RISK MANAGEMENT PLAN

for

Denosumab

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

Version Number: 0.3

Dated: 28-Mar-2025

[redacted]

Risk Management Plan – Denosumab

Risk Management Plan for:	Denosumab
RMP Version number:	0.3
Data lock point for this RMP:	31-Oct-2024
Date of final sign off:	28-Mar-2025
Rationale for submitting an updated RMP:	In response to CHMP day 150 assessment
Summary of significant changes in this RMP:	• Under PART VI: Subsection PART II.B. Summary of important risks, the heading of Table 10, the risk name, was corrected to "Skin infection leading to hospitalization" from "Serious infections (including mycobacterial and salmonella infections)" as recommended in the CHMP Day 150 Assessment Report. • Updated the list of excipients in PART I: Product(s) Overview in alignment with EU SmPC of Denosumab BBL 60 mg solution for injection in pre-filled syringe.
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
Signature	[redacted]
E-mail address of contact person	[redacted]

Table of Contents

List of Tables

List of Abbreviations

Term/Abbreviation	Explanation
ADA	Anti-Drug Antibodies
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,
CrCl	Creatinine Clearance
CSR	Clinical Study Report
EEA	European Economic Area
EMA	European Medicines Agency
EOS	End of Study
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GC	Glucocorticoid
GIOP	Glucocorticoid-induced osteoporosis
GLSMs	Geometric Least Squares Means
GVP	Good Pharmacovigilance Practices
HALT	Hormone ablation therapy
HIV	Human immunodeficiency virus
HLGT	High Level Group Term
HR	Hazard ratio
ICF	Informed Consent Form
lgE	Immunoglobulin E
lgG2	lmmunoglobulin G 2 Subclass
INN	International Nonproprietary Name

MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Male Osteoporosis
OI	Osteogenesis Imperfecta
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
OPG-Fc	Osteoprotegerin bound to Fe
PMO	Postmenopausal osteoporosis
PL	Package leaflet
PK	Pharmacokinetics
PTH	Parathyroid hormone
Q3M	Every 3 months
Q6M	Every 6 months
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
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: Binds to and neutralizes the activity of the human RANK ligand (RANKL). In blocking RANKL, denosumab reduces osteoclast-medicated bone resorption.
	Composition: Bmab1000 pre-filled syringe contains 60 mg of denosumab in 1 mL of solution (60 mg/mL). Important information about its composition: Denosumab is a fully human IgG2 monoclonal antibody that specifically inhibits RANKL (receptor activator of nuclear factor kappa-B ligand) and produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology. List of excipients: Acetic acid, glacial Sodium acetate trihydrate Sodium hydroxide Sorbitol Polysorbate 20

	Water for injections
Hyperlink to the Product Information	Bmab1000 Product information (Module 1.3.1)
Indication (s) in the EEA	Current: Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Bmab1000 significantly reduces the risk of vertebral, non-vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Bmab1000 significantly reduces the risk of vertebral fracture. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended dose of Bmab1000 is 60 mg administered as a single subcutaneous (SC) injection once every 6 months (Q6M) into the thigh, abdomen, or upper arm. Patients must be adequately supplemented with calcium and vitamin D. Proposed: Not applicable.
Pharmaceutical form (s) and strengths	Current: Bmab1000 is supplied as a sterile, preservative-free solution intended for SC use (solution for injection). Bmab1000 is provided in prefilled syringes at a concentration of 60 mg/ml, filled to a target deliverable volume of 1.0 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[5.] "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 Prolia® and EU-Approved Prolia®.

The key safety findings from non-clinical studies reported for reference product Prolia® and relevance to human use are summarized below[4.]:

Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity **Reproductive toxicity** At area under the curve (AUC) exposures up to 100-fold higher than the human exposure (Q6M), denosumab showed no evidence of impaired fertility in cynomolgus monkeys. In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (Q6M), there was no evidence of maternal or fetal harm. In this study, fetal lymph nodes were not examined. In cynomolgus monkeys dosed with denosumab throughout pregnancy, effects including stillbirths and increased postnatal mortality; abnormal bone growth, reduced hematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth were noted at AUC exposures up to 119-fold higher than the human exposure (60 mg Q6M). There was no evidence of maternal harm prior to labor; adverse maternal effects occurred	Monkeys exposed to denosumab in utero phenotypically resembled human infants with osteoclast-poor osteopetrosis due to inactivating mutations of RANK or RANKL. Therefore, 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 Prolia®. 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 on whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP. These populations are not included in the intended indications. In addition, risk minimization via product labelling to avoid pregnancy and breastfeeding is in place.

Important Nonclinical Safety Findings	Relevance to Human Usage
infrequently during labor. Maternal mammary gland development was normal. 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. **Developmental toxicity** In neonatal rats, administration of the RANKL inhibitor osteoprotegerin (OPG) bound to Fe (OPG-Fc) resulted in reduced weight gain, reduced bone growth, and inhibited tooth eruption. Despite reductions in bone growth, most bone strength parameters were increased with these treatments. 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 generally returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralization in multiple tissues was seen in 1 recovery animal. Adolescent cynomolgus monkeys who received doses of denosumab 150 times the expected clinical exposure had enlargement of epiphyseal growth plates with decreased removal of cartilage matrix in this area, considered to be consistent with the pharmacological activity of denosumab.	Treatment with denosumab may inhibit eruption of dentition in pediatric patients and may impair bone growth in pediatric patients with open growth plates. Denosumab is not approved for use in pediatric patients and should not be used in pediatric patients. Risk minimization is in place via product labeling with respect to use in pediatric patients.

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, will be submitted later during the MA procedure.

Clinical trial development programme for Bmab 1000 consisted of the following two clinical trials (*B1000-NHV-01-G-01* and 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 is is 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:

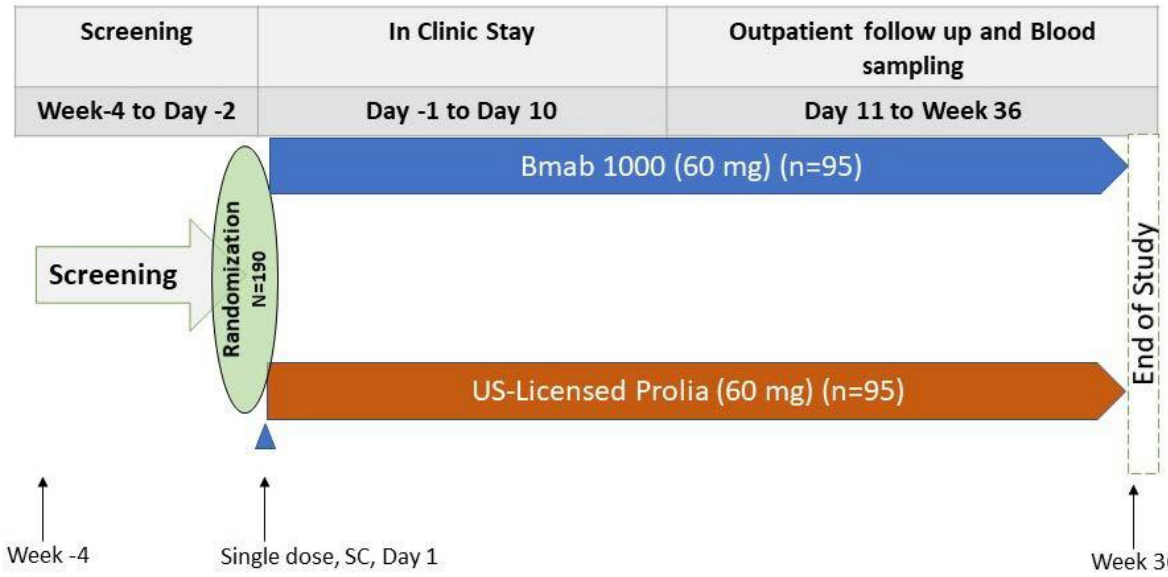
- US Prolia®

- 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).

	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 behaviour 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.

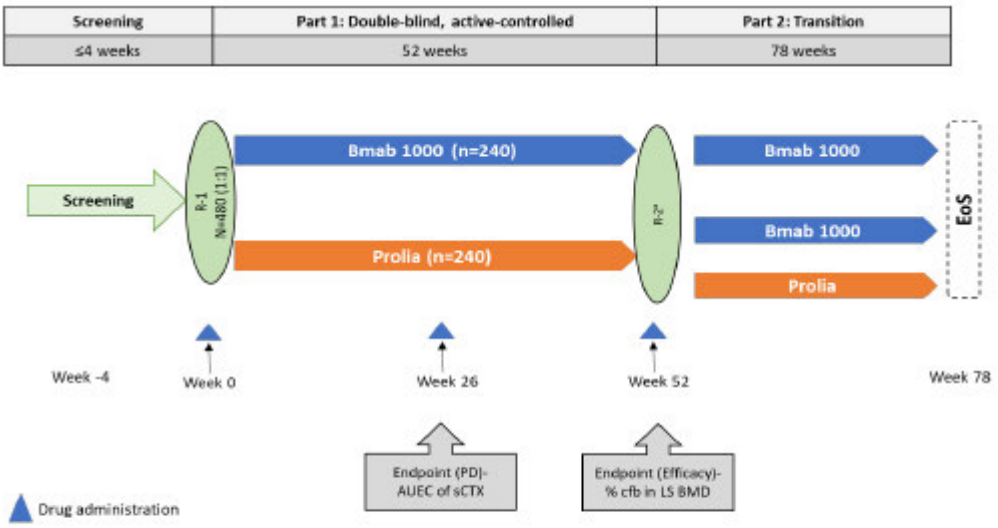
Part 1, Double-Blind Active-Controlled Period (from Week 0 [Day 1] to Week 52 Pre-dose)
In the double-blind active-controlled period, eligible patients will be randomly assigned (1:1) to receive either Bmab 1000 (60 mg) or Prolia® (60 mg) via SC injection on Day 1 (Week 0, the same date as randomization) 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 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.

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 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 below tables.

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 <18 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.

Part 1:

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 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 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. In the reference product Prolia® Studies[4], subgroup analyses by baseline lumbar spine and total hip T-score for the range of T-scores enrolled in the large pivotal PMO study (20030216), denosumab was effective in each subgroup. Therefore, no special dosing recommendations for patients with BMD T-scores <-4.0 are considered necessary. Furthermore, subjects with BMD T-scores < -4.0 were not excluded from the pivotal study in the Glucocorticoid induced osteoporosis (GIOP) population (Study 20101217 (reference product study4)) because the study was active-controlled (risedronate).
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 confound the efficacy results.	No	Denosumab is not indicated for use in these other patient populations. Information from reference product Prolia® studies[4] subjects with RA were not excluded from the pivotal study in the glucocorticoid-induced osteoporosis (GIOP) population (Study 20101217), because RA is a common indication for glucocorticoid (GC) use.
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	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 Prolia® study details are as follows[4]

	previous bisphosphonate treatment.		In Study 20050234, a double-blind, alendronate-controlled, in postmenopausal women with low BMD who had received bisphosphonates for at least 6 months preceding study entry, safety results were similar in the denosumab and alendronate treatment groups. In addition, Studies 20080099, 20080562, and 20110153 evaluated the effects of denosumab and a bisphosphonate (risedronate, ibandronate, or zoledronic acid, respectively) in postmenopausal women transitioning from previous bisphosphonate therapy. There were no new safety findings in these studies.
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.

BMD = bone mineral density; GC = glucocorticoid; GIOP = glucocorticoid-induced osteoporosis; HALT= hormone ablation therapy induced bone loss; OI = osteogenesis imperfecta; PMO = postmenopausal osteoporosis; RA = rheumatoid arthritis; SmPC = summary of product characteristics

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 the use of Bmab1000 in children. Information from the reference product Prolia®[4] as below: Male: A total of 17 subjects (45.7 subject-years), 29 subjects (83.9 subject-years), and 46 subjects (136.0 subject-years) aged 2 to 6 years, 7 to 10 years, and 11 to

	17 years, respectively, were exposed to Prolia®, in the clinical development program. Female: A total of 22 subjects (59.8 subject-years), 26 subjects (73.6 subject-years), and 31 subjects (83.9 subject-years) aged 2 to 6 years, 7 to 10 years, and 11 to 17 years, respectively, were exposed to Prolia®, in the clinical development program. As per Prolia® SmPC[3], Denosumab should not be used in children aged < 18 years because of safety concerns of serious hypercalcaemia, and potential inhibition of bone growth and lack of tooth eruption. Some clinical trial cases were complicated by acute renal injury. A single-arm phase 3 study of Prolia® evaluating the efficacy, safety, and pharmacokinetics was conducted in children with osteogenesis imperfecta, aged 2 to 17 years and reported serious adverse events of hypercalcaemia during every 3 months dosing. The studies were terminated early due to the occurrence of life-threatening events and hospitalisations due to hypercalcaemia.
Elderly population	In the Phase 1 (B1000-NHV-01-G-01) clinical 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 is no overall differences in safety or efficacy observed in the elderly population. Information from the reference product Prolia®[4] as below: Male: A total of 688 subjects (1428.9 subject-years), 607 subjects (1372.3 subject years), and 68 subjects (168.5 subject-years) aged 65 to 74 years, 75 to 84 years and ≥ 85 years, respectively, were exposed to Prolia®, in the clinical development program. Female: A total of 6124 subjects (28015.0 subject-years), 2505 subjects (10273.4 subject-years), and 119 subjects (301.7 subject-years) aged 65 to 74 years, 75 to 84 years, and 85 years, respectively, were exposed to Prolia®, in the clinical development program. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out[35]

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.
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 Prolia®.
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 Prolia®(Amgen) Therefore, the safety profile of Bmab 1000 is based on the general safety profile of denosumab, which resulted from the extensive experience with Prolia® (date of authorisation in EU: 26-May-2010) 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 26-May-2010, product Prolia® was authorised by the European Commission according to EMA product number- EMEA/H/C/001120. 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 Prolia® (RMP version 31.0, date 11-Jan-2023)[4].

-**Summary of safety concerns**	
Important identified risks	• Hypocalcemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy

Missing information	• None

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 Prolia® 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 Prolia®. (Prolia-EPAR-Risk Management Plan Version 31.0 dated 11 Jan 2023)[4]

Summary of safety concerns	
Important identified risks	• Hypocalcemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	• None

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

Important Identified Risk: Hypocalcemia

Potential mechanisms:

Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of

calcium from bone into the bloodstream.

Evidence source(s) strength of evidence

In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. This risk was identified in the phase 3, randomized, double-blind, and placebo- or active-controlled studies of reference product Prolia®

Characterization of the Risk

Frequency in BBL's clinical development programme:
Studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02**:** No pertinent, serious TEAEs were reported.

Frequency with reference product:
In the pooled pivotal studies (Prolia ® for PMO and HALT subject incidence of hypocalcemia adverse events was < 0.1% in denosumab-treated subjects and 0.1% in placebo-treated subjects. The incidence of hypocalcemia adverse events was lower in denosumab-treated subjects than in placebo-treated subjects; thus, 95% Cls were not calculated. In the 24-month final analysis of the GIOP study, subject incidence of hypocalcemia adverse events was 0.3% in the denosumab group; there were no adverse events of hypocalcemia in the risedronate group thus, 95% Cls were not calculated[4].

The SmPC of the reference product lists hypocalcaemia as a rare undesirable effect[3].

Severity: While most hypocalcemia events are mild to moderate in severity; severe events have occurred. (Prolia®-EPAR-RMP)[4].
In the post-marketing settings of reference product, severe symptomatic hypocalcaemia (including fatal cases) has been reported, with most cases occurring in the first weeks of initiating therapy. Examples of clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status (including coma). Symptoms of hypocalcaemia in clinical studies included paraesthesia or muscle stiffness, twitching, spasms and muscle cramps (Prolia® SmPC[3])
Reversibility: Hypocalcemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, IV calcium supplementation may be required.

Long-term outcome: No long-term complications are anticipated for properly treated hypocalcemia.

Impact on quality of life: For severe symptomatic hypocalcemia, patients may be hospitalized for treatment. Generally, patients recover when their hypocalcemia is treated.

Risk factors and risk groups
Risk factors include severe renal impairment and hyperphosphatemia Other risks factors may include a history of hypoparathyroidism, Parathyroid hormone (PTH) resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (CrCL < 30 ml/min), dialysis, and some medications (Wing, Cecil Essentials of Medicine, 10th ed, 2020:757-766[7])).

Preventability

Pre-existing hypocalcemia should be corrected by adequate intake of calcium and vitamin D before initiating therapy, and supplementation with calcium and vitamin D is important during therapy in all patients receiving denosumab. Clinical monitoring of calcium levels is recommended during treatment, especially in those with renal impairment.

Impact on the risk-benefit balance of the product
The risk of hypocalcemia has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health Impact:

A significant public health impact is not expected as this risk is preventable and treatable with the appropriate risk mitigating measures communicated clearly in the SmPC.

MedDRA terms: PT Hypocalcaemia; Blood calcium decreased

Important Identified Risk: Skin Infection Leading to Hospitalisation

Potential mechanisms:

Keratinocytes can express RANKL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response (Loser et al, 2006;[8] · Yamagunchi and sakaguchi, 2006[9]).

Evidence source(s) strength of evidence

In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. This risk was identified in phase 3, randomized, double-blind, placebo- or active-controlled studies of reference product Prolia®.

Characterization of the Risk

Frequency in BBL's clinical development programme:

Study B1000-NHV-01-G-01 and B1000-PMO-03-G-02: No SAEs reporting Skin infection leading to hospitalization were observed in Bmab 1000 clinical development program.

Frequency with reference product:

In pooled PMO/HALT pivotal studies, subject incidence of skin infection was 1.4% with denosumab and 1.3% with placebo; the hazard ratio (HR) was 1.09 (95% CI: 0.78, 1.53). Subject incidence of serious adverse events of skin infection was 0.4% with denosumab and 0.2% with placebo (HR [95% CI]= 2.55 [1.13, 5.76]). In the 24-month final analysis of the GIOP study, subject incidence of adverse events of skin infection was 1.8% with denosumab and 0.5% with risedronate; the HR was 3.62 (95% CI= 0.75, 17.42). Subject incidence of serious adverse events of skin infection was 0.5% in both the denosumab and risedronate groups (HR [95% CI]= 1.03 [0.15, 7.34]) . (Prolia®-EPAR-RMP)[4].
As per the reference product SmPC, Skin infections leading to hospitalisation were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving Prolia®. These cases were predominantly cellulitis. The SmPC of the reference product lists cellulitis as an uncommon undesirable effect.(Prolia® SmPC)[3].

Severity: Serious adverse events of skin infection were mostly severe in intensity.

Reversibility: These events are typically resolved with the administration of antibiotics.

Long-term outcome: No long-term complications are anticipated for properly treated patients who are hospitalized due to skin infections

Impact on quality of life: Requires a hospital stay; patients generally recover with antibiotic treatment.

Risk factors and risk groups

Risk factors for infection, in general, include increasing age, immunosuppression associated with cancer, diabetes, HIV/acquired immune deficiency syndrome {AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.

Preventability

No preventive measures are known.

Impact on the risk-benefit balance of the product

The risk of skin infection leading to hospitalisation has been considered in product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health Impact:

Since the frequency of skin infection leading to hospitalisation is relatively low, the absolute difference between denosumab and placebo groups is relatively small, and the adverse events can be effectively treated by antibiotics, the negative impact on public health is relatively small.

MedDRA terms: SOC Infections and infestations

Important Identified Risk: Osteonecrosis of the 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 remodeling, 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[10] ; Aghaloo et al, 2015 [11]).

Evidence source(s) strength of evidence

In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. This risk was identified in open-label long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies of reference product Prolia®.

Characterization of the Risk

Frequency in BBL's clinical development programme:

Study B1000-NHV-01-G-01 and B1000-PMO-03-G-02 : No SAEs reporting osteonecrosis of the jaw were observed in Bmab 1000

Frequency with reference product:

No cases of ONJ have been reported in placebo-controlled studies (although cases were

reported in open-label extensions to the pivotal PMO study and a HALT study); thus, 95% CIs were not calculated. No cases of ONJ were reported in the GIOP study.

Overall, across the Amgen-sponsored clinical development program for Prolia®, positively adjudicated ONJ cases have been reported rarely (17 ONJ cases in 23 280 subjects, 0.073%) in subjects cumulatively exposed to denosumab (60 mg) clinical studies.(Prolia® -EPAR-RMP)

The SmPC of the reference product lists osteonecrosis of jaw as an uncommon undesirable effect. (Prolia® SmPC[3])

Severity: Most events leading to adjudication as ONJ were assessed as moderate in severity. Mild and severe events were also reported.

Reversibility: In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required.

Long-term outcome: No data on long-term outcomes are 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 (eg, decreased hydration and decreased nutritional intake).

Risk factors and risk groups

Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, 2006**[12]**; Ruggiero et al 2006**[13]**).

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.

Impact on the risk-benefit balance of the product

The risk of osteonecrosis of the jaw has been considered in the product benefit-risk assessment. In light of the product labeling and additional risk minimization activities addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health Impact:

Significant public health impact is not expected with Denosumab as the event is rare and the actions taken to minimize the likelihood of developing ONJ are described in the prescribing information.

Important Identified Risk: Hypersensitivity Reactions

Potential mechanisms:

Two types of allergic reactions, immunoglobulin E (IgE)- and non-IgE-mediated, appear to be related to monoclonal antibody administration. The IgE-mediated reactions can cause both wheal and flare reactions at the injection site but may also be associated with urticaria and anaphylaxis. The mechanism of non-IgE reactions is unclear.

Evidence source(s) strength of evidence

In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. This risk was identified in the post-marketing setting of the reference product Prolia® based on a clinically plausible association between administration of denosumab and hypersensitivity reactions.

Characterization of the Risk

Frequency in BBL's clinical development programme:

Studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02: No SAEs reporting hypersensitivity reactions were observed in Bmab 1000 clinical development program.

Frequency with reference product:

In the pooled PMO/HALT (innovator) pivotal studies, subject incidence of hypersensitivity and drug hypersensitivity was 1.0% in denosumab-treated subjects and 0.8% in placebo-treated subjects; HR= 1.26 (95% CI: 0.83, 1.90). Subject incidence of potential clinical consequences of hypersensitivity was 1.3% in both treatment groups; HR= 0.94 (95% CI: 0.66, 1.33). In the 24-month final analysis of the GIOP study, subject incidence of adverse events potentially associated with hypersensitivity was 6.3% in denosumab-treated subjects and 4.7% in risedronate-treated subjects (HR [95% CI]= 1.41 [0.77, 2.59]) .(Prolia® -EPAR-RMP [4])

The SmPC of the reference product lists drug hypersensitivity as a rare undesirable effect. (Prolia® SmPC[3])

Severity: Most hypersensitivity reactions are mild to moderate in severity; severe events have occurred.

Reversibility: Hypersensitivity reactions are generally reversible with discontinuation of the medication, though treatment may be required.

Long-term outcome: No long-term complications are anticipated for properly treated hypersensitivity reactions

Impact on quality of life: For severe hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalized for treatment. Generally, patients recover when denosumab is discontinued with or without additional treatment.

Risk factors and risk groups

Known hypersensitivity to denosumab and any of its excipients

Preventability

No data is available on potential measures to prevent hypersensitivity reactions to denosumab. The appropriate contraindication information on hypersensitivity to denosumab and any of its

excipients is included in the SmPC.

Impact on the risk-benefit balance of the product

The risk of hypersensitivity reactions has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health Impact:

No significant public health impact is expected as reports of severe events (e.g., anaphylaxis) are rare.

MedDRA Term search criterion:

SMQ: Hypersensitivity (narrow).

Important Identified Risk: Atypical Femoral 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 the causes of AFF are likely multi-factorial. Based on nonclinical studies, 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[14]; Shane et al, 2010 [15]).

Evidence source(s) strength of evidence

In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. This risk was identified in an open-label long-term extension to a phase 3, randomized, double-blind, active-controlled study of reference product Prolia®.

Characterization of the Risk

Frequency in BBL's clinical development programme:

Studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02: No SAEs reporting Atypical femoral fracture were observed in Bmab 1000 clinical development program

Frequency with reference product:

No cases of confirmed AFF have been reported in placebo-controlled studies; thus, 95% Cls were not calculated. In the GIOP study, subject incidence of confirmed AFF was 0.3% (1 event) in the denosumab group; there were no adverse events of AFF in the risedronate group thus, 95% Cls were not calculated.

Overall, as of 26 September 2016, adjudicated-positive cases of AFF have been reported rarely (5 of 23 280 subjects, 0.021%) in subjects exposed to denosumab (60 mg) in clinical studies. (Prolia®-EPAR-RMP)[4].
The SmPC of the reference product lists atypical femoral fractures as a rare undesirable effect (Prolia® SmPC)[3].

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. The few events from Prolia® studies leading to the adjudication of AFF were considered severe in intensity.

Reversibility:

Atypical femoral fracture is generally treatable with surgical intervention. It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued.

Long-term outcome:

No data on long-term outcomes are available

Impact on quality of life:

As with other femur 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, 2016[16]; Unnanuntana et al, 2013[17]).

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, 2012[18] ; Giusti et al, 2011[19]). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, 2010 [15]).

Preventability

No data is currently available on potential measures to prevent AFF. Patients using long-term antiresorptive 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 atypical femoral fracture has been considered in the product benefit-risk assessment. In light of the product labeling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health Impact:

Based on the infrequency of AFF in patients treated with denosumab, no significant additional public health impact is expected.

MedDRA Term search criterion:

PT: atypical femur fracture.

Important Identified Risk: Hypercalcemia in Pediatric Patients Receiving Denosumab and After Treatment Discontinuation

Potential mechanisms:

The exact mechanism of hypercalcemia occurring in pediatric patients both during the dosing interval and following discontinuation is not certain but may be a consequence of the following, alone, or in combination:

- Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. 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 resorbing bone matrix via an autocrine/paracrine mechanism.
- The magnitude of the resorptive response following treatment and withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons.
- The response of the osteoclast lineage to loss of inhibition of osteoclasto genesis may be intrinsically more robust in individuals with growing skeletons. The increased skeletal metabolism related to bone modeling and growth in children is therefore likely to impact on the frequency of hypercalcemia occurring both between the dosing interval and following discontinuation.

Evidence source(s) strength of evidence

In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. Data to evaluate safety concerns were derived from Prolia® clinical trials in pediatric subjects with OI XGEVA clinical studies, and reference product post-marketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.

Characterization of the Risk

Frequency in BBL's clinical development programme*:* No pediatric patient exposed in studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02 conducted by BBL.

Frequency with reference product:

In the pediatric OI studies (as of 02 November 2021 for Study 20130173 and 05 November 2021 for Study 20170534), 49 of 153 subjects (32%; 95% CI: 24.72, 40.04) who received at least 1 dose of every 3 months (Q3M) or every 6 months (Q6M) denosumab dosing regimen had hypercalcemia events, of which 7 subjects (4.6%) had serious events.

Severity: Most subjects (approximately 80%) in the pediatric OI studies who had hypercalcemia events experienced mild events. Life-threatening events have been reported.(Prolia® - EPAR-RMP)·
Reversibility: Hypercalcemia is reversible when treated. In severe cases, use of rescue medications may be required.

Long-term outcome: No long-term adverse effects are anticipated for properly treated hypercalcemia.

Impact on quality of life: Pediatric patients may present with severe hypercalcemia requiring hospitalization. Generally, patients recover when hypercalcemia is treated.

Risk factors and risk groups
Pediatric patients with growing skeletons and high bone turnover disease states (such as Osteogenesis imperfecta).

Preventability
Denosumab is not indicated in pediatric patients (age< 18 years) and should not be used in pediatric patients. If used in a clinical trial setting, such as for pediatric GIOP (Reference product Prolia® study) , monitoring for signs and symptoms and periodic serum calcium is advisable.

Impact on the risk-benefit balance of the product
The benefit-risk profile of Bmab 1000 (denosumab) is not favorable in the pediatric patient population.

Public health Impact:
Significant public health impact is not expected as this risk is preventable with the appropriate risk-mitigating measures communicated clearly in the SmPC.

MedDRA Term search criterion:

PT: Hypercalcemia.

Important Potential Risk: Fracture Healing Complications

Potential mechanisms:
Because denosumab directly suppresses bone resorption and (indirectly) bone formation, it has the theoretical potential to delay fracture healing.

Evidence source(s) strength of evidence
In line with the RMP of the reference product Prolia®, this safety concern has been classified as important potential risk. This is a theoretical risk based on the mechanism of action.

Characterization of the Risk

Frequency in BBL's clinical development programme

No cases of delay in fracture healing have been reported in studies B1000-NHV-01-G-01 and B1000-PMO-03-G-02.

Frequency with reference product:
Of the subjects who had nonvertebral fractures in the large pivotal PMO study, fracture healing complications (delayed healing or nonunion) were reported in 2 of 386 subjects in the denosumab group (0.5%) and 5 of 465 subjects (1.1% in the placebo group. Of the subjects who had nonvertebral fractures in the pivotal study for HALT-breast cancer, fracture healing complications were reported in O of 8 subjects in the denosumab group and 1 of 8 subjects (12.5%) in the placebo group.
Because of the low incidence of fracture healing complications, 95% Cls were not calculated.

No fracture healing complications were reported in the male osteoporosis (MOP) study

No fracture healing complications were reported in the glucocorticoid-induced osteoporosis (GIOP) study. (Prolia® -EPAR-RMP)[4].

Severity:
This risk has not been substantiated; however, impaired fracture healing could have significant impact on patient wellbeing.

Reversibility:
This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible.

Long-term outcome:
This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility.

Impact on quality of life:

Fracture healing complications can cause short-term or long-term disability. Surgery may be required.

Risk factors and risk groups

General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez et al, 2012[20]; Gaston and Simpson, 2007[21]).

Preventability

No preventive measures are known.

Impact on the risk-benefit balance of the product

The potential risk of fracture healing complications has been considered in overall assessment supporting a positive benefit-risk profile.

Public health Impact:

No significant impact on public health is anticipated.

MedDRA Term search criterion:

HLGT- Bone and joint injuries

Important Potential Risk: Infection

Potential mechanisms:

RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low BMD. No evidence of a treatment effect of denosumab on immunoglobulin production was observed.

Evidence source(s) strength of evidence

In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important potential risk. This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the post-marketing experience of the reference product.

Characterization of the Risk

Frequency in BBL's clinical development programme

In study B1000-PMO-03-G-02, a total of three serious adverse events (SAEs) involving infections were reported. Of which, two SAEs were reported in Bmab1000 group (urosepsis (n=1) and vestibular neuronitis (n=1)). The remaining one SAE was reported in the Prolia® group (staphylococcal sepsis (n=1)). All the events were assessed as not related/unrelated to Bmab 1000/Prolia® by the Investigator and Sponsor.
No SAEs were reported with infections for study B1000-NHV-01-G-01.

Frequency with reference product:

	Subject Incidence[a] (percent)	Hazard ratio (95% CI)
Adverse events		

Placebo	50.6	0.98 (0.92, 1.03)
Denosumab	50.1	
Serious adverse events		
Placebo	3.4	1.25 (1.02, 1.53)
Denosumab	4.3	
Serious adverse events not including skin infection		
Placebo	3.3	1.18 (0.95, 1.45)
Denosumab	3.9	
Opportunistic infection		
Placebo	0.1%	--
Denosumab	0.1%	

a Pooled pivotal studies for PMO (20030216, 20040132) and HALT and 20040138 in prostate cancer and 20040135 in breast cancer, Safety Analysis Set.

In the 24-month final analysis of the GIOP study, the subject incidence of infections was 36.3% with denosumab and 36.4% with risedronate; HR= 1.06 (0.84, 1.34). Subject incidence of serious adverse events of infection was 5.8% in the denosumab group and 6.5% in the risedronate group (HR [95% CI] = 0.95 [0.54, 1.68]). (Prolia® -EPAR-RMP)[4].

Severity:

The majority of reported events of infection were non serious. Serious adverse events were most commonly reported as severe in intensity.

Reversibility:

Infections when treated appropriately are generally reversible.

Long-term outcome:

Infection generally responds to appropriate treatment and as such no long-term effects are anticipated.

Impact on quality of life:

For severe infection, patients may be hospitalized for treatment. Generally, patients recover when their infection is treated.

Risk factors and risk groups

Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.

Preventability

No preventive measures are known.

Impact on the risk-benefit balance of the product

The potential risk of infection has been considered in the overall assessment which supports a positive benefit-risk profile in the indicated populations.

Public health Impact:

No significant public health impact is expected for this unsubstantiated risk as effective treatments are available.

MedDRA terms:

SOC Infections and infestations

Important Potential Risk: Cardiovascular Events

Potential mechanisms:

Elevated levels of 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) strength of evidence

In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important potential risk .This is a theoretical risk based on epidemiological data demonstrating elevated OPG in patients with cardiovascular disease.

Characterization 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 the 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.

No SAEs were reported with cardiovascular events in study B1000-NHV-01-G-01

Frequency with reference product:

In a pooled analysis of the large pivotal PMO study (20030216) and the pivotal HALT-prostate study, the overall subject incidence of adjudicated-positive serious cardiovascular events was 5.8% with denosumab and 5.6% with placebo (HR [95% Cl] = 1.00 [0.85, 1.19]).

The subject incidence of positively adjudicated, pre-defined categories of serious cardiovascular event was comparable between the treatment groups in the pooled analysis, as shown below:

Studies 20030216 and **20040138**[a]	Subject Incidence (percent)	Hazard Ratio (95% CL)
Acute coronary syndrome • Placebo • Deonsumab	1.4 1.4	0.96 (0.68, 1.35)
Congestive heart Failure • Placebo • Deonsumab	0.7 0.8	1.03 (0.64, 1.65)
Stroke/transient ischemic attack • Placebo • Deonsumab	1.5 1.7	1.06 (0.77, 1.46)
Arrhythmia • Placebo • Deonsumab	1.3 1.5	1.15 (0.82, 1.63)
Other vascular disorders • Placebo • Deonsumab	0.9 1.1	1.13 (0.75, 1.71)
Cardiovascular Death		

• Placebo • Deonsumab	1.1 0.9	0.79 (0.52, 1.18)

a Safety Analysis set

During the placebo-controlled phase of the pivotal study for MOP, adverse events in the cardiac disorders system organ class (SOC) were reported in 8 (6.7% denosumab-treated and 3 (2.5%) placebo-treated subjects (note: 2 events of angina tonsillitis in the denosumab group were incorrectly coded to the cardiac disorders adverse event category). The incidence of adverse events in the vascular disorders SOC was 5.0% in denosumab-treated and 6.7% in placebo-treated subjects.

In the GIOP study, adverse events in cardiovascular disorders or vascular disorders SOC were reported in 65 (16.5% denosumab-treated subjects and 53 (13.8%) risedronate-treated subjects (HR [95% CI]= 1.27 [0.88, 1.82]). Subject incidence of serious adverse events in the cardiovascular or vascular SOC was 3.8% on the denosumab group and 3.9% in the risedronate group.

In Study 20190038 (a retrospective cohort study assessing the incidence of cardiovascular and cerebrovascular events among postmenopausal women and men with osteoporosis treated with denosumab or zoledronic acid for up to 36 months of treatment), the unadjusted incidence rates of myocardial infarction, stroke, and MI-stroke composite outcome were 0.23 to 0.72 per 100 person-years. The differences in the unadjusted incidence rates of outcome between denosumab and zoledronic acid treatment groups were small (< 0.1 risk difference) (Prolia® -EPAR-RMP).

Severity:

This risk has not been substantiated; however, cardiovascular events may be severe/life-threatening.

Reversibility:

This risk has not been substantiated; however, effects of denosumab to block RANKL are fully reversible.

Long-term outcome:

This risk has not been substantiated; however, cardiovascular events could impact patient long-term outcome.

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 cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz et al, 2005[22];Hak et al, 2000[33]).

Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, 2007[23]; Smith et al, 2004[34]).

Preventability

No preventive measures are known.

Impact on the risk-benefit balance of the product
The potential risk of cardiovascular events has been considered in overall assessment supporting a positive benefit-risk profile.

Public health Impact:
Significant public health impact of denosumab on cardiovascular disease severity or incidence is not anticipated.

MedDRA terms:
SOC: Cardiac disorders

Important Potential Risk: Malignancy

Potential mechanisms:
RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumor types provide no evidence for carcinogenic risk associated with RANKL inhibition (Armstrong et al, 2008[24]; Jones et al, 2006[25]; Mori et al, 2007[26].). In in vivo rodent cancer models, RANKL inhibition has been shown to have a beneficial effect (Canon et al, 2008[27].; Vanderkerken et al, 2003[28]; Castellano et al, 2011[29].; Zhang et al, 2001[30]).
If denosumab did affect immune function, a hypothetical association with malignancies linked to immune modulation could exist and would be expected to show the pattern of malignancy associated with immune deficiency.

Evidence source(s) strength of evidence
In line with the RMP of the reference product Prolia®, this safety concern has been classified as important potential risk. This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the post-marketing experience of reference product.

Characterization 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 large pivotal PMO study (20030216), the subject incidence of new primary malignancy was 4.8% with denosumab and 4.3% with placebo (HR [95% CI]= 1.11 [0.90, 1.37]).
In the pivotal HALT prostate cancer study (20040138), the subject incidence of new primary malignancy was 5.1% with denosumab and 4.6% with placebo (HR [95% CI]= 1.08 [0.67, 1.72]), and overall survival was 94.1% in each treatment group (HR [95% CI] = 0.99 [0.65, 1.52]). During the placebo-controlled phase of the MOP study, 4 subjects in the denosumab group (3.3%) and no subject in the placebo group reported events of malignancy. The events were prostate cancer in 3 subjects and basal cell carcinoma in 1 subject. Two prostate cancer cases were likely present at baseline based on past medical history.

In the 24-month final analysis of the GIOP study, subject incidence of malignancy was 3.0% with denosumab and 1.8% with risedronate (HR [95% CI]= 1.75 [0.69, 4.44]). The subject incidence of serious adverse events of malignancy was 1.8% with denosumab and 1.6% with risedronate.

Severity:
Malignancy is a clinically important event requiring medical intervention.

Reversibility:
Although some malignancies will respond to treatment, long-term survival will depend upon multiple factors and as such onset of malignancy is rarely considered reversible.

Long-term outcome:
New primary malignancy or progression of existing malignancy may be. fatal, life-threatening and long-term outcomes will likely be impacted.

Impact on quality of life:
Malignancy can be life-threatening and generally requires intervention e.g., surgery, radiation, and/or chemotherapy.

Risk factors and risk groups
General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, 2008[31]; World Health Organization [WHO], 2022[32]).

Preventability
No preventive measures are known.

Impact on the risk-benefit balance of the product
The potential risk of malignancy has been considered in the product benefit-risk assessment which supports a positive benefit-risk profile in the indicated populations.

Public health Impact:
Significant public health impact is not anticipated.

MedDRA terms:
SMQ (narrow): Malignancies

SVII.3.2. Presentation of the Missing Information

In line with the RMP of the reference product Prolia®, there is no missing information

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 (Prolia®).

Table 4: *Summary of safety concerns*

Summary of safety concerns	
Important identified risks	• Hypocalcemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions

	• Atypical femoral fracture • Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	• None

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	
Safety Concern	**Purpose/Description**
Hypocalcemia	To monitor the nature of hypocalcemia in patients treated with Bmab1000 in the post marketing environment
Skin infection leading to hospitalisation Infection	To monitor the nature of skin infections leading to hospitalisation and infections of any type reported in patients treated with Bmab1000 in the post marketing environment
Osteonecrosis of the jaw	To monitor the nature of ONJ in patients treated with Bmab1000 in the post marketing environment.
Atypical femoral fracture	To monitor the nature of AFF reported in patients treated with Bmab1000 in the post marketing environment
Fracture healing complications	To monitor the nature of fracture healing complications reported in patients treated with Bmab1000 in the post marketing environment
Malignancy	To monitor the nature of malignancy adverse events reported in patients treated with Bmab1000 in the post marketing environment.
Hypersensitivity reactions	To monitor the nature of hypersensitivity reported 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

Table 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
Hypocalcemia	**Routine risk communication**: • SmPC Section 4.2, 4.3, 4.4, and 4.8 • Package leaflet (PL) Section 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation for correction of hypocalcemia prior to initiating treatment with Denosumab and clinical monitoring of calcium levels during treatment with Denosumab is included in SmPC Section 4.4.
Skin infection leading to hospitalisation	**Routine risk communication:** • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None
Osteonecrosis of the jaw	**Routine risk communication:** • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendation for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedures, and temporary interruption of treatment if ONJ occurs is included in SmPC Section 4.4
Hypersensitivity reactions	**Routine risk communication:** • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None

Atypical femoral fracture	**Routine risk communication:** • SmPC Section 4.4 and 4.8 • PL Section 2 and 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 in SmPC Section 4.4.
Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	**Routine risk communication:** • SmPC Section 4.2 and 4.4, 4.8 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None
Important Potential Risk	
Fracture healing complications	**Routine risk communication:** • SmPC Section 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None
Infection	**Routine risk communication:** • SmPC Section 4.8 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None
Cardiovascular events	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None
Malignancy	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None

Missing information	
None	

ONJ = osteonecrosis of the jaw; PL = package 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 Bmab 1000 (denosumab) injections for osteoporosis and bone loss, including: • the risk of osteonecrosis of the jaw during treatment with Bmab 1000. • the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment; • the need to ensure good oral hygiene during treatment; • the need to inform their dentist of treatment with Bmab1000 and to contact their doctor or dentist if problems with the mouth or teeth occur during treatment.
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.

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

Hypocalcemia	**Routine risk minimization measures:** • SmPC sections 4.4 where recommendation regarding correction and monitoring of calcium levels is provided. • SmPC section 4.2, 4.3 and 4.8 • PL Section 2 and 4 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for hypocalcemia. **Additional pharmacovigilance activities:** • None
Skin infection leading to hospitalisation	**Routine risk minimization measures:** • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for infections. **Additional pharmacovigilance activities:** • None
Osteonecrosis of jaw	**Routine risk minimization measures:** • SmPC Section 4.4 where oral hygiene and dental management guidance is provided. • SmPC Section 4.8 • PL Section 2 and 4 **Additional risk minimization measures:** • Patient reminder card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for ONJ. **Additional pharmacovigilance activities:** • None
Hypersensitivity Reactions	**Routine risk minimization measures:** • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for hypersensitivity. **Additional pharmacovigilance activities:** • None
Atypical Femoral Fracture	**Routine risk minimization measures:** • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for Atypical Femoral fracture.

	• SmPC Section 4.8 • PL Section 2 and 4 **Additional risk minimization measures:** • None	**Additional pharmacovigilance activities:** • None
Hypercalcemia in Paediatric patients receiving denosumab and after treatment discontinuation	**Routine risk minimization measures:** • SmPC Section 4.2. • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None. **Additional pharmacovigilance activities:** • None
Important potential risk		
Fracture healing complications	**Routine risk minimization measures:** • SmPC Section 5.3 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for fracture healing complications **Additional pharmacovigilance activities:** • None
Infection	**Routine risk minimization measures:** • SmPC Section 4.8 • PL Section 4 **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Follow-up questionnaire for infections. **Additional pharmacovigilance activities:** • None
Cardiovascular events	**Routine risk minimization measures:** • None **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None. **Additional pharmacovigilance activities:** • None
Malignancy	**Routine risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

	Additional risk minimization measures: • None	• Follow-up questionnaire for malignancy. **Additional pharmacovigilance activities:** • None
Missing information		
None		

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 the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous injection.

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 about Bmab1000'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 patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report 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.

In the case of Bmab 1000, these routine measures are supplemented with additional risk minimization measures, mentioned under relevant risk 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

List of important risks and missing information	
Important identified risks	• Hypocalcemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing information	• None

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: Hypocalcemia

Important Identified Risk: Hypocalcemia	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. This risk was identified in the phase 3, randomized, double-blind, and placebo- or active-controlled studies of reference product Prolia®
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone

	resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance < 30 mUmin), dialysis, and some medications (Wing, Cecil Essentials of Medicine, 10th ed, 2020:757-766[7])).
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendation regarding correction and monitoring of calcium levels is provided. • SmPC Section 4.2, 4.3, and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 10: Important Identified Risk: Skin infection leading to hospitalization

Important Identified Risk: Skin infection leading to hospitalization	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. This risk was identified in phase 3, randomized, double-blind, placebo- or active-controlled studies of reference product Prolia®.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4, and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 11: Important identified Risk: Osteonecrosis of Jaw

Important Identified Risks: Osteonecrosis of Jaw	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk .This risk was identified in open-label long-term extensions to phase 3, randomized, double-blind, placebo-controlled studies of reference product Prolia®.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, Hematology, 2006;356-360[12]; Ruggiero et al, J Oneal Pract, 2006;2:7-14[13])
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimization measures: • Patient reminder card
Additional Pharmacovigilance activities	None

Table 12: Important identified Risk: Hypersensitivity reactions

Important Identified Risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Prolia®, this safety concern has been classified as important identified risk. This risk was identified in the post marketing setting of the reference product Prolia® based on a clinically plausible association between administration of denosumab and hypersensitivity reactions
Risk factors and risk groups	Known hypersensitivity to denosumab and any of its excipients
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 13: Important Identified risks: Atypical femoral fracture

Important identified risks: Atypical femoral fracture	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. This risk was identified in an open-label long-term extension to a phase 3, randomized, double-blind, active-controlled study of reference product Prolia®.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture (Meier et al, Arch Intern Med, 2012;172:930-936[18]; Giusti et al, Bone, 2011; 48(5):966-971[19]). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al, J Bone Miner Res, 2010;25:2267-2294[15]).
Risk minimisation measures	Routine risk minimization measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided • SmPC Section 4.8 • PL Section 2 and 4 Additional risk minimisation measures: None.
Additional Pharmacovigilance activities	None

Table 14: Important identified risks: hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation

Important Identified risk: hypercalcemia in pediatric patients receiving denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important identified risk. Data to evaluate safety concern were derived from Prolia® clinical trials in pediatric subjects with 01, XGEVA clinical studies, and reference product post marketing adverse event reporting involving pediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use.
Risk factors and risk groups	Paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis Imperfecta).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, 4.4, 4.8 • PL Section 2 Additional risk minimization measures: • None

Additional Pharmacovigilance activities	None

Table 15: Important potential risks: Fracture healing complication

Important potential risk: Fracture healing complication	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Prolia®, this safety concern has been classified as important potential risk. This is a theoretical risk based on the mechanism of action.
Risk factors and risk groups	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Hernandez et al, Acta Orthopaedica, 2012;83(6):653-660[20]; Gaston and Simpson, J Bone Joint Surg [Br], 2007;89-B:1553-1560[21]).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 5.3 Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 16: Important potential risks: Infection

Important potential risk: Infection	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Prolia®, this safety concern has been classified as important potential risk .This is considered a potential risk based on theoretical concerns which has not been substantiated in the extensive clinical study program or in the post marketing experience of the reference product.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • PL Section 4 Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 17: Important potential risks: Cardiovascular events

Important potential risk: cardiovascular events	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Prolia®, this safety concern has been classified as an important potential risk .This is a theoretical risk based on epidemiological data demonstrating elevated OPG in patients with cardiovascular disease.
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 cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz et al, J Clin Endocrinol Metab, 2005[22].;89:4246-4253; Hak et al, Arterioscler Thromb Vase Biol, 2000;20:1926-1931[33]). Risk factors for atherosclerosis include age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, Drug Safety, 2007;30(9):783-804[23].; Smith et al, Circulation, 2004;109(21):2613-2616[34].
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional Pharmacovigilance activities	None

Table 18: 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 Prolia®, this safety concern has been classified as important potential risk. This is considered a potential risk based on theoretical concerns and has not been substantiated in the extensive clinical study program or in the post marketing experience of reference product.
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al, Pharm Res.2008[31]; 25(9):209-72116; World Health Organization, Global Status Report on Noncommunicable Diseases 2010, http://www.who.int)[32].
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 1 – EudraVigilance Interface

Annex 2 - Summary of on-going and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed and on-going studies in the pharmacovigilance plan

Annex 4 - Specific adverse event follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

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

Annex 7 - Other supporting data (including referenced material)

Annex 8 - Summary of changes to the risk management plan over time

Annex 4 - Specific adverse event follow-up forms

Table of Contents

Targeted Follow-up Questionnaire (TFUQ) for Hypocalcemia

Targeted Follow-up Questionnaire (TFUQ) for Infection

Targeted Follow-up Questionnaire (TFUQ) for Osteonecrosis of the Jaw

Targeted Follow-up Questionnaire (TFUQ) for Post marketing reports of potential atypical facture

Targeted Follow-up Questionnaire (TFUQ) for fracture healing

Targeted Follow-up Questionnaire (TFUQ) for Malignancy

Targeted Follow-up Questionnaire (TFUQ) for Hypersensitivity

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

TARGETED FOLLOW UP FORM-HYPOCALCEMIA
BBL Case No.:

1. Patients/case administrative information (please included 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	
☐ Clinical trial	☐ Post-marketing
Study Number (if applicable)	
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 _____
Denosumab Dose	☐60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

TARGETED FOLLOW UP FORM-HYPOCALCEMIA
BBL Case No.:

	☐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. SIGNS AND SYMPTOMS (check all that apply)

☐Numbness (Specify if involving digits and/or peri-oral region) _____ ☐other _____	☐Convulsions ☐Muscle cramping ☐Syncope ☐Muscle twitching	☐Paraesthesia ☐Tetany ☐None

4. DIAGNOSIS (Check all that apply)

Serum calcium at time of event _____mg/dL ☐ Unknown

Please provide serum albumin result_____

Serum albumin at the time of event 4.0 g/dL? ☐ Yes☐ No ☐ Unknown

If yes, what were the ionized calcium levels? _____mmol/dL

Serum creatinine at time of event >2.0 X times upper limit of normal?

(Please provide result)_____☐ Yes☐ No ☐ Unknown

TARGETED FOLLOW UP FORM-HYPOCALCEMIA
BBL Case No.:

Hypocalcemia induced EKG changes (QT prolongation)? ☐ Yes☐ No ☐ Unknown

5. TREATMENT

Treated only as an outpatient	☐ Yes☐ No
If yes, route of calcium replacement	☐ IV☐ oral☐ unknown
Treated in the ER?	☐ Yes☐ No
If yes, route of calcium replacement	☐ IV☐ oral☐ unknown
Treatment included general hospital admission for calcium replacement	☐ Yes☐ No ☐ Unknown
If yes, route of calcium replacement	☐ IV☐ oral☐ unknown
Treatment included ICU admission?	☐ Yes☐ No ☐ Unknown
If yes, route of calcium replacement	☐ IV☐ oral☐ unknown
Overall length of hospital stay:	☐ =<1 day ☐ >1 day ☐= <7 days ☐ >7 days
Anit-arrhythmic medications?	☐ Yes☐ No ☐ Unknown
If yes, please provide the details such as name and date of treatment Anti-arrhythmic medications_____ _____	
Other treatment?	☐ Yes☐ No ☐ Unknown
If yes specify_____	

6. **RISK FACTORS (check all that apply)**

Medical History Risk Factors

Does the patient have any of the following risk factors: ☐ Yes☐ No

☐ Acute pancreatitis

☐ History of parathyroid disease

☐ History of malignancy (please specify)

☐ Hyperphosphatemia

☐ Recent surgery

TARGETED FOLLOW UP FORM-HYPOCALCEMIA
BBL Case No.:

☐ History of chronic renal disease

☐ History of hypoalbuminemia

☐ Hypoproteinemia

☐ Magnesium deficiency☐ Sepsis

If yes please provide dates and details: _____

_____

_____

_____

☐ Vitamin D deficiency (if patient has a history of vitamin D deficiency, were the vitamin D levels normal at the time of event?

Please provide the vitamin D Levels at the time of the hypocalcemia event.

_____

_____

_____

☐ Prior hypocalcemia event (before denosumab treatment)

Please provide dates and details of prior hypocalcemia event.

_____

_____

_____

Medical Risk Factors

Antineoplastic agents? (check which apply); ☐ cisplatin ☐ cytosine arabinoside ☐ other _____ _____☐ None

Antimicrobials? (check which apply); ☐ pentamidine ☐ketaconazole ☐ other _____

☐ None

Concomitant Medications

Taking vitamin D supplement? ☐ Yes☐ No ☐ Unknown (please provide dose and dates)_____

_____

Taking calcium supplement? ☐ Yes☐ No ☐ Unknown (please provide dose and dates)_____

_____

_____

TARGETED FOLLOW UP FORM-HYPOCALCEMIA
BBL Case No.:

Other Concomitant medications

Hypocalcemic event Resolved: ☐ Yes☐ No ☐ Unknown

If yes, What date (DD/MM/YYY)_____

REPORTER

Name:

Address:

State/ Province:

City:

Postal Code:

Country:

Email:

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-INFECTION
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	
☐ Clinical trial ☐ Post marketing	
Study Number (if applicable)	
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-INFECTION
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. SIGNS AND SYMPTOMS (check all that apply, provide dates of onset, resolution, if available)

☐Fever_____ ☐Cough_____ ☐Swelling____ Location___ ☐Shortness of breath _____	☐Pain_____ Location___ ☐Rash_____ Location___ ☐Prolonged fatigue_____ ☐Diarrhea____ _____	☐Discharge___ _____ Location_____ Description_____ _____ ☐Chills_____ _____ ☐Night sweats_____ ☐Other_____	☐Organ system affected: ☐Cardiac ☐Ear/nose ☐Throat ☐Gastrointestinal ☐Respiratory	☐Musculoskeletal (including joints) ☐Nervous (cerebrospinal fluid) ☐Skin Location _____ ☐Kidney/genito-urinary _____ ☐Systemic (bacteremia and/or sepsis) ☐other_____

Biocon Biologics
Transforming Healthcare. Transforming Lives.

TARGETED FOLLOW UP FORM-INFECTION
BBL Case No.:

4. EVALUATIONS, DIAGNOSIS AND LABORATORY MEASURES (please attach copy of report):

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached YIN	

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached YIN	

TARGETED FOLLOW UP FORM-INFECTION
BBL Case No.:

5. REPORTS/RELEVANT FINDINGS (Please provide dates, baseline information and indicate attachments if available)

☐Cardiac infections	☐ Endocarditis _____ ☐ Pericarditis (purulent; tuberculous) _____ ☐ Other, please specify: _____
☐ Ear and labyrinth infections	☐ Otitis media _____ ☐ Otitis externa _____ ☐ Other, please specify: _____
☐ Gastrointestinal/abdominal infections	☐ Colitis _____ ☐ Diverticulitis _____ ☐ Appendicitis _____ ☐ Abdominal sepsis (including peritonitis) _____ ☐ Hepatic abscess _____ ☐ Hepatitis B _____ ☐ Hepatitis C _____ ☐ Other, please specify: _____
☐ Musculoskeletal and connective tissue infections	☐ Osteomyelitis_____ ☐ Septic arthritis _____ ☐ Other, please specify: _____
☐Nervous system infections	☐ Meningitis_____ ☐ Encephalitis _____ ☐ Other, please specify: _____
☐ Respiratory tract infections	☐ Pneumonia _____ ☐ Pulmonary TB _____
☐ Mycobacterium tuberculosis _____	☐ Lung abscess ☐ Legionella pneumonia ☐Mycoplasma pneumonia ☐ Other, please specify:
☐ Kidney and genito-urinary tract infections	☐ Cystitis ☐ Pyelonephritis ☐ Urinary tract infection

TARGETED FOLLOW UP FORM-INFECTION
BBL Case No.:

	☐ Other, please specify: _
☐ Systemic infections	☐ Bacteremia _____ ☐ Sepsis _____ ☐ Toxic shock syndrome _____ ☐ Other, please specify:
☐Wound and skin infections	☐Cellulitis _____ ☐ Erysipelas _____ ☐ Necrotizing fasciitis _____ ☐ Abscess _____ ☐Other skin infections, please specify: _____
☐ Opportunistic infections	☐ Aspergillus (invasive forms only) _____ ☐ Blastomycosis pulmonary or extra-pulmonary infections _ ☐ Candidiasis systemic _____ ☐ Coccidioidomycosis secondary/systemic _____ ☐ Cryptococcal infection- pulmonary and non-pulmonary ☐ Cytomegalovirus - include systemic site _____ ☐ Herpes simplex (meningitis or encephalitis) _____ ☐Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes) _____ ☐Histoplasma infections - chronic disseminated or severe acute ☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin _____ ☐ Mycobacterium tuberculosis _____ ☐Non-tuberculosis mycobacterium _____ ☐Nocardia infection - of brain, lungs, kidney, skin _____ ☐Paracoccidioides infections of lungs, skin other _____ ☐Pneumocystis carinii pneumonia _____ ☐Sporotrichosis - disseminated infections _____ ☐ Toxoplasmosis encephalitis or disseminated _____ ☐Other opportunistic infections, please specify: _____

TARGETED FOLLOW UP FORM-INFECTION
BBL Case No.:

	☐Other infections, please specify: _____ ☐ Parasitic evaluation (ova, etc.) _____

DIAGNOSTICS

☐ Cultures done	☐ Yes☐ No ☐ Unknown If yes, please specify_____
☐ Blood culture	☐ Culture positive ☐ Yes☐ No ☐ Unknown If yes, which ☐ Bacterial ☐ Fungal ☐ Viral Pathogen identified: _____
☐ Urine Culture	☐ Culture positive ☐ Yes☐ No ☐ Unknown If yes, which ☐ Bacterial ☐ Fungal ☐ Viral Pathogen identified: _____
☐ Sputum Culture	☐ Culture positive ☐ Yes☐ No ☐ Unknown If yes, which ☐ Bacterial ☐ Fungal ☐ Viral Pathogen identified: _____
☐Synovial culture	☐ Culture positive ☐ Yes☐ No ☐ Unknown If yes, which ☐ Bacterial ☐ Fungal ☐ Viral Pathogen identified: _____
☐ Cerebrospinal fluid culture	☐ Culture positive ☐ Yes☐ No ☐ Unknown If yes, which ☐ Bacterial ☐ Fungal ☐ Viral Pathogen identified: _____
☐ Tissue culture	If yes, specify ☐ Brain ☐ Lung ☐ Liver ☐ Kidney ☐ Skin ☐ Bone ☐ Other ☐ Culture positive ☐ Yes☐ No ☐ Unknown If yes, which ☐ Bacterial ☐ Fungal ☐ Viral

TARGETED FOLLOW UP FORM-INFECTION
BBL Case No.:

	Pathogen identified: _____
☐ Catheter Tip/line	☐ Culture positive ☐ Yes☐ No ☐ Unknown If yes, which ☐ Bacterial ☐ Fungal ☐ Viral Pathogen identified: _____
☐ PPD Placement	☐ Yes☐ No ☐ Unknown If yes, PPD positive ☐ Yes☐ No ☐ Unknown _____ _____
☐ Parasitic evaluation (ova, etc) _____	☐ X-ray ☐ Yes☐ No ☐ Unknown_____ ☐ MRI ☐ Yes☐ No ☐ Unknown_____ ☐ CT scan ☐ Yes☐ No ☐ Unknown_____ _____ ☐ Bone Scan ☐ Yes☐ No ☐ Unknown_____ _____ ☐ Other_____ ☐ Rapid Test_____ ☐ serum titres_____ ☐ Hospital discharge report_____ _____ ☐ other consult report_____ _____ ☐ Provide final diagnosis and treatment if available (please specify)_____

TARGETED FOLLOW UP FORM-INFECTION
BBL Case No.:

	_____ ☐ outcome and resolution date_____ _____

6. TREATMENT

☐ ER antibiotics	☐ Yes☐ No ☐ Unknown If yes, route ☐ IV ☐ Oral ☐ SC ☐ Both oral and IV Pathogen identified: _____
☐ Required hospital admission	☐ Yes☐ No ☐ Unknown ☐ ICU admission ☐Yes☐ No ☐ Unknown If yes, the reason for ICU admission_____ Overall length of hospital stay ☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days _____ ☐ In-hospital antibiotics ☐ Yes☐ No ☐ Unknown ☐ If yes, route of administration ☐ IV ☐ Oral ☐ Both oral and IV ☐ other in-hospital treatment ☐ Antivirals ☐ Yes☐ No ☐ Unknown If yes, route of administration ☐ IV ☐ oral ☐ Antifungals ☐ Yes☐ No ☐ Unknown If yes, route of administration ☐IV ☐ oral ☐ Surgery ☐ Yes☐ No ☐ Unknown ☐ Hyperbaric oxygen ☐ Yes☐ No ☐ Unknown

TARGETED FOLLOW UP FORM-INFECTION
BBL Case No.:

7. PATIENT HISTORY /RISK FACTORS (Please provide history, dates, severity of reaction and intervention)

Please specify any post-operative complications, chronic disease or infection, etc.

☐ Chronic lung disease_____

☐ Hepatitis_____

☐ Chronic kidney disease_____

☐ Liver disease_____

☐ congenital infection /malformations_____

☐ Osteomyelitis_____

☐HIV_____

☐ Diabetes mellitus_____

☐ Cancer (specify)_____

☐ Recent wounds/infections_____

☐ Immunosuppression_____

☐ Known exposure to TNF inhibitors_____

☐ Chemotherapy_____

☐ Malnutrition /failure to thrive_____

☐ Exposure to infectious agents_____

- ☐ Personal contact_____ ☐ Body Fluids_____
- ☐ Share personal items (razor, needles, etc) _____
- ☐ Potentially contaminated food/liquid_____
- ☐ Hospital acquired_____
- ☐ Other _____

☐ Steroid exposure_____

☐ Insect/tick bite_____

☐ Drug or IV drug abuse: type _____

Amount_____

Frequency_____

TARGETED FOLLOW UP FORM-INFECTION
BBL Case No.:

☐ Alcohol/tobacco use: Type:_____

Amount_____

Frequency_____

☐ Indwelling catheters_____

☐ Recent skin injury _____

☐ Recent travel (specify)_____

☐ Exposure to animals /zoonotic disease (exposure to infected animal) _____

_____

☐ Unprotected sex_____

☐ Immobility _____

☐ Indwelling catheters_____

☐ Nursing home resident_____

☐ Occupational exposure_____

☐ Ostomy_____

☐ Post influenza_____

☐ Surgery < 30 days _____

☐ TB exposure _____

☐ other history/risk factors_____

REPORTER

Name:

Address:

City:

Country:

Email:

State/ Province:

Postal Code:

TARGETED FOLLOW UP FORM-INFECTION
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: _____

_____

_____

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

1. Patients/case administrative information (please included 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	
☐ Clinical trial	☐ Post-marketing
Study Number (if applicable)	
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 _____
Denosumab Dose	☐60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

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

	☐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 probe that has persisted for more than eight weeks:

☐ Yes☐ No ☐ Unknown_____

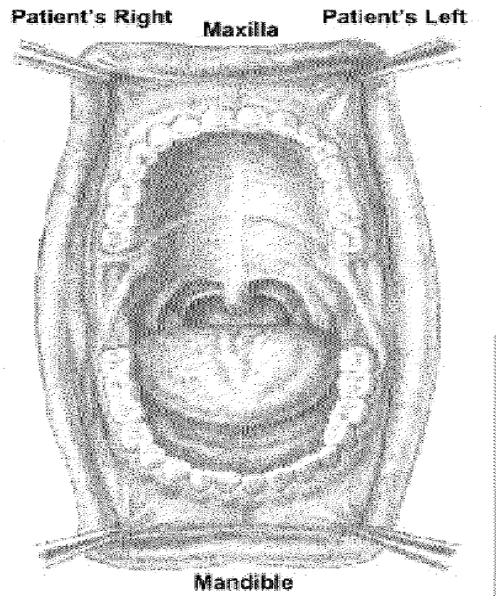
Prior history of radiation therapy to jaw:

☐ Yes☐ No ☐ Unknown_____

Prior history of metastatic disease of jaw:

☐ Yes☐ No ☐ Unknown; please describe _____
_____

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – 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 FOR DENOSUMAB – 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

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 _____

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

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

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 I ☐ Type II

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – 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 FOR DENOSUMAB – ATYPICAL FEMUR FRACTURE
BBL Case No.:

1. Patients/case administrative information (please included 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	
☐ Clinical trial	☐ Post-marketing
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 FOR DENOSUMAB – ATYPICAL FEMUR 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 FOR DENOSUMAB – ATYPICAL FEMUR 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 FOR DENOSUMAB – ATYPICAL FEMUR 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 (S ☐ Bisphosphonate (please indicate) ☐ Intravenous ☐ oral If yes, how long has therapy been received? (months, years)

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – ATYPICAL FEMUR 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 FOR DENOSUMAB – ATYPICAL FEMUR 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: _____

_____

_____

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – FRACTURE HEALING
BBL Case No.:

1. Patients/case administrative information (please included 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	
☐ Clinical trial	☐ Post marketing
Study Number (if applicable)	
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 _____
Denosumab Dose	☐60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – FRACTURE HEALING
BBL Case No.:

	☐Other (please specify)_____ ☐ Don't know
Denosumab Exposure	Denosumab first administered (date)_____(Study#) 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. Diagnosis (check all that apply, please indicate dates as DD/MM/YYYY):

Date of Fracture	
Date of fracture delayed healing	
Date of fracture non-healing	
Fracture to upper body	Specify location (check all apply): ☐Cervical spine ☐ Clavicle ☐ Hand/metacarpal/phalange ☐ Head/face/skull ☐ Humerus ☐ Olecranon ☐ Radius ☐ Rib ☐ Scapula ☐ Sholder ☐ Sternum ☐ Ulna

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – FRACTURE HEALING
BBL Case No.:

	☐ Wrist/Carpal ☐ Other location (specify): _____ _____
Fracture to Lower body (i.e., Below waist)	Specify location (check all apply): ☐Ankle ☐ Femur (Please specify location: neck subtrochanteric, mid shaft etc) _____ _____ ☐ Foot/larsal/metatarsal/phalange ☐ Hip ☐ Patella ☐ Pelvis ☐ Tibia ☐ Fibula ☐ Other: _____ _____
Type of trauma reported at time of fracture (check one):	☐Severe Trauma (e.g., falling from roof, motor vehicle accident) ☐ Minimal trauma (e.g., falling from standing position or less) ☐ Non-traumatic
Characteristics of fracture (check all apply)	☐Comminuted ☐ Compound ☐ Pathologic ☐ Poor Alignment ☐ Poor immobilization of segments ☐ Soft tissue injury ☐ Unknown

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

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – FRACTURE HEALING
BBL Case No.:

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

Did the fracture heal (union)? ☐ Yes☐ No ☐ Unknown

If yes, provide date of union (DD/MM/YYYY): _____

If yes, was healing confirmed through imaging? ☐ Yes☐ No ☐ Unknown

If yes, what diagnostic imaging (check all that apply): ☐ X-rays☐ CT-scan ☐ MRI

If yes, is patient able to walk without assistance? ☐ Yes☐ No ☐ Unknown

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

☐Current smoker /tobacco use: _____
_____
_____
_____

☐History or current corticosteroid use: _____
_____
_____
_____

☐ Prior fracture history _____
_____
_____
_____

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – FRACTURE HEALING
BBL Case No.:

☐ Diabetes _____

_____

_____

REPORTER

Name:

Address: State/ Province:

City: Postal Code:

Country:

Email:

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 FOR DENOSUMAB - MALIGNANCIES
BBL Case No.:

1. Patients Details:

Patient's Initials	
Age/Date of birth	
Gender	
Weight	
Height	

2. Drug information at the time of event:

Tradename	
Strength	
Batch number	
Expiry date	
Route of administration	
Dose	
Dose frequency	
Start date	
Stop date	
Onset date for event	

3. Event details:

Date of event onset (DD/MM/YYYY):

Is this a new primary malignancy? Yes ☐ No ☐ Unknown ☐

If no, is this a recurrence of a previous cancer? Yes ☐ No ☐Unknown ☐

Does patient have history of other malignancy? Yes ☐ No ☐ Unknown ☐

If yes, date of prior cancer (DD/MM/YYYY): ___/___/

Tumor stage, if known: _____

TARGETED FOLLOW-UP FORM FOR DENOSUMAB - MALIGNANCIES
BBL Case No.:

Primary site of malignancy: _____

Tumor **Stage:**

Tumor Size (Check which one applies):

TX ☐ TO ☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐

Tumor Grade (Check which one applies):

GX ☐ G1 ☐ G2 ☐ G3 ☐

Localized (no regional involvement/no distant metastasis)? Yes ☐ No ☐

(If yes, skip next 2 questions)

Lymph Node Involvement (Check which one applies):

NX ☐ N1 ☐ N2 ☐ N3 ☐

Metastases (Check which one applies):

MX □ MO□ M1 □

TREATMENT:

Hospitalized?	Yes ☐	No☐	Unknown	☐
ICU admission?	Yes ☐	No☐	Unknown	☐
Overall length of hospital stay:	1 day ☐	> 1 day or <=7days ☐	> 7 days	☐
Surgical treatment?	Yes ☐	No☐	Unknown	☐
Chemotherapy (includes biologics)?	Yes ☐	No☐	Unknown	☐
Hormonal treatment?	Yes ☐	No☐	Unknown	☐
Radiation treatment?	Yes ☐	No☐	Unknown	☐

TARGETED FOLLOW-UP FORM FOR DENOSUMAB - MALIGNANCIES
BBL Case No.:

Bone marrow transplant? Yes ☐ No☐ Unknown ☐

If yes Atuologus ☐ ☐ Heterologus

Was the malignancy treated with curative intention? Yes☐ No☐ Unknown ☐

RISK FACTORS (Check all that apply):

Smoking ☐

Prior Malignancy ☐

Positive Family History (Check all that apply):

Same cancer ☐

Different cancer ☐

Prior therapeutic radiation exposure ☐

Environmental exposure ☐

Specify: _____

4. 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 FOR DENOSUMAB – HYPERSENSITIVITY
BBL Case No.:

1. Patients/case administrative information (please included 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	
☐ Clinical trial	☐ Post marketing
Study Number (if applicable)	
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 _____
Denosumab Dose	☐60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – HYPERSENSITIVITY
BBL Case No.:

	☐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_____
☐ Denosumab Antibody Testing performed: (provide dates and results):_____ _____ If not performed, do you have interest in antibody testing? ☐ Yes☐ No _____ _____	

3. SIGNS AND SYMPTOMS (check all that apply)

☐Anaphylaxis ☐Angioneurotic edema ☐Colic	☐Facial edema ☐Hypotension ☐Laryngeal edema	☐Rash ☐Shortness of breath ☐Stridor	☐Diarrhea: ☐Pruritis ☐Swelling	☐Tachycardia ☐Urticaria ☐Wheezing ☐Other _____

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – HYPERSENSITIVITY
BBL Case No.:

4. EVALUATIONS, DIAGNOSIS AND LABORATORY MEASURES (please attach copy of report):

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached YIN	
Results at Baseline (prior to BBL drug)					
CBC with differential					
WBC					
RBC					
Eosinophils					
Hgb					
Hct					
Platelets					
Other					
Albumin					
Total Protein					
BUN					
Serum Creatinine					
ALT					
AST					
ALP					
Bilirubin					
Calcium					
K+					
Na+					
Phosphorus					
Mg++					
Cl-					
CrCl					

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached YIN	
Result at the time of event					
CBC with differential					
WBC					
RBC					
Eosinophils					
Hgb					
Hct					
Platelets					
Other					
Albumin					
Total Protein					
BUN					
Serum Creatinine					
ALT					
AST					
ALP					
Bilirubin					
Calcium					
K+					
Na+					
Phosphorus					
Mg++					
Cl-					
CrCl					

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – HYPERSENSITIVITY
BBL Case No.:

5. TREATMENT

☐ ER corticosteroids	Route ☐ IV☐ oral
☐ ER anti-histamines	Route ☐ IV☐ oral☐ both oral and IV
☐ Required hospital admission	☐ Yes☐ No
☐ overall length of hospital stay	☐ <1 day ☐ >1 day or <7 days☐ >7 days
☐ICU admission	☐ Yes☐ No ☐ Unknown
☐ overall length of hospital stay	☐ <1 day ☐ >1 day or <7 days☐ >7 days
☐ In-hospital corticosteroids	Route ☐ IV☐ oral☐ both oral and IV
☐ other in-hospital treatment	☐ IV vasopressors ☐ Yes ☐ No ☐ Unknown ☐ Intubation/mechanical ventilation ☐ Yes ☐ No ☐ Unknown

☐ Hospital admissions/Discharge report (please attach if available)_____

CONCOMITANT MEDICATION

☐ ACE Inhibitors
☐ Allopurinol
☐ Cancer chemotherapy
☐ Dapsone
☐ IV contrast
☐ NSAIDS/aspirin
☐ Penicillamine
☐ Rifampin

☐ Anticonvulsants(check which apply):
- ☐ Phenytoin
- ☐ Carbamazepine
- ☐ Phenobarbital

☐ Antibiotics (check which apply):
- ☐ Beta-lactams including penicillin and cephalosporin
- ☐ Macrolides
- ☐ Sulfonamides
- ☐ Quniolones

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – HYPERSENSITIVITY
BBL Case No.:

☐ Hypersensitivity event resolved ☐ Yes☐ No ☐ Unknown

If yes, date (DD/MM/YYYY): _____

☐ Final diagnosis or etiology (incl, start date). Please send supporting documents for diagnosis__

_____

_____

☐ other consult report (please indicate any attachments)_____

_____

_____

REPORTER

Name:

Address:

City:

Country:

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.

TARGETED FOLLOW-UP FORM FOR DENOSUMAB – HYPERSENSITIVITY
BBL Case No.:

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 with national competent authority prior to launch.

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

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) 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 will 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:

- the risk of osteonecrosis of the jaw during treatment with Bmab1000;
- the need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment;
- the need to ensure good oral hygiene during treatment;
- the need to inform their dentist of treatment with Bmab1000 and to contact their doctor and dentist if problems with the mouth or teeth occur during treatment.