization procedure however, they will continue to receive Bmab 1000.

In Study B1000-PMO-03-G-02, 479 patients with postmenopausal women with osteoporosis were initially randomized in a 1:1 ratio to receive Bmab 1000 or US-approved Prolia®. Out of 479 patients, 238 were enrolled to receive Bmab 1000 and 241 patients were enrolled to receive Prolia® based on the randomization scheme (1;1).

The estimated exposure of Bmab 1000, B1000-PMO-03-G-02 (Phase 3) is provided in the tables below.

SIII.1 Duration of Exposure

Total exposed population (N=238)		
Duration of exposure	**Persons (%)**	**Person time (subject-years)***
≥ 0 months to <6 months	16 (6.7)	0.04
≥ 6 months to <12 months	24 (10.1)	21.70
≥ 12 months to <1**8** months	198 (83.2)	198.37

SIII.2 By Age Group and Gender

Total population (N=238)				
Age group (years)	**Persons (%)**		**Person time (subject-years)***	
	M (%)	F (%)	M	F
<25	0	0	0	0
25 to 40	0	0	0	0
40 to 64	0	84 (35.3)	0	77.11
65 to 74	0	134 (56.3)	0	124.08
75 to 84	0	20 (8.4)	0	18.93
≥85	0	0	0	0
Total	0	238 (100)	0	220.12

SIII.3 By Dose

Total population (N=238)		
Dose of exposure	**Persons (%)**	**Person time (Subject - years)***

1 dose (60 mg)	16 (6.7)	0.05
2 doses	4 (1.7)	1.99
3 doses	218 (91.6)	218.08
Total	238 (100)	220.12

SIII.4 By Ethnic or Racial Origin

Total population (N=238)		
Ethnic/racial origin	**Persons (%)**	**Person time (subject years) ***
American Indian or Alaska Native	0	0
Asian	1 (0.4)	1.00
Black or African American	0	0
White	237 (99.6)	219.12
Other	0	0
Total	238 (100)	220.12

*Person time (subject-years) = (the last exposure date-first nonmissing dose date +1)/365.5, where last exposure date is the min ([date of last nonmissing dose +180 days - 1], end of study date, data lock Point date).

Safety Summary

The safety results are presented according to study parts:

- **Part 1** (from Day 1 to predose Week 52), compared Bmab 1000 vs. Prolia
- **Part 2** (from Week 52 to Week 78 [EoS]) compared treatment groups as below:
  - Prolia-Bmab 1000 vs. Prolia-Prolia
  - Bmab 1000-Bmab 1000 vs. Prolia-Bmab 1000 and
  - Bmab 1000-Bmab 1000 vs. Prolia-Prolia

  In Part 2, the 1:1 re-randomization of patients in the Prolia treatment group led to unequal (~2:1:1) number of patients in the Bmab 1000-Bmab 1000: Prolia-Bmab 1000: Prolia-Prolia treatment groups.

<u>Part 1</u>:

The proportion of patients reporting TEAEs and study drug-related TEAEs was similar between the Bmab 1000 and Prolia treatment groups. A total of 59.2% and 63.8% patients in the Bmab 1000 and Prolia treatment groups, respectively reported TEAEs; out of which 8.0% and 11.3% patients reported study drug related TEAEs, respectively.

The most common TEAEs by PT were reported in approximately similar proportion of patients in both the treatment groups. The majority of the TEAEs were of Grade 1 or Grade 2 severity and the proportion of patients with TEAEs of Grade 3 or higher severity TEAEs was similar between both the Bmab 1000 and Prolia treatment groups.

The incidence of serious TEAEs was low (in 4.4% of total treated patients) and a total of 27 serious TEAEs were reported in 21 patients (18 events in 5.9% patients and 9 events in 2.9% patients in the Bmab 1000 and Prolia treatment groups, respectively). None of the serious TEAEs in either treatment group was considered as related to the study drug. Except for the serious TEAEs of pancreatic carcinoma and dizziness (in 2 patients, each), no other serious TEAE was reported in >1 patient. Two serious TEAEs in 2 patients and 1 serious TEAE in 1 patient, respectively were of Grade 4 and Grade 5 severity. The Grade 5 TEAE was the

cerebrovascular event reported in Prolia treatment group was deemed unrelated to study drug by the investigator.

None of the serious events were of a nature that could be attributed to the mechanism of action of denosumab. The nominal difference between the two groups in terms of the number of SAEs does not indicate any specific safety pattern and could be attributed to underlying disease conditions, demographic risk factors, or relevant medical histories and appear to be incidental.

The incidence of TEAEs that led to discontinuation of study drug was also low (in total 9 patients) which included 4 patients in the Bmab 1000 treatment group and 5 patients in the Prolia treatment group.

The incidence of AESIs was low (in 4.6% of total treated patients) and were reported in similar proportion of patients between both the Bmab 1000 and Prolia treatment groups (3.4% and 5.8% patients, respectively). Injection site reactions were also low and except for 1 moderate event in the Prolia treatment group, all other injection site reactions were mild. Drug-related hypersensitivity/allergic reaction of Grade 1 injection site erythema lasting for 1 day was reported in 1 patient in the Prolia treatment group.

Two new fracture events were reported in 2 patients in the Bmab 1000 treatment group.

Part 2:

Prolia-Bmab 1000 vs. Prolia-Prolia

The proportion of patients reporting TEAEs and study drug related TEAEs was similar between patients in the Prolia-Bmab 1000 and Prolia-Prolia treatment groups; suggesting no safety concerns in patients who transitioned from Prolia to Bmab 1000 compared to patients who continued to receive Prolia at Week 52.

Study drug related TEAEs were reported in 1.9% and 3.8% patients in the Prolia Bmab 1000 and Prolia Prolia treatment groups respectively, with no study drug-related TEAE being reported in >1 patient. The most common TEAEs by PT were reported in approximately similar proportion of patients in both the treatment groups. The majority of the TEAEs were of Grade 1 or Grade 2 severity. Grade 3 or higher TEAEs were reported in 2 patients (1 patient each in either treatment group).

The incidence of serious TEAEs was low and 1.9% patients each in Prolia-Bmab 1000 and Prolia Prolia treatment group reported serious TEAEs. None of the serious TEAEs in either treatment group was considered as related to the study drug. All 4 serious TEAEs (2 each in either treatment group) were of Grade 2 or Grade 3 severity. No individual serious TEAE was reported in >1 patient.

None of the patients in the Prolia-Bmab 1000 or Prolia-Prolia treatment group reported AESI or TEAE leading to death, study drug discontinuation, or study discontinuation. One patient in the Prolia-Prolia treatment group reported mild injection site reaction and no injection site reaction in the Prolia Bmab 1000 treatment group. No fracture or drug-related hypersensitivity/allergic reaction events were reported in either of the treatment groups.

Bmab 1000-Bmab 1000 vs. Prolia-Bmab 1000

The proportion of patients reporting TEAEs and study drug related TEAEs was similar between patients in the Bmab 1000 Bmab 1000 and Prolia-Bmab 1000 treatment groups; suggesting

no safety concerns in patients who transitioned from Prolia to Bmab 1000 compared to patients who received Bmab 1000 at Week 52.

Study drug related TEAEs were reported in 2.8% and 1.9% patients in the Bmab 1000 Bmab 1000 and Prolia Bmab 1000 treatment groups respectively, with no study drug-related TEAE being reported in >1 patient. The most common TEAEs by PT were reported in approximately similar proportion of patients in both the treatment groups. The majority of the TEAEs were of Grade 1 or Grade 2 severity. Grade 3 or higher TEAEs were reported in 3 patients (2 and 1 patient in the Bmab 1000 Bmab 1000 and Prolia Bmab 1000 treatment groups, respectively).

The incidence of serious TEAEs was low, 2.3% and 1.9% of patients in Bmab 1000 Bmab 1000 and Prolia Bmab 1000 treatment group reported serious TEAEs. None of the serious TEAEs in either treatment group was considered as related to the study drug. All 7 serious TEAEs (5 and 2 SAEs in the Bmab 1000 Bmab 1000 and Prolia Bmab 1000 treatment groups, respectively) were of Grade 2 or Grade 3 severity. No individual serious TEAE was reported in >1 patient.

Three AESIs were reported in 3 patients (all in the Bmab 1000 Bmab 1000 treatment group). None of the AESIs were considered as serious or study drug related. None of the patients in the Bmab 1000 Bmab 1000 and Prolia Bmab 1000 treatment group reported TEAE leading to death, study drug discontinuation, or study discontinuation.

One patient in the Bmab 1000 Bmab 1000 treatment group reported mild injection site reaction and no injection site reaction in the Prolia Bmab 1000 treatment group. No fracture or drug related hypersensitivity/allergic reaction events were reported in either of the treatment groups.

Bmab 1000-Bmab 1000 vs. Prolia-Prolia

The proportion of patients reporting TEAEs and study drug related TEAEs was similar between patients in the Bmab 1000 Bmab 1000 and Prolia-Prolia treatment groups. Study drug related TEAEs were reported in 2.8% and 3.8% patients in the Bmab 1000 Bmab 1000 and Prolia-Prolia treatment groups respectively, with no study drug related TEAE being reported in >1 patient. The most common TEAEs by PT were reported in approximately similar proportion of patients in both the treatment groups. The majority of the TEAEs were of Grade 1 or Grade 2 severity. Grade 3 or higher TEAEs were reported in 3 patients (2 and 1 patient in the Bmab 1000 Bmab 1000 and Prolia-Prolia treatment groups, respectively).

The incidence of serious TEAEs was low, 2.3% and 1.9% of patients in Bmab 1000 Bmab 1000 and Prolia-Prolia treatment group reported serious TEAEs. None of the serious TEAEs in either treatment group was considered as related to the study drug. All 7 serious TEAEs (5 and 2 SAEs in the Bmab 1000 Bmab 1000 and Prolia-Prolia treatment groups, respectively) were of Grade 2 or Grade 3 severity. No individual serious TEAE was reported in >1 patient.

Three AESIs were reported in 3 patients (all in the Bmab 1000 Bmab 1000 treatment group). None of the AESIs were considered as serious or study drug related. None of the patients in the Bmab 1000 Bmab 1000 and Prolia-Prolia treatment group reported TEAE leading to death, study drug discontinuation, or study discontinuation.

One patient each in the Bmab 1000 Bmab 1000 and Prolia-Prolia treatment group reported mild injection site reaction. No fracture or drug related hypersensitivity/allergic reaction events were reported in either of the treatment groups.

Safety conclusion:

The safety results of Bmab 1000 were similar to Prolia and demonstrate that Bmab 1000 is well tolerated as Prolia in postmenopausal women with osteoporosis. No major safety concerns were observed following transition from Prolia to Bmab 1000 compared to patients who continued with Prolia.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 2: Important Exclusion Criteria in Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
Hypocalcemia	Hypocalcemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients receiving denosumab must have adequate intake of calcium and vitamin D. This information is provided in the Summary of Product Characteristics (SmPC).	No	It is a contraindication as per the SmPC 4.3 (Contraindications). Hypocalcemia is an important identified risk for Bmab1000. Additional information regarding hypocalcaemia which occur during treatment with Bmab1000 is included in SmPC 4.4 (Special Warnings and Precautions for Use)
Hypersensitivity to the active substance or to any of the excipients	Patients who are hypersensitive to denosumab or to any of the excipients listed in Section 6.1 of the SmPC should not receive Denosumab.	No	It is a contraindication in the SmPC 4.3 (Contraindications). Hypersensitivity reactions are an important identified risk for Bmab1000. It is impossible to predict which patient may develop a hypersensitivity reaction to Bmab1000. Additional information regarding hypersensitivity reactions that occur during the treatment with Bmab1000 is provided in SmPC section 4.4 (Special warnings and Precautions for use).
BMD T-score < -4.0	Patients with T-score of <−4.0 at the lumbar spine, total hip, or femoral neck were excluded from the Bmab 1000 clinical studies.	No	The safety and efficacy of denosumab is not expected to differ in subjects with lower BMD T-scores.
Other bone diseases	Patients with other bone diseases such as RA, OI, and Paget's disease etc were excluded from the pivotal osteoporosis studies because other bone diseases could	No	Denosumab is not indicated for use in these other patient populations.

	confound the efficacy results.		
Previous bisphosphonate treatment	Subjects with previous bisphosphonate treatment were excluded from pivotal osteoporosis studies in accordance with regulatory guidance to demonstrate fracture benefit in a PMO population. Because bisphosphonates incorporate into bone and long-term use of bisphosphonates is associated with continued effects of the drug after treatment is stopped, it was deemed most appropriate to exclude previous bisphosphonate treatment.	No	Patient previously treated with bisphosphonate treatment before start of denosumab treatment was considered as risk factor for Osteonecrosis of the Jaw. Osteonecrosis of the Jaw was considered as Important identified risk for Bmab1000. Additional information regarding osteonecrosis of jaw that occur during the treatment with Bmab1000 is provided in SmPC section 4.4 (Special warnings and Precautions for use). Reference product Xgeva® study details are as follows**Error! Reference source not found.**: A study was conducted of denosumab in cynomolgus monkeys transitioned from bisphosphonate therapy and 2 clinical studies of bisphosphonate-transition in bone loss settings. Results from these studies did not demonstrate an increased risk of skeletal adverse effects over the period exposed in patients who received denosumab following bisphosphonate use. Therefore, no special dosing recommendations or limitation of use for patients previously treated with bisphosphonates are considered necessary in the SmPC
Subjects who are pregnant or breastfeeding, or planning to become pregnant	Adequate and well-controlled studies with denosumab have not been conducted in pregnant women due to the potential risk to the fetus. It is not known whether denosumab is transferred into human milk.	No	These populations are not included in the intended indications. Risk minimization via product labelling instructing patients to avoid pregnancy and breast feeding is in place SmPC section 4.6 (fertility, pregnancy and lactation)[3]. No additional pharmacovigilance activities or additional risk minimization are warranted.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Therefore, the clinical trials data and post marketing experience gained with the reference product is considered to relevantly complement the data gathered for Bmab1000. Consequently, publicly available information on the reference product is carefully reviewed for this RMP and safety concerns identified for the reference product, if any, are addressed in this document.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 3: Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	Exposure
Pregnant women	Women of childbearing potential had to be willing to use a reliable method of contraception throughout the study period in the Phase 1 (B1000-NHV-01-G-01) clinical study program for Bmab1000, and women who (inadvertently) became pregnant had to discontinue the study. A pregnancy was reported in the female partner of a male participant in Bmab 1000 group in B1000-NHV-01-G-01. The female partner underwent spontaneous abortion. The event was considered not related to the Bmab 1000. From the isolated occurrence of (unintended) pregnancy that was reported, there is no indication of a safety concern. There are no adequate data from the use of denosumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. Denosumab is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with Denosumab. Any effects of Denosumab 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.
Breastfeeding Women	There are no clinical trial data on use of denosumab in breast feeding women. Not included in the clinical development program. It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has

	been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL (during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum A decision on whether to abstain from breast-feeding or to abstain from therapy with Denosumab should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Denosumab therapy to the woman.
Paediatric population	There are no clinical trial data on use of Bmab1000 in children.
Elderly population	In the Phase 1 (B1000-NHV-01-G-01) study program for denosumab no elderly patients were exposed. Phase 3 (B1000-PMO-03-G-02) study: A total of 478 patients were randomized, out of which 154 elderly patients were exposed to Bmab1000 and 153 elderly patients were exposed to Prolia (reference product). There are no overall differences in safety or efficacy observed in the elderly population. Based on the reference product information Xgeva®[4]. No eligibility upper limit on age; 954 subjects (1518.8 subject years) 75 years were included in clinical studies.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Dedicated studies in people with renal or hepatic or cardiovascular impairment have not been carried out. And, clinical trials are not conducted in immunocompromised patients. Patients with a disease severity different from inclusion criteria in clinical trials were not included in the clinical development program. Based on the reference product information Xgeva®[4] Patients with hepatic impairment were not specifically excluded from the clinical development program (except for baseline alanine and aspartate aminotransaminases > 5 X upper limit of normal [ULN], total bilirubin > 2 X ULN) and no classification of liver functional status were collected Patients with severe renal impairment were excluded from most registration studies in cancer populations. Clinical studies included 1055 subjects (1551.4 subject years) with moderate renal impairment and 36 subjects (49.5 subject years) had severe renal impairment or end-stage renal disease at entry No specific exclusions regarding CV function and no classification of cardiac function status were collected

	No specific exclusions with exception of human immunodeficiency virus (HIV) positive and no classification of liver functional status were collected
Population with relevant different ethnic origin	The clinical development programme included mostly white patients in the both the studies. In phase 1 study (B1000-NHV-01-G-01), 64 black American (33 from Bmab1000 group, 31 from Prolia® group), 2 American Indian or Alaska native (both from Bmab1000 group), 42 Asian (18 from Bmab1000 group, 24 from Prolia® group) are exposed to denosumab. In the phase III study (B1000-PMO-03-G-02), only one patient was Asian (from Bmab1000 group), and the rest of the patients 478 exposed were white (237 from Bmab1000 group, 241 from Prolia® group). Although not systematically evaluated, no particular risk or safety concern specific to individuals of certain racial and/or ethnic origin were observed. There is also no indication for any safety concerns specific to patients of certain racial and/or ethnic origin from experience with the reference product Xgeva®.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

Part II: Module SV - Post-authorisation experience

Bmab 1000 has not yet been authorised in any country worldwide. This module is not applicable

SV.1 Post-authorisation exposure

Not applicable

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

Part II Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

The product is restricted by prescription only. This is not a substance abuse drug and no potential for misuse of Bmab 1000 (biosimilar to Denosumab) for illegal purposes is foreseen.

No evidence to suggest a potential for drug abuse or misuse with denosumab has been observed.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Bmab 1000 is a biosimilar product to Xgeva®(Amgen) Therefore, the safety profile of Bmab 1000 is based on the general safety profile of denosumab, which resulted from the extensive experience with Xegeva® (date of authorisation in EU: 13-July-2011) but also considering the development programme for Bmab 1000. Nonetheless, the development programme for Bmab 1000, did not raise new safety concerns; all clinically relevant adverse effects reported in the respective clinical studies corresponded to the known safety profile of denosumab (for full information on reported adverse events within the clinical development programme for Bmab 1000, refer to - Section 2.5 Clinical Overview

On 13-July-2011, product Xgeva®was authorised by the European Commission according to EMA product number- EMEA/H/C/002173. Accordingly, the safety concerns for Bmab 1000 are based on the list of safety concerns as presented in the European Public Assessment Report (EPAR) for Xgeva® (RMP version 36.0, date 11 Dec 2020)[4]

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone • Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable, as all risks from reference product RMP have been considered in this RMP.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

All safety concerns in the RMP for the biosimilar product Bmab 1000 are solely based on the safety concerns for the reference medicinal product Xgeva® containing Denosumab. Same are listed under SVII.1

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable as this is the initial RMP for Bmab 1000.

SVII.3 Details of important identified risks, important potential risks, and missing information

All the risks and missing information presented here in line with reference product Xgeva® (Xgeva-EPAR-Risk Management Plan Version 36.0, date 11 Dec 2020)[4].

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone • Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity.

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Osteonecrosis of the Jaw

Important Identified Risk: Osteonecrosis of the Jaw
MedDRA terms: PT- Osteonecrosis of jaw

Potential mechanisms:	Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodelling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact (Fassio et al, 2017[7]; Aghaloo et al, 2015[8]).
Evidence source(s) and strength of evidence:	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as important identified risk. the risk was identified in randomized, controlled, Phase 3 clinical trials of the reference product Xgeva®. The risk was further supported by postmarketing reports of reference product Xgeva®.
Characterisation of the risk:	<u>Frequency in BBL's clinical development programme:</u> Study B1000-NHV-01-G-01: no SAEs reporting osteonecrosis of the jaw were observed in Bmab 1000 Study B1000-PMO-03-G-02: no SAEs reporting osteonecrosis of the jaw were observed in Bmab 1000 clinical development program. <u>Frequency with reference product:</u> In the pooled pivotal SRE Solid Tumor studies, the subject incidence of positively adjudicated adverse events of ONJ was 1.8% in the denosumab group and 1.3% in the zoledronic acid group; the hazard ratio was 1.38 (95% CI: 0.91, 2.11). In the SRE multiple myeloma study, the subject incidence of positively adjudicated adverse events of ONJ was 4.1% in the denosumab group and 2.8% in the zoledronic acid group; the hazard ratio was 1.47 (95% CI: 0.88, 2.48). In clinical trials, the incidence of ONJ was higher with longer duration of exposure (XGEVA® SmPC, May 2018). In Study 20101363, a non-interventional post marketing observational study of 2877 patients with cancer treated with XGEVA® or zoledronic acid for SRE prevention, the incidence rates (95% CI) of medically confirmed ONJ per 100 person-years were 3.0 (2.3, 3.7) in the XGEVA® inception cohort, 1.0 (0.6, 1.5) in the zoledronic acid inception cohort, and 4.3 (2.8, 6.3) in the XGEVA®-switch cohort (this cohort included patients who switched to XGEVA® after having started antiresorptive therapy with bisphosphonates for SRE prevention of no more than 2 years' net duration). The SmPC of the reference product lists Osteonecrosis of the jaw as a common undesirable effect.. *Severity*: Most events leading to adjudication as ONJ were assessed as moderate to severe. Life-threatening events have been reported[3]. *Reversibility:* In general, ONJ events are clinically reversible. The majority of ONJ cases resolve with denosumab treatment interruption or discontinuation. Surgical treatment may be required; bone resection is not usually necessary.

	Long-term outcome: No long-term outcome is available. *Impact on quality of life:* Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (e.g., decreased hydration and decreased nutritional intake).
Risk factors and risk groups:	Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa and Woo, J Amer Dental Assoc, 2009; 140:864-875[9]; Estilo et al, J Clin Oncol, 2008; 26:4037-4038[10]; Mehrotra and Ruggiero, Hematol, 2006; 2006:356-360[11]; Ruggiero et al, J Oncol Pract, 2006; 2:7-14 [12]).
Preventability:	A dental examination with appropriate preventive dentistry is recommended prior to treatment with Denosumab, especially in patients with risk factors. While on treatment, patients should avoid invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while on Denosumab should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with Denosumab, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves. Good oral hygiene practices should be maintained during treatment with Denosumab, and dental health should be monitored.
Impact on the risk-benefit balance of the product:	The risk of ONJ events has been considered in the product benefit-risk assessment. In light of the product labeling and a patient reminder card that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact:	Significant public health impact is not expected based on the relative frequency observed in clinical trials and with the observations that most ONJ events appear to be moderate to severe in severity and resolve without requiring extensive surgical treatment

IV=intravenous; ONJ = osteonecrosis of the jaw; SRE = skeletal-related event; SmPC = Summary of Product Characteristics

Important Identified Risk: Atypical Femoral Fracture

Important Identified Risk: Atypical Femoral Fracture MedDRA terms: PT: atypical femur fracture	
Potential mechanisms:	Prolonged suppression of bone turnover may be associated with increased risk of atypical femoral fracture (AFF), but the pathogenesis remains unclear and causes of AFF are likely multifactorial. Based on nonclinical studies of

	bisphosphonates, collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF {Ismail et al, 2018;[13] Shane et al, 2010[14]).
Evidence source(s) and strength of evidence:	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as important identified risk. This risk was identified in randomized, controlled, phase 3 clinical trials and in open-label, phase 2 clinical trials of the reference product Xgeva®. This risk was further supported by post marketing reports of the reference product Xgeva®.
Characterisation of the risk:	*Frequency in BBL's clinical development programme:* Studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02: Cumulatively, no SAEs reporting atypical femoral fracture were observed in Bmab 1000 clinical development program. *Frequency with reference product:* In a comprehensive evaluation of denosumab 120 mg clinical trials, 15 subjects experienced 17 events meeting the American Society for Bone and Mineral Research criteria for AFF. This corresponds to 0.2% (15 of 8342) of all subjects who received at least 1 dose of denosumab (Similar results are observed when consideration is limited to studies utilizing monthly dosing throughout [0.1%, 6 subjects with AFF in 6101 subjects]). All of these adjudicated events of AFF occurred in subjects who received denosumab 120 mg for at least 4 years corresponding to 0.7% (15 of the 2228) of subjects who were followed for 4 or more years. In the clinical trial program, AFF has been reported uncommonly in patients treated with XGEVA® 120 mg and the risk increased with longer duration of treatment. Events occurred during treatment and up to 9 months after treatment was discontinued. Severity: Atypical femoral fracture is a medically important adverse event that generally requires significant medical interventions such as surgery and ongoing monitoring to mitigate risk for and severity of contralateral fractures. Reversibility: It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF is reversible after treatment is discontinued. Long-term outcome: No data on long-term outcomes are available Impact on quality of life: As with other hip fractures, AFF can cause short-term or long-term disability. Some data

	suggests that healing of AFF may be more prolonged than a typical femoral fracture (Bubbear et al, 2016; Unnanuntana et al, 2013[15]).
Risk factors and risk groups:	Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier et al, Arch Intern Med, 2012; 172:930-936[16]; Giusti et al, Bone, 2011; 48(5):966-971[17]). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, J Bone Miner Res, 2010; 25:2267-2294[Error! 14]).
Preventability:	No data is currently available on potential measures to prevent AFF. Patients using long-term antiresorptives may experience pain over the femur, which requires radiological examination if atypical fracture is suspected.
Impact on the risk-benefit balance of the product:	The risk of AFF events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact:	Based on the frequency of AFF, the size of the indicated populations, and usage patterns of denosumab in clinical practice, no significant additional public health impact is expected

AFF = atypical femoral fracture; RA = rheumatoid arthritis

Important Identified Risk: Hypercalcemia Several Months After the Last Dose in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons

Important Identified Risk: Hypercalcemia Several Months After the Last Dose in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons	
MedDRA terms: PT- Hypercalcemia	
Potential mechanisms:	The mechanism(s) of hypercalcemia several months after the last dose of denosumab in patients with GCTB and in patients with a growing skeletonare not well characterized, but may be a consequence of the following, alone, or in combination: Denosumab treatment and resultant RANK/RANKL pathway inhibition in adults with giant-cell containing lesions such as GCTB leads to histopathologic evidence of a dramatic decrease in osteoclast-like giant cells which is complemented by woven bone formation and calcification within the tumors and even at sites of distant metastases (Ghermandi et al, 2016[18]; Yamagishi et al, 2016[19]; Branstetter et al,

	2012[20]). It is possible this calcium could serve as a depot that is mobilized with reactivation of tumor-associated, RANKL driven giant cell mediated osteolysis following cessation of Denosumab. Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification such as in patients with a growing skeleton. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from the skeleton either near the growth plates (as can be the case with the young adult and adolescent patients) or from the giant cell tumors themselves that have partially ossified in the cases of the adult patients with tumor recurrence via an autocrine/paracrine mechanism (Cowan et al, 2011[21]). The magnitude of the resorptive response following treatment withdrawal in the patients with GCTB and in those with an immature skeleton could be dictated by the normal high rate of bone turnover within the GCTB lesion or in the growing skeleton of young patients. The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in young individuals or may be affected by intratumor signaling pathways (eg, parathyroid hormone-related protein) in GCTB.
Evidence source(s) and strength of evidence:	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as an important identified risk. This risk was identified in phase 2 clinical trials of adolescent and adult patients with GCTB, and in post marketing reports of pediatric patients using reference product (Xgeva®) for unauthorized indications.
Characterisation of the risk:	Frequency in BBL's clinical development programme: Study B1000-NHV-01-G-01: no SAEs reporting hypercalcemia were observed in Bmab 1000 Study B1000-PMO-03-G-02: no SAEs reporting hypercalcemia were observed in Bmab 1000 clinical development program. *Frequency with reference product:* Based on the 4 relevant clinical trial case reports (2 adults and 2 adolescents) identified from the completed Amgen clinical study 20062004 of subjects with GCTB (526 subjects having received at least 1 dose of XGEVA®), the frequency of hypercalcemia in patients with GCTB following discontinuation of XGEVA® is 0.8 events per 100 subjects which corresponds to an uncommon frequency (0.1 and < 1 event per 100 subjects). In addition, clinically significant cases of post-treatment have

	been identified from literature case reports of denosumab use in pediatric patients for unapproved indications such as fibrous dysplasia, aneurysmal bone cysts, and juvenile Paget's disease. *Severity*: In the GCTB study, the events of hypercalcemia in the 4 subjects from Study 20062004 were considered grade 2, 3, or 4 in severity. All subjects had acute renal injury, and all were hospitalized. Three of 4 subjects had more than 1 event. The severity of the events in the post marketing literature case reports appears qualitatively similar. *Reversibility:* Hypercalcemia is reversible with appropriate supportive therapy. *Long-term outcome*: No data on long-term outcomes are available *Impact on quality of life:* Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury
Risk factors and risk groups:	Patients with GCTB and young patients with growing skeletons following discontinuation of Denosumab. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola et al, BMJ, 2015;350:h2723[22]). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements (Machado et al, J Clin Med, 2015; 4:414-424[23]; Minisola et al, BMJ, 2015;350:h2723[22]).
Preventability:	No preventive measures are known. Monitor patients for signs and symptoms of hypercalcemia and treat appropriately. Periodic serum calcium assessments should be given to at-risk patients as clinically indicated. The need for calcium and vitamin D supplementation should be reassessed if denosumab is discontinued.
Impact on the risk-benefit balance of the product:	The risk of hypercalcemia events several months after the last dose in patients with GCTB and in patients with growing skeletons has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive
Public health impact:	No significant public health impact is expected as hypercalcemia several months after the last dose in patients with GCTB occurs uncommonly and GCTB is a rare tumor. Off-label use of denosumab in pediatric patients appears to be limited to rare conditions for which there is significant unmet medical need.

GCTB = giant cell tumor of bone; RANK = receptor activator of nuclear factor kappa-B; RANKL = RANK ligand

Important Potential Risk: Cardiovascular Events

Important Potential Risk: Cardiovascular Events MedDRA terms: SOC: Cardiac disorders	
Potential mechanisms:	Elevated levels of osteoprotegerin (OPG) have been associated with coronary artery disease in cross-sectional studies, but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists.
Evidence source(s) and strength of evidence:	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as an important potential risk. The risk of CV events is a regulatory concern based on the epidemiological association between OPG levels and CV disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable CV outcomes.
Characterisation of the risk:	Frequency in BBL's clinical development programme: In study B1000-PMO-03-G-02, a total of two serious adverse events (SAEs) involving cardiovascular events were reported. No SAEs were reported in Bmab1000 group. The two SAEs reported were in Prolia® group (acute myocardial infarction (n=1) and myocardial infarction (n=1)). All the events were assessed as not related/unrelated to Prolia® by the Investigator and Sponsor *Frequency with reference product:* In the pooled pivotal SRE Solid Tumor studies, the subject incidence of CV adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% CI: 0.89, 1.08). In a pivotal study with denosumab 120 mg Q4W in subjects with CRPC (Study 20050147), the subject incidence of CV adverse events was 33.1% in the denosumab group and 27.0% in the placebo group; the hazard ratio was 1.23 (95% CI: 1.02, 1.49). In the SRE multiple myeloma study, the subject incidence of adverse events of cardiac disorders was 11.6% in the denosumab group and 13.5% in the zoledronic acid group; the hazard ratio was 0.85 (95% CI: 0.65, 1.12). The subject incidence of adverse events of vascular disorder was 20.9% in the denosumab group and 19.8% in the zoledronic acid group; the hazard ratio was 1.07 (95% CI: 0.86, 1.31). *Severity*: The majority of CV events were mild to moderate. Life-threatening and fatal events have been reported *Reversibility:* No data on reversibility are available

	Long-term outcome: No data on long-term outcomes are available *Impact on quality of life:* Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalized for treatment and disability may occur.
Risk factors and risk groups:	The denosumab development program comprises studies of older subject populations (e.g, osteoporosis, cancer) that are likely to have a higher incidence of pre-existing CV conditions and, thus, a higher incidence of CV toxicities than that of the general population (Schulz[24] et al, J Clin Endrocrinol Metab, 2004, 89:4246-4253; Hak[25] et al Arterioscler Thromb Vasu Biol, 2000;20:1926-1931). Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors (Murphy[26] and Dargie, Drug Safety, 2007; 30(9):783-804; Smith[27] et al, Circulation, 2004; 109(21):2613-2616).).
Preventability:	Based on clinical data to date, denosumab has not been associated with an increased incidence or severity of CV adverse effects; therefore, no preventive measures are defined. Patients with potential CV events should be managed according to usual standards of care
Impact on the risk-benefit balance of the product:	The risk of CV events has been considered in the product benefit-risk assessment, and the overall benefit-risk balance is considered to be positive
Public health impact:	Significant public health impact on CV disease severity or incidence is not expected based on the information from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis (PMO)/hormone ablation therapy (HALT} settings.

COX-2 = cyclooxygenase-2; CV = cardiovascular; CRPC = castrate-resistant prostate cancer; HALT = hormone ablation therapy; OPG = osteoprotegerin; PMO = postmenopausal osteoporosis; Q4W = every 4 weeks; RANKL = RANK ligand; SRE = skeletal-related event

Important Potential Risk: Malignancy

Important Potential Risk: Malignancy MedDRA terms: SMQ (narrow): Malignancies	
Potential mechanisms:	The risk of malignancy is a theoretical concern that RANKL inhibition may lead to an increased risk for a new primary malignancy (NPM) by impairing immune surveillance mechanisms.
Evidence source(s) and strength of evidence:	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as important potential risk. Imbalance is observed in the NPM events between the zoledronic acid and XGEVA® treatment groups in the pivotal clinical studies. The results of Study 20170728, a post marketing retrospective cohort study, showed NPM

	incidence rates for XGEVA® were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with XGEVA®.
Characterisation of the risk:	Frequency in BBL's clinical development programme: In the B1000-PMO-03-G-02, a total of five serious adverse events (SAEs) involving malignancy were reported. Of which, four malignancy events were reported in the Bmab1000 group (breast cancer (n=1), colon cancer (n=1), pancreatic carcinoma (n=2)). The remaining one SAE was reported in the Prolia® group (clear cell renal cell carcinoma (n=1)). All the events were assessed as not related/unrelated to Bmab1000/Prolia® by the Investigator and Sponsor. Although the number of malignancy events appear nominally higher in Bmab1000 group upon further evaluation it can be concluded that the majority of the events could be attributed to age related factors and had underlying medical history.No SAEs were reported with malignancy in study B1000-NHV-01-G-01 *Frequency with reference product:* In the primary, double-blind treatment phases of 4 phase 3 active-controlled clinical trials in patients with advanced malignancies involving bone, NPM was reported in 54/3691 (1.5%) of patients treated with XGEVA® (median exposure of 13.8 months; range: 1.0 to 51.7) and 33/3688 (0.9%) of patients treated with zoledronic acid (median exposure of 12.9 months; range: 1.0 to 50.8). The cumulative incidence at 1 year was 1.1% for denosumab and 0.6% for zoledronic acid, respectively. In the SRE multiple myeloma study, the subject incidence of adverse events of NPM was 2.6% in the denosumab group and 1.4% in the zoledronic acid group; the hazard ratio was 1.81 (95% CI: 0.90, 3.66). Subjects who had new malignancies in this study generally had underlying risk factors for malignancy and no pattern was apparent in the types of new primary malignancies. In clinical Study 20062004 in GCTB, based on medical review and a data cut-off date of the final analysis of 15 August 2018, a total of 20 subjects (3.8%; N = 526) developed new malignancy in GCTB. Of these 20 subjects, 9 subjects developed new malignancies that were unrelated to GCTB: 2 events (0.4%) of ductal breast carcinoma and single events of each, adenocarcinoma of colon, breast cancer stage I, neoplasm, oesophageal adenocarcinoma, osteosarcoma, papillary thyroid cancer, renal cancer, rhabdomyosarcoma, and thyroid cancer. A total of 11 subjects (2.1%) developed new malignancy in GCTB: 5 subjects were deemed to have had primary malignant GCTB, 5 subjects were assessed to have had sarcomatous transformation, and 1 subject had secondary malignant GCTB (post-radiation). In Study 20170728, a retrospective observational cohort study of 9710 patients with bone metastases from breast, prostate, or lung cancer treated with XGEVA® or IV zoledronic acid, the overall rate of NPM for the breast cancer cohort was 11.5 per 1000 person-years of follow-up (PY) in the XGEVA® group and 16.2 per 1000 PY in the zoledronic acid group; for the prostate

	cancer cohort was 19.6 per 1000 PY in the XGEVA® group and 20.1 per 1000 PY in the zoledronic acid group; and for the lung cancer cohort was 9.5 per 1000 PY in the XGEVA® group and 11.5 per 1000 PY in the zoledronic acid group. The 3-year cumulative incidence of NPM for the breast cancer cohort was 0.022 (95% CI: 0.014, 0.035) in the XGEVA® group and 0.032 (95% CI: 0.023, 0.045) in the zoledronic acid group; for the prostate cancer cohort was 0.034 (95% CI: 0.026, 0.044) in the XGEVA® group and 0.036 (95% CI: 0.026, 0.049) in the zoledronic acid group; and for the lung cancer cohort was 0.007 (95% CI: 0.004, 0.012) in the XGEVA® group and 0.008 (95% CI: 0.005, 0.014) in the zoledronic acid group. *Severity*: not applicable *Reversibility:* No data on reversibility are available *Long-term outcome*: No data on long-term outcomes are available *Impact on quality of life:* Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy
Risk factors and risk groups:	General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
Preventability:	Second malignant neoplasms have become increasingly recognized and current recommendations include vigilance for these cancers in adult cancer survivors
Impact on the risk-benefit balance of the product:	The risk of malignancy events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk considered to be positive.
Public health impact:	Significant public health impact is not expected based on the information from studies in the PMO/HALT and advanced cancer settings.

GCTB = giant cell tumor of bone; HALT = hormone ablation therapy; IV = intravenous; NPM = new primary malignancy; PMO = postmenopausal osteoporosis; PY = person-years of follow-up; RANKL = RANK ligand; SRE = skeletal-related event.

Important Potential Risk: Delay in Diagnosis of Primary Malignancy in Giant Cell Tumor of Bone

Important Potential Risk: Delay in Diagnosis of Primary Malignancy in Giant Cell Tumor of Bone MedDRA terms: SMQ-Malignancies (Narrow)	
Potential mechanisms:	Due to well described sampling error at the time of GCTB diagnosis, primary malignancy in giant cell tumor of bone (PMGCTB) may be missed and benign GCTB may be presumed. Based on the mechanism of action and pathology of GCTB, denosumab is only expected to treat benign GCTB. However, there was a theoretical concern that treatment of

<table>
<tr><td></td><td>an undiagnosed PMGCTB with denosumab could delay the diagnosis of PMGCTB</td></tr>
<tr><td>Evidence source(s) and strength of evidence:</td><td>In line with the RMP of the reference product Xgeva®, this safety concern has been classified as an important potential risk. The risk of delay in diagnosis of PMGCTB is a regulatory concern based on the difficulties in diagnosing PMGCTB in Study 20062004 (reference product study).</td></tr>
<tr><td>Characterisation of the risk:</td><td>Frequency in BBL's clinical development programme:
No cases of delay in Delay in Diagnosis of Primary Malignancy in Giant Cell Tumor of Bone have been reported in studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02.
Frequency with reference product:
In clinical studies in GCTB, based on medical review, 11 subjects (2.1%; N = 523) had GCTB bone malignancies. Of these, 5 subjects (1.0%) had PMGCTB.
<table>
<tr><td></td><td>Time to PMGCTB</td></tr>
<tr><td>Number of cases</td><td>5</td></tr>
<tr><td>Mean time (Q1, Q3) to malignancy (Months)</td><td>19.12 (11.99, 24.18)</td></tr>
<tr><td>Median (min, max) denosumab exposure (months)</td><td>8.44 (2.8, 14.8)</td></tr>
</table>
Time from diagnosis of GCTB to diagnosis of malignancy of GCTB Source: Table GCTB Table 200-6.21.06
Severity: Not applicable
Reversibility: Not applicable
Long-term outcome: No data on long-term outcomes are available
Impact on quality of life: Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy</td></tr>
<tr><td>Risk factors and risk groups:</td><td>Patients with GCTB are known to be at risk for PMGCTB.</td></tr>
<tr><td>Preventability:</td><td>No preventive measures are known.</td></tr>
<tr><td>Impact on the risk-benefit balance of the product:</td><td>The risk of delay in diagnosis of PMGCTB events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.</td></tr>
<tr><td>Public health impact:</td><td>Given that GCTB is a very rare condition, no impact on public health is expected.</td></tr>
</table>

GCTB = giant cell tumor of bone; PMGCTB = primary malignant giant cell tumor of bone

Important Potential Risk: Hypercalcemia Several Months After the Last Dose in Patients Other Than Those with Giant Cell Tumor of Bone or Growing Skeletons

Important Potential Risk: Hypercalcemia Several Months After the Last Dose in Patients Other Than Those with Giant Cell Tumor of Bone or Growing Skeletons MedDRA terms: Hypercalcemia	
Potential mechanisms:	The pathogenesis of hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in bone turnover activity. Upon cessation of denosumab, the disinhibition of RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (ie, subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodeling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcemia in susceptible individuals if the normal homeostatic mechanism regulating serum calcium is not appropriately maintained.
Evidence source(s) and strength of evidence:	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as an important potential risk. Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and pediatric populations.
Characterisation of the risk:	*Frequency in BBL's clinical development programme*: No cases of delayed hypercalcemia have been reported in studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02. *Frequency with reference product:* Cases of hypercalcemia in the off-treatment period have been reported in clinical studies, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcemia in patients other than those with GCTB or with growing skeletons cannot be attributed to discontinuation of XGEVA® based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups Severity: Not applicable *Reversibility:* No data on reversibility are available. *Long-term outcome*: No data on long-term outcomes are available *Impact on quality of life:* Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury
Risk factors and risk groups:	Patients other than those with GCTB or growing skeletons following cessation of Denosumab
Preventability:	No preventive measures are known

Impact on the risk-benefit balance of the product:	The risk of hypercalcemia events following treatment discontinuation in patients other than those with GCTB or growing skeletons has been incorporated in the product benefit-risk assessment, and the overall benefit-risk balance remains positive.
Public health impact:	No significant public health impact is expected as the potential events remain infrequent despite extensive market exposure.

GCTB = giant cell tumor of bone; RANKL = RANK ligand

SVII.3.2. Presentation of the Missing Information

Missing Information: Use in Patients with Prior Intravenous Bisphosphonate Treatment

Evidence source	According to reference product RMP the incidence of ONJ in patients with prior IV bisphosphonate use was similar to that of patients who only received XGEVA® in the completed Study 20101363. No notable association was evident between ONJ and prior use of bisphosphonates.
Population in need of further characterization	There is information from studies in patients with cancer showing that there is no increased risk of serious complications caused by bone metastases in patients who received Denosumab following treatment with bisphosphonates. However, more information is needed.

Missing Information: Safety With Long-term Treatment and With Long-term Follow-up After Treatment in Adults and Skeletally Mature Adolescents With GCTB

Evidence source	The overall safety profile of XGEVA® in the completed Study 20062004 was similar to the safety profile of XGEVA® observed in the treatment of subjects with advanced cancer and bone metastases.
Population in need of further characterization	Information on safety with long-term treatment and with long-term follow-up in adults or adolescents with GCTB will be monitored by routine pharmacovigilance activities.

Missing Information: Off-label Use in Patients with GCTB That is Resectable Where Resection is Unlikely to Result in Severe Morbidity

Evidence source	No formal studies have been completed to determine XGEVA®'s effect on off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.
Population in need of further characterization	Information is not available on safety in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Part II: Module SVIII - Summary of the safety concerns

The identified and potential risks historically known with Denosumab are discussed below in the light of experience gained with the reference product (Xgeva®).

Table 4: *Summary of safety concerns*

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone • Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in below Table.

Specific Adverse Reaction Follow-up Questionnaires		
Follow-up questionnaire	**Safety Concern**	**Purpose/Description**
Potential Osteonecrosis of the Jaw	Osteonecrosis of the Jaw	To monitor the reporting rate and nature of ONJ in patients treated with Bmab1000 in the post marketing environment.
Potential atypical fracture	Atypical femoral fracture	To monitor the reporting rate and nature of AFF in patients treated with Bmab1000 in the post marketing environment.

III.2 Additional pharmacovigilance activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable, as routine pharmacovigilance only is proposed and there are no studies or other additional activities from the pharmacovigilance plan, whether ongoing, planned or completed.

Part IV: Plans For Post-Authorisation Efficacy Studies

Part IV.1: Planned and ongoing post authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Not applicable.

Part V: Risk Minimisation Measures

V.1. Routine Risk Minimisation Measures

Table 5: Description of routine risk minimization measures by safety concern.

Safety concern	Routine risk minimization activities
Important identified Risks	
Osteonecrosis of the jaw	**Routine risk communication:** •SmPC Section 4.3 •SmPC Section 4.4 •SmPC Section 4.8 •SmPC Section 5.1 •PIL Section 2 •PIL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with • unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC. **Other risk minimization measures beyond the PI:** • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.
Atypical femoral fracture	**Routine risk communication**: •SmPC Section 4.4 •SmPC Section 4.8 •PIL Section 2 •PIL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC. **Other risk minimization measures beyond the PI:** • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.
Hypercalcemia several months after the last dose in patients with giant cell tumor of	**Routine risk communication**: •SmPC Section 4.4 •SmPC Section 4.8 •PIL Section 2 •PIL Section 4 **Routine risk minimization activities recommending**

bone and in patients with growing skeletons	**specific clinical measures to address the risk**: •Recommendations for monitoring the patients for signs and symptoms of hypercalcaemia after discontinuation of Bmab1000 treatment is included in Section 4.4 of SmPC and Section 4 of the PIL. **Other risk minimization measures beyond the PI**: • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.
Important Potential Risks	
Cardiovascular events	**Routine risk communication**: • Not applicable **Other risk minimization measures beyond the PI:** • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.
Malignancy	**Routine risk communication:** •SmPC Section 4.4 •SmPC Section 4.8 •SmPC Section 5.1 •PIL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: •Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in Section 4.4 of SmPC. **Other risk minimization measures beyond the PI:** • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.
Delay in diagnosis of primary malignancy in giant cell tumor of bone	**Routine risk communication**: •Not applicable **Other risk minimization measures beyond the PI**: • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.
Hypercalemia several months after the last dose in patients other than those with GCTB or growing skeletons	**Routine risk communication**: • Not applicable **Other risk minimization measures beyond the PI:** • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.
Missing information	
Patients with previous	**Routine risk communication**: •SmPC Section 4.5

intravenous treatment with bisphosphonate treatment	•SmPC Section 5.1 •PIL Section 2 **Other risk minimization measures beyond the Pl**: • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents **with GCTB**	**Routine risk communication:** • Not applicable **Other risk minimization measures beyond the Pl:** • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity	**Routine risk communication**: • Not applicable **Other risk minimization measures beyond the Pl:** • Legal status: Bmab1000 is a medicinal product subject to restricted medical prescription.

GCTB = giant cell tumor of bone; ONJ = osteonecrosis of the jaw; Pl= Product Information; PIL = Patient Information Leaflet; SmPC = Summary of Product Characteristics

V.2. Additional Risk Minimisation Measures

In line with the reference product, this medicine has additional risk minimisation measure of "Patient Reminder Card" for the important identified risk of Osteonecrosis of the jaw.

Table 6: Additional Risk Minimization Measure: Patient Reminder Card

Objectives	Patient reminder cards will be provided to address the following risk: • Osteonecrosis of the jaw
Rationale for the additional risk minimization activity	The purpose of the patient reminder card is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (Bmab1000) injections for osteoporosis and bone loss, including: • To tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment; • To maintain good oral hygiene and receive routine dental check-ups during treatment; • To inform their doctor and tell their dentist that they are being treated with denosumab (Bmab1000) if they are under dental treatment or will undergo dental surgery; and • To contact their doctor and dentist immediately if they

	experience any problems with their mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge
Target audience and planned distribution path	Target audience will be the patients. The patient reminder card will be distributed to prescribers with instruction to provide it to patients.
Plans to evaluate the effectiveness of the interventions and criteria for success	The company will monitor effectiveness of risk minimisation measures by routine pharmacovigilance activities during PSUR preparation (as per the EURD list), signal detection activity and medical review, as per internal procedures. The incidence of adverse reactions will be compared with those described in the SmPC. If there is an increased incidence of adverse reactions or if the reports are different in seriousness, severity or outcome to that described in the SmPC, labelling changes or risk minimisation will be considered. Additionally, effectiveness of additional RMMs will be evaluated on annual basis after MA approval. The distribution of the patient reminder card will be tracked to ensure that it is distributed in accordance with the plan agreed with national agencies.

EU = European Union; ONJ = osteonecrosis of the jaw; PSUR = Periodic Safety Update Report

V.3 Summary of risk minimisation measures and Pharmacovigilance Activities

Table 7: Summary table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety concern	Routine risk minimisation measures	Pharmacovigilance Activities
Important identified risk		
Osteonecrosis of the jaw	**Routine risk minimization measures:** • SmPC Section 4.3 • SmPC Section 4.4, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and temporary interruption are discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 2, where recommendations for oral examination, maintenance of	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Denosumab core questionnaire - Osteonecrosis of the Jaw • . **Additional pharmacovigilance activities**: None

	good oral hygiene, management of patients with unavoidable invasive dental procedure, and sign of ONJ are discussed. • PIL Section 4, where symptoms of ONJ is discussed. **Additional risk minimization measures:** • Patient reminder cards	
Atypical femoral fracture	**Routine risk minimization measures:** • SmPC Section 4.4, where recommendations for reporting new or unusual thigh, hip or groin pain is discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for reporting new or unsual pain in you thigh hip or groin is discussed. • PIL Section 4, where signs of thigh bone fracture is discussed. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Denosumab core questionnaire -postmarketing reports of potential atypical fracture. **Additional pharmacovigilance activities:** None
Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	**Routine risk minimization measures:** • SmPC Section 4.4, where recommendations for monitoring the patients for signs and symptoms of hypercalcemia after discontinuation of Denosumab are discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for monitoring the patients for signs and symptoms of hypercalcemia after discontinuation of Denosumab treatment is discussed. . • PIL Section 4 **Additional risk minimization measures**:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	• None	
Important potential risks		
Cardiovascular events	No risk minimization measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Malignancy	**Routine risk minimization measures:** • SmPC Section 4.4, where recommendations for monitoring the patients for radiological signs of malignancy, new malignancy or osteolysis is discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 4 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None
Delay in diagnosis of primary malignancy in giant cell tumor of bone	No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None
Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons	No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None
Missing information		
Patients with prior intravenous bisphosphonate treatment	**Routine risk minimization measures:** • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None.

	Additional risk minimization measures: • None	**Additional pharmacovigilance activities:** None
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None
Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None

MOMS = American Association of Oral Maxillofacial Surgeons; AFF = atypical femoral fracture;

GCTB = giant cell tumor of bone; ONJ = osteonecrosis of the jaw; PIL = patient information leaflet; SmPC = summary of product characteristics

Part VI: Summary of the risk management plan

Summary of risk management plan for Bmab1000 (Denosumab).

This is a summary of the risk management plan (RMP) for Bmab1000. The RMP details important risks of Bmab1000, how these risks can be minimized, and how more information will be obtained about Bmab1000's risks and uncertainties (missing information).

Bmab1000's summary of product characteristics (SmPC) and package leaflet give essential information to healthcare professionals and patients on how Bmab1000 should be used.

Important new concerns or changes to the current ones will be included in updates of Bmab1000's RMP.

I. The medicine and what it is used for

Bmab1000 is authorized for prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone and for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (see SmPC for the full indication). It contains denosumab as an active substance and it is given by subcutaneous administration.

Further information about the evaluation of Bmab1000's benefits can be found in Bmab1000's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Bmab1000, together with measures to minimize such risks and the proposed studies for learning more aboutBmab1000's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals,
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Bmab1000, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Bmab1000 is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Bmab1000 are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Bmab1000. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 8: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture • Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons
Important potential risks	• Cardiovascular events • Malignancy • Delay in diagnosis of primary malignancy in giant cell tumor of bone • Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone • Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

Table 9: Important Identified Risk: Osteonecrosis of the Jaw

Important Identified Risk: Osteonecrosis of the Jaw	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as important identified risk. the risk was identified in randomized, controlled, Phase 3 clinical trials of the reference product Xgeva®. The risk was further supported by postmarketing reports of reference product Xgeva®.
Risk factors and risk groups	Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates

	delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa and Woo, J Amer Dental Assoc, 2009[9]; 140:864-875; Estilo et al, J Clin Oncol, 2008[10]; 26:4037-4038;Mehrotra and Ruggiero, Hematol, 2006[11]; 2006:356-360; Ruggiero et al, J Oncol Pract, 2006; 2:7-14[12]).
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • Patient Information Leaflet (PIL) Section 2 • PIL Section 4 Additional risk minimization measures: • Patient reminder cards
Additional Pharmacovigilance activities	None

Table 10: Important Identified Risk: Atypical Femoral Fracture

Important Identified Risk: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as important identified risk. this risk was identified in randomized, controlled, phase 3 clinical trials and in open-label, phase 2 clinical trials of the reference product Xgeva®. This risk was further supported by post marketing reports of the reference product.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier et al, Arch Intern Med, 2012; 172:930-936[16]; Giusti et al, Bone, 2011; 48(5):966-971[17]). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, J Bone Miner Res, 2010; 25:2267-2294[14]).

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 11: Important identified Risk: Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons

Important Identified Risks: Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as important identified risk. This risk was identified in phase 2 clinical trials of adolescent and adult patients with GCTB, and in postmarketing reports of pediatric patients using reference product (Xgeva®) for unauthorized indications.
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of Denosumab. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older (Minisola et al, BMJ, 2015;350:h2723[22]). Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements (Machado et al, J Clin Med, 2015; 4:414-424[23]; Minisola et al, BMJ, 2015;350:h2723[22]).
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 12: Important potential risks: Cardiovascular events

Important potential risks: Cardiovascular events

Evidence for linking the risk to the medicine	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as important potential risk. The risk of CV events is a regulatory concern based on the epidemiological association between OPG levels and CV disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable CV outcomes.
Risk factors and risk groups	The denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing CV conditions and, thus, a higher incidence of CV toxicities than that of the general population (Schulz[24] et al, J Clin Endrocrinol Metab, 2004, 89:4246-4253; Hak[25] et al Arterioscler Thromb Vasu Biol, 2000;20:1926-1931). Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors (Murphy[26] and Dargie, Drug Safety, 2007; 30(9):783-804; Smith[27] et al, Circulation, 2004; 109(21):2613-2616).
Risk minimisation measures	Routine risk minimization measures: • None Additional risk minimisation measures: None.
Additional Pharmacovigilance activities	None

Table 13: Important potential risks: Malignancy

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as important potential risk. Imbalance is observed in the NPM events between the zoledronic acid and XGEVA® treatment groups in the pivotal clinical studies. The results of Study 20170728, a post marketing retrospective cohort study, showed NPM incidence rates for XGEVA® were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with XGEVA®.
Risk factors and risk groups	General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8

	• SmPC Section 5.1 • PIL Section 4 Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 14: Important potential risks: Delay in diagnosis of primary malignancy in giant cell tumor of bone

Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumor of bone	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as important potential risk. The risk of delay in diagnosis of PMGCTB is a regulatory concern based on the difficulties in diagnosing PMGCTB in Study 20062004 (reference product study).
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 15: Important potential risks: Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons

Important potential risk: Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Xgeva®, this safety concern has been classified as an important potential risk. Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and pediatric populations.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of Denosumab
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 16: Missing Information: Patients With Previous Intravenous Treatment With Bisphosphonate Treatment

Missing Information: Patients With Previous Intravenous Treatment With Bisphosphonate Treatment	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 17: Missing Information: Safety with long term treatment and with long term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone

Missing Information: Safety with long term treatment and with long term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 18: Missing Information: Off label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

Missing Information: Off label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies, which are conditions of the marketing authorization or specific obligation of Bmab1000.

II.C.2 Other studies in post-authorisation development plan

Not applicable

Part VII: Annexes

List of Annexes

Annex 4 - Specific adverse event follow-up forms

Annex 6 - Details of proposed additional risk minimisation measures (if applicable)

Annex 4 - Specific adverse event follow-up forms

Table of Contents

Questionnaire for Potential Osteonecrosis of the Jaw

Questionnaire for Potential Atypical Fracture

Note: The above questionnaires are utilized in conjunction with standard case follow-up procedures to obtain complete case information.

TARGETED FOLLOW UP FORM-OSTEONECROSIS OF THE JAW
BBL Case No.:

1. Patients/case administrative information (please include date as DD/MM/YYY)Details:

Patient identifier	
Patient's Initials	
Date of event onset	
Date of this report	
Event reported term	
Age at the time of event	
Gender	☐ Male ☐ Female
Weight (lb/kg)	
Height	
Study Number (if applicable)	☐ Clinical trial ☐ Post-marketing
Study Database No	

2. Denosumab Administrative/information (please indicate date as DD/MM/YYY):

Denosumab Indication	☐ Postmenopausal osteoporosis ☐ Bone loss from hormone ablation therapy Please specify diagnosis _____ ☐ Advanced cancer with bone metastasis Please specify cancer: _____ ☐Other (please specify)_____ ☐Don't Know _____

TARGETED FOLLOW UP FORM-OSTEONECROSIS OF THE JAW
BBL Case No.:

Denosumab Dose	☐60 mg SC every 6 months ☐ 120 mg SC every 4 weeks ☐Other (please specify)_____ ☐ Don't know
Denosumab Exposure	Denosumab first administered (date)_____ Last denosumab dose before event(date)_____ ☐Doses of denosumab were skipped ☐ Yes☐ No ☐ Unknown If yes, please specify _____ ☐Doses of denosumab given after event began ☐ Yes☐ No ☐ Unknown If yes, date of first dose following start of event_____ _____

3. EVIDENCE OF EXPOSED BONE (please indicate date as DD/MM/YYY)

Visible evidence of exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region

☐ Yes☐ No ☐ Unknown; please describe _____
_____

Date exposed bone was first visualized/probed:_____

Exposed bone or probed that has persisted for more than eight weeks:

☐ Yes☐ No ☐ Unknown_____

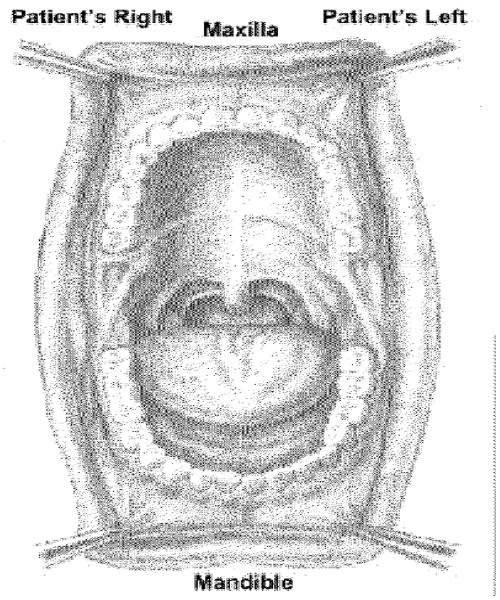
Prior history of radiation therapy to jaw:

☐ Yes☐ No ☐ Unknown_____

Prior history of metastatic disease of jaw:

☐ Yes☐ No ☐ Unknown; please describe _____
_____

TARGETED FOLLOW UP FORM-OSTEONECROSIS OF THE JAW
BBL Case No.:

Please indicate the location of involved area(s) on the diagram at right (mark site(s) clearly with 'X').  	Please describe location(s): ☐ Right maxilla, teeth and lateral jaw ☐ Left maxilla, teeth and lateral jaw ☐ Right maxilla, medial jaw ☐ Left maxilla, medial jaw ☐ Right mandible teeth and lateral jaw ☐ Left Mandible teeth and lateral jaw ☐ Right mandible, medial jaw ☐ Left Mandible, medial jaw ☐ Maxilla hard palate ☐Other (please specify)_____ _____

Oral Findings:

Evidence of infection ☐ Yes☐ No ☐ Unknown; please describe _____
_____

Exposed bone at the site of extraction ☐ Yes☐ No ☐ Unknown

Complete coverage of involved area(s) by mucosa: ☐ Yes☐ No ☐ Unknown

If yes, date of complete mucosal coverage_____

Clinical Symptoms (Please indicate dates a (DD/MM/YYYY)

Date of first clinical signs/symptoms in the mouth (e.g. infection, pain, inflammation):_____
_____

Please describe _____
_____

TARGETED FOLLOW UP FORM-OSTEONECROSIS OF THE JAW
BBL Case No.:

Consultations (Please indicate all dates as DD/MM/YYYY)

Dental/oral surgery/ stomatology consultations ☐ Yes☐ No ☐ Unknown

If yes please give date of examination _____

Please provide any consult reports, radiographs, pictures if Available _____

4. TREATMENT INFORMATION (Please indicate what treatments were administered and indicate dates as DD/MM/YYYY)

Antibiotics ☐ Yes☐ No ☐ Unknown If yes, agent (s)/route/dose_____

Start date_____Stop date: _____

Please describe outcome of treatment_____

Oral rinses ☐ Yes☐ No ☐ Unknown If yes, agent(s)/dose_____

Please describe outcomes of treatment_____

Oral surgery ☐ Yes☐ No ☐ Unknown If yes, type of surgery_____

Start date_____Stop date: _____

Please describe outcome of treatment_____

Hospitalizations ☐ Yes☐ No ☐ Unknown If yes, reason for hospitalization_____

Hospitalization begin date_____Hospitalization end date: _____

Please describe outcomes of treatment_____

5. DENTAL HISTORY (please indicate all date as DD/MM/YYYY)

History of poor oral hygiene☐ Yes☐ No ☐ Unknown _____

TARGETED FOLLOW UP FORM-OSTEONECROSIS OF THE JAW
BBL Case No.:

Dental extraction recently ☐ Yes☐ No ☐ Unknown If yes, date of procedure_____

Dental surgery recently ☐ Yes☐ No ☐ Unknown If yes, date of procedure_____

Periodontal disease including gingival bleeding, calculus, etc. ☐ Yes☐ No ☐ Unknown

Start date_____Stop date: _____

Draining fistula in affected area ☐ Yes☐ No ☐ Unknown

Start date_____Stop date: _____

Dental abscess in affected area ☐ Yes☐ No ☐ Unknown

Start date_____Stop date: _____

Osteomyelitis if affected area ☐ Yes☐ No ☐ Unknown

Start date_____Stop date: _____

Root Canal treatment near affected area ☐ Yes☐ No ☐ Unknown

If yes, date of treatment_____

Dental treatment, surgery or tooth extraction to the involved area within the last 4-6 months PRIOR to the onset of the oral lesion ☐ Yes☐ No ☐ Unknown

History of dentures /dental appliance /implant ☐ Yes☐ No ☐ Unknown

if yes please specify ☐ Upper☐ Lower

Area of lesion at or near a contact point ☐ Yes☐ No ☐ Unknown

6. MEDICATIONS (please indicate all date as DD/MM/YYYY)

PO bisphosphonate ☐ Yes☐ No ☐ Unknown

If yes, agent(s)/dose _____

Start date_____Stop date: _____

IV bisphosphonate ☐ Yes☐ No ☐ Unknown

If yes, agent(s)/dose _____

Start date_____Stop date: _____

Glucocorticoid use within the past 12 months ☐ Yes☐ No ☐ Unknown

If yes, agent(s)/dose _____

Start date_____Stop date: _____

Immunosuppressant use within the past 12 months ☐ Yes☐ No ☐ Unknown

If yes, agent(s)/dose _____

Start date_____Stop date: _____

Chemotherapy within the past 12 months ☐ Yes☐ No ☐ Unknown

If yes, agent(s)/dose _____

Start date_____Stop date: _____

Anti-angiogenic agents (e.g. bevacizumab) within the past 12 months ☐ Yes☐ No ☐ Unknown

If yes, agent(s)/dose _____

Start date_____Stop date: _____

6. OTHER HISTORY (please indicate all date as DD/MM/YYYY)

Current smoker ☐ Yes☐ No ☐ Unknown

If yes, estimated number of pack-year_____

If past smoker, stop date _____

Alcohol consumption☐ Yes☐ No ☐ Unknown

If yes, estimated of drinks per week_____

Diabetes ☐ Yes☐ No ☐ Unknown

If yes, ☐ Type 1☐ Type II

TARGETED FOLLOW UP FORM-OSTEONECROSIS OF THE JAW
BBL Case No.:

7. PATIENT REMINDER CARD STATUS (FOR EU PATIENTS)

Received a patient reminder card prior to the ONJ event:

☐ Yes☐ No ☐ Unknown

_____

_____

REPORTER

Name:

Address:

City:

Country:

Email:

State/ Province:

Postal Code:

6. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

Occupation: Date:

Biocon Biologics is committed to holding patient's and reporter's personal data in strict confidence. Personal data, here, means any information by which a person is, directly or indirectly, identified or identifiable, which includes, but is not limited, to name, address, contact number, email address, genetic data and data concerning health. Biocon Biologics strictly adheres to applicable data privacy and data integrity laws, including, but not limited to, General Data Protection Regulations [EU] 2016/679 ["GDPR"] or its equivalent, as amended from time to time.

Additional Information: _____

_____

_____

TARGETED FOLLOW UP FORM-POTENTIAL ATYPICAL FRACTURE`
BBL Case No.:

1. Patients/case administrative information (please include date as DD/MM/YYY)Details:

Patient identifier	
Patient's Initials	
Date of event onset	
Date of this report	
Event	
Age at time of event	
Gender	☐ Male ☐ Female
Weight (lb/kg)	
Height	
Study Number (if applicable)	

2. Denosumab Administrative information:

Denosumab Indication	☐ Postmenopausal osteoporosis ☐ Bone loss from hormone ablation therapy Please specify diagnosis _____ ☐ Advanced cancer with bone metastasis Please specify cancer: _____ ☐Other (please specify)_____ ☐Don't Know _____
Denosumab Dose	☐60 mg SC every 6 months ☐ 120 mg SC every 4 weeks ☐Other (please specify)_____☐ Don't know
Denosumab Exposure	Denosumab first administered (date)_____ Last denosumab dose before event(date)

TARGETED FOLLOW UP FORM-POTENTIAL ATYPICAL FRACTURE`
BBL Case No.:

	Doses of denosumab were skipped ☐ Yes☐ No ☐ Unknown If yes, please specify_____ Doses of denosumab given after event began ☐ Yes☐ No ☐ Unknown If yes, date of first dose following start of event_____

3. Diagnosis (check all that Apply):

Location of fracture	☐Femur neck ☐ Femur distal ☐ Femur midshaft ☐ Femur intertrochanter ☐ Femur subtrochanter ☐ Other location (specify): _____
Diagnostic imaging used to confirm fracture:	☐ X-ray ☐ CT Scan ☐ MRI
Date of imaging at time of femure fracture (DD/MM/YYY)	
Was this a pathological fracture associated with bone tumor or miscellaneous bone diseases (e.g. Paget's disease, fibrous dysplasia)?	☐ Yes☐ No ☐ Unknown
Type of Fracture	☐ Transverse ☐ Oblique

TARGETED FOLLOW UP FORM-POTENTIAL ATYPICAL FRACTURE`
BBL Case No.:

	☐ Spiral ☐ Not reported
Fracture radiology report includes	Simple transverse or oblique (30 degree) fracture breaking of the cortex: ☐ Yes☐ No ☐ Not reported Diffuse cortical thickening of the proximal femoral shaft: ☐ Yes☐ No ☐ Not reported
Type of trauma reported at the time of fracture	☐ No Trauma ☐ Fall from standing height or less ☐ Fall on stairs, steps or curbs ☐ Fall from the height of stool, chair, first rung on a ladder or equivalent (about 20 inches) ☐ Minimal trauma other than a fall ☐ Fall from than the height of a stool, chair, first rung on a ladder or equivalent(> 20 inches) ☐ Severe trauma other than a fall (e.g., car accident) ☐ Unknown type of trauma
Early symptom of pain over fracture site:	☐ Pain at site at rest ☐ Pain at site with weight bearing ☐ None
Fracture healed within 6 months	☐ Yes☐ No ☐ Unknown If yes: ☐ Date of fracture union (DD/MM/YYYY): _____ ☐ Patient able to walk without assistance: ☐ Yes ☐ No ☐Unknown

TARGETED FOLLOW UP FORM-POTENTIAL ATYPICAL FRACTURE`
BBL Case No.:

	☐ Fracture union confirmed through imaging: ☐ Yes ☐ No ☐ Unknown If yes, check all diagnostic imaging that applies: ☐ X-ray ☐ CT scan ☐MRI
☐ Please attach a copy of the applicable radiology reports:	

4. Treatment: (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture	☐Non-surgical reduction _____ ☐Casting _____ ☐Surgery _____ ☐Revision surgery (2nd surgery) _____ ☐Other_____ _____ ☐Unknown_____ _____

5. Medical HISTORY/RISK FACTORS (check all the apply, provide dates and attach relevant reports)

General	☐ History or current corticosteroid use ☐ Affected hip with prior surgical pinning ☐ Affected hip with prior hip replacement
Prior osteoporosis therapy	☐ Estrogen ☐ Selective estrogen receptor modulator (SERM) ☐ Bisphosphonate (please indicate) ☐ Intravenous ☐ oral If yes, how long has therapy been received? (months, years)

TARGETED FOLLOW UP FORM-POTENTIAL ATYPICAL FRACTURE`
BBL Case No.:

	_____ ☐ Parathyroid hormone
Cancer	Evidence of any metastases: ☐ Yes☐ No ☐ Unknown If yes, did metastasis involve bone? ☐ Yes☐ No ☐ Unknown Metastasis in femur where fracture occurred? ☐ Yes☐ No ☐ Unknown

Past medical and surgical history: _____
_____
_____
_____

Medication history (include, dose, frequency, and dates of treatment): _____
_____
_____
_____

Copies of records/consults: radiology report attached? ☐ Yes☐No _____
_____
_____
_____

REPORTER

Name:

Address:

City:

Country:

Email:

State/ Province:

Postal Code:

TARGETED FOLLOW UP FORM-POTENTIAL ATYPICAL FRACTURE`
BBL Case No.:

6. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name: Sign

Occupation: Date:

Biocon Biologics is committed to holding patient's and reporter's personal data in strict confidence. Personal data, here, means any information by which a person is, directly or indirectly, identified or identifiable, which includes, but is not limited, to name, address, contact number, email address, genetic data and data concerning health. Biocon Biologics strictly adheres to applicable data privacy and data integrity laws, including, but not limited to, General Data Protection Regulations [EU] 2016/679 ["GDPR"] or its equivalent, as amended from time to time.

Additional Information: _____

_____

_____

Annex 6 - Details of proposed additional risk minimisation measures (if applicable)

The proposed key message for additional risk minimisation measures is provided below. Their actual content and communication plan in individual countries will be agreed upon with national competent authority prior to the launch.

The additional risk minimization measures consist of a patient reminder card to address the risk of Osteonecrosis of the jaw.
Educational material:

- Patient reminder card:

Patient Reminder Cards for osteonecrosis of the jaw will be distributed to prescribers of Bmab1000 with background information on the purpose of the patient reminder card and instructions to provide it to patients.
The patient reminder card is intended to remind patients about important safety information that they need to be aware of before and during treatment with denosumab injections for cancer-related conditions, including:

- to tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment;
- to maintain good oral hygiene and receive routine dental check-ups during treatment;
- to inform their doctor and tell their dentist that they are being treated with denosumab (Bmab1000) if they are under dental treatment or will undergo dental surgery;
- to contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, nonhealing of sores, or discharge.