EU Risk Management Plan (RMP) for Obodence (Denosumab)

RMP version to be assessed as part of this application:

RMP version number:	1.2
Data lock point for this RMP:	Sep 24, 2024
Date of final sign off:	Oct 09, 2024
Rationale for submitting an updated RMP:	Not applicable.
Summary of significant changes in this RMP:	Not applicable.
Other RMP versions under evaluation:	Not applicable.

Details of the currently approved RMP:

Version number:	Not applicable.
Approved with procedure:	Not applicable.
Date of approval (opinion date):	Not applicable.

QPPV name:	John Hart

The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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AIDS	Acquired immunodeficiency syndrome
ATC	Anatomical therapeutic chemical classification
AUC	Area under the plasma concentration-time curve
DNA	Deoxyribonucleic acid
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
Fc	fragment crystallisable
FREEDOM	Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months
HIV	Human immunodeficiency virus
Ig	Immunoglobulin
INN	International nonproprietary name
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
OPG	Osteoprotegerin
OPG-Fc	Osteoprotegerin bound to fragment crystallisable
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RANK	Receptor activator of nuclear factor κB
RANKL	Receptor activator of nuclear factor κB ligand
RMP	Risk Management Plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
TNF	Tumour necrosis factor
TRAIL	Tumour necrosis factor-related apoptosis inducing ligand
US	United States

Part I: Product(s) overview

Table Part I.1: Product(s) overview

Active substance(s) (INN or common name)	Denosumab
Pharmacotherapeutic group(s) (ATC Code)	M05BX04
Marketing Authorisation Applicant	Samsung Bioepis NL B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	OBODENCE
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Denosumab is a fully human monoclonal IgG2 antibody against the receptor activator of nuclear factor κB (RANK) ligand (RANKL).
	Summary of mode of action: Denosumab targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.
	Important information about its composition: Denosumab is produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the Product Information	Product Information
Indication(s) in the EEA	**Current:** Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral, and hip fractures.

Table Part I.1: Product(s) overview

	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, denosumab significantly reduces the risk of vertebral fractures. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
Dosage in the EEA	**Current:** The recommended dose is 60 mg denosumab administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.
Pharmaceutical form(s) and strengths	**Current:** Solution for injection. Each pre-filled syringe contains 60 mg of denosumab in 1.0 mL of solution (60 mg/mL).
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC = anatomical therapeutic chemical classification; DNA = deoxyribonucleic acid; EEA = European Economic Area; EU = European Union; Fc = fragment crystallisable; IgG2 = immunoglobulin G2; INN = international non-proprietary name.

Part II: Safety specification

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

Based on the Guideline on good pharmacovigilance practices Module V – Risk management systems (Rev. 2), this module is not applicable for the medicinal product(s) seeking a marketing authorisation according to Article 10(4) of Directive 2001/83/EC, as amended.

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

A series of *in vitro* pharmacodynamics studies were performed in order to demonstrate the similarity between OBODENCE (denosumab biosimilar) and the reference product PROLIA (denosumab). The data from the comparative structural analyses, physicochemical analyses, as well as *in vitro* non-clinical studies and functional assays demonstrated the similarity between OBODENCE and PROLIA. Following a stepwise and risk-based approach, *in vivo* non-clinical studies for OBODENCE were not deemed necessary for the development of OBODENCE.

In addition, no safety pharmacology, genotoxicity, carcinogenicity, reproductive and development toxicity, local tolerance, or other toxicity studies were conducted fully in line with the European Medicines Agency (EMA) guideline EMA/CHMP/BMWP/42832/2005 Rev 1.

A detailed description of the non-clinical development programme for OBODENCE is provided in the eCTD Module 2.4 (Non-Clinical Overview).

Since the overall non-clinical programme for OBODENCE showed that the toxicity profile of OBODENCE was similar to that of the reference product PROLIA, the key non-clinical safety findings in Table SII.1 are based on the data collected for the reference product PROLIA.

Table SII.1: Key safety findings from non-clinical studies and relevance to human use

Key safety findings	Relevance to human usage
Transient decrease in calcium levels Calcium levels were transiently decreased and parathyroid hormone levels transiently increased in ovariectomised monkeys treated with denosumab [1].	Hypocalcaemia represents an important identified risk of denosumab (refer to Part II: Module SVII).
Delayed callus remodelling Denosumab was found to delay callus remodelling in human RANKL knock-in mouse animal model, though callus strength and stiffness were greater in treated animals than in controls [2]. There was no effect of denosumab on fracture union or initial callus formation in this animal model.	Fracture healing complications represent a theoretical, important potential risk of denosumab (refer to Part II: Module SVII).
Immunogenicity Denosumab was highly immunogenic in 1-, 6-, and 12-month studies in cynomolgus monkeys [1].	The relevance of this finding to human use cannot be drawn from the non-clinical data. While a high prevalence of binding and/or neutralising antibodies was seen at all doses in cynomolgus monkeys treated with denosumab, no corresponding production of antibodies was seen in humans. In clinical studies with denosumab, neutralising antibodies to denosumab have not been detected and less than 1% of the subjects

Key safety findings	Relevance to human usage
	treated with denosumab for up to 5 years developed non-neutralising binding antibodies, which were mostly transient, with no evidence of altered pharmacokinetics, toxicity, or clinical response [1].
Reproductive and developmental toxicity Denosumab is a potent inhibitor of RANKL. In non-clinical studies conducted in knock-out mice lacking RANK or RANKL, impairment of lymph node formation was observed in the foetus [3]. An absence of lactation due to inhibition of mammary gland maturation (lobuloalveolar gland development during pregnancy) was also observed in knock-out mice lacking RANK or RANKL [4, 5]. Absence of osteoclasts and bone resorption in RANK/RANKL knock-out mice during skeletal development results in osteopetrosis and failure of tooth eruption [6, 7]. In neonatal pre-weaning rats, inhibition of RANKL with high doses of a construct of OPG-Fc was associated with inhibition of bone growth and tooth eruption [1].	The use of denosumab during pregnancy is not recommended. It is unknown whether denosumab is excreted in human milk. A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made, considering the benefit of breastfeeding to the newborn/infant and the benefit of denosumab therapy to the woman. The safety of denosumab has not been established in the paediatric population other than skeletally mature paediatric patients with giant cell tumour of bone. Denosumab should not be used in paediatric population because of safety concerns of serious hypercalcaemia (refer to Part II: Module SVII), and potential inhibition of bone growth and lack of tooth eruption.
Denosumab had no effect on male or female fertility [1]. At AUC exposures up to 100-fold higher than the human exposure (60 mg every 6 months), denosumab showed no evidence of impaired fertility in cynomolgus monkeys [8].	There are no data on the effect of denosumab on human fertility.
In a embryo-foetal development study in 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 (60 mg every 6 months), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined [8]. In a pre-postnatal development study in cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 119-fold higher than the human dose (60 mg every 6 months), there were increased	The safety of denosumab has not been established in the paediatric population other than in the case of skeletally mature paediatric patients with giant cell tumour of bone. Denosumab 60 mg should not be used in paediatric population because of safety concerns of serious hypercalcaemia (refer to Part II: Module SVII), and potential inhibition of bone growth and lack of tooth eruption.

Key safety findings	Relevance to human usage
stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment, absence of peripheral lymph nodes; and decreased neonatal growth [8]. A no observed adverse effect level for reproductive effects was not established. There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal [8]. Following a 6-month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal (relation to treatment uncertain) [8]. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality, osteopetrosis and reduced haematopoiesis, absence of peripheral lymph nodes, and decreased neonatal growth [8]. In general, the effects observed in mothers and infants were consistent with the pharmacological action of denosumab and similar to those seen in RANKL-deficient humans. Thus, denosumab given early in pregnancy did not cause maternal or foetal harm, however, denosumab given throughout pregnancy did have an impact on the mother at delivery, the foetus in late gestation, and on the viability of the infant [8]. Adolescent primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates [1]. In nonhuman primates dosed for 1 year with up to 50 mg/kg of denosumab, no changes in adolescent mammary tissue were observed [8].	Molar tooth eruption in rats and humans is considered to share similar mechanisms. Molar eruption is often inhibited in osteopetrotic humans with impaired osteoclast activity and delayed tooth eruption has been reported in children with osteogenesis imperfecta treated with bis phosphonates [8]. With respect to safety of denosumab in adolescent girls, human mammary gland development would be expected to resemble that of the nonhuman primate. Based on the lack of findings in multiple nonhuman primate studies, effects on development of the lactating mammary tissue is not anticipated to be a significant issue. Further, since denosumab clears from the circulation, it is not anticipated that there will be long-term consequences in mammary gland development [8].

Key safety findings	Relevance to human usage
Carcinogenicity No carcinogenicity studies were conducted in accordance with available regulatory guidance. Ovariectomised monkeys treated for up to 16 months with denosumab showed no evidence of pre-neoplastic lesions. However, potential to interfere with the immune system cannot be discounted [1].	The multiple signalling pathways involved in OPG effects, and by analogy possibly also relevant in the case of denosumab, indicate a potential for dysregulation of functions that could be critical in e.g., cancer pathogenesis. Malignancy and infection represent important potential risks of denosumab (refer to Part II: Module SVII).

AUC = area under the plasma concentration-time curve; OPG = osteoprotegerin; OPG-Fc = osteoprotegerin bound to fragment crystallisable; RANK = receptor activator of nuclear factor κB; RANKL = receptor activator of nuclear factor κB ligand

Part II: Module SIII - Clinical trial exposure

The clinical development programme for OBODENCE included a single-dose Phase I study in healthy male subjects (SB16-1001), comparing the pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of denosumab (OBODENCE and PROLIA), and a comparative Phase III study in postmenopausal women with osteoporosis (SB16-3001).

Study SB16-3001 was a Phase III randomised, double-blind, multicentre study aimed to compare the efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity between OBODENCE and the reference product PROLIA.

The subject exposure to OBODENCE and PROLIA, including the treatment duration, in study SB16-3001 is provided in Table SIII.1, while the subjects' demographic characteristics are detailed in Table SIII.2 (for study SB16-1001) and Table SIII.3 (for study SB16-3001).

A detailed description of the clinical development programme for OBODENCE is provided in the eCTD Module 2.5 (Clinical Overview) and Module 2.7.4 (Summary of Clinical Safety).

The safety profile of denosumab and its positive benefit-risk balance is based solely on the data collected for the reference product PROLIA [9, 10], taking into account data collected in studies SB16-1001 and SB16-3001.

Table SIII.1: Summary of exposure to investigational product in study SB16-3001 (Safety Set 1)

Exposure	OBODENCE (N = 225)	PROLIA (EU sourced)			Total (N = 456)[b]
		Overall (N = 231)	OBODENCE (N = 100) [a]	PROLIA (N = 101) [a]	
Number of IP administration, n (%)					
1 injection	9 (4.0)	20 (8.7)	-	-	29 (6.4)
2 injections	10 (4.4)	10 (4.3)	-	-	20 (4.4)
3 injections	206 (91.6)	201 (87.0)	100 (100.0)	101 (100.0)	407 (89.3)
Duration of exposure to IP (days) in Main period (up to Month 12)					
n	225	231	-	-	456
Mean (SD)	351.8 (45.74)	338.2 (74.50)	-	-	344.9 (62.31)
Median	359.0	359.0	-	-	359.0
Min, max	16, 372	6, 372	-	-	6, 372
Duration of exposure to IP (days) in Overall study period (up to Month 18)					
n	225	231	100	101	456
Mean (SD)	518.5 (88.04)	496.4 (129.03)	543.4 (3.99)	542.9 (4.29)	507.3 (111.15)
Median	541.0	541.0	542.0	541.0	541.0
Min, max	16, 553	6, 561	540, 561	523, 554	6, 561

IP = investigational product; max = maximum; min = minimum; SD = standard deviation.

[a] Based on subjects in the Safety Set 2, PROLIA+OBODENCE and PROLIA+PROLIA may not add up to PROLIA Overall.

[b] Among 457 randomised subjects, one subject did not receive the IP. Therefore, 456 subjects were evaluated in the Safety Set.

Note: Percentages were based on the number of subjects in the Safety Set 1.

Table SIII.2: Demographic characteristics of subjects in study SB16-1001 (Randomised Set)

Characteristics	OBODENCE (N = 56)	PROLIA (EU sourced) (N = 56)	PROLIA (US sourced) (N = 56)	Total (N = 168)
Age (years)				
Mean (SD)	39.1 (7.71)	40.2 (8.13)	40.8 (7.88)	40.0 (7.89)
Median	39.5	40.5	41.0	41.0
Min, max	28, 55	28, 55	28, 55	28, 55
Sex, n (%)				
Male	56 (100.0)	56 (100.0)	56 (100.0)	168 (100.0)
Race, n (%)				
White	38 (67.9)	36 (64.3)	41 (73.2)	115 (68.5)
Black or African American	17 (30.4)	17 (30.4)	12 (21.4)	46 (27.4)
Asian	1 (1.8)	3 (5.4)	3 (5.4)	7 (4.2)
Ethnicity, n (%)				
Hispanic or Latino	10 (17.9)	9 (16.1)	4 (7.1)	23 (13.7)
Not Hispanic or Latino	46 (82.1)	47 (83.9)	52 (92.9)	145 (86.3)

EU = European Union; max = maximum; min = minimum; SD = standard deviation; US = United States.
Note: Percentages were based on the number of subjects in the Randomised Set.

Table SIII.3: Demographic characteristics by treatment groups for study SB16-3001 (Randomised Set)

Exposure	OBODENCE (N = 225)	PROLIA			Total (N = 457)
		Overall (N = 232)	OBODENCE (N = 100) [a]	PROLIA (N = 101) [a]	
Age (years)					
Mean (SD)	66.5 (5.87)	66.3 (6.03)	65.8 (5.73)	66.4 (6.05)	66.4 (5.95)
Median	67.0	66.0	66.0	66.0	66.0
Min, max	55, 81	52, 80	55, 77	55, 80	52, 81
Age group, n (%)					
< 65 years	89 (39.6)	95 (40.9)	39 (39.0)	44 (43.6)	184 (40.3)
≥ 65 years	136 (60.4)	137 (59.1)	61 (61.0)	57 (56.4)	273 (59.7)
Race, n (%)					
Asian	18 (8.0)	23 (9.9)	10 (10.0)	11 (10.9)	41 (9.0)
White	207 (92.0)	208 (89.7)	89 (89.0)	90 (89.1)	415 (90.8)
Other	0 (0.0)	1 (0.4)	1 (1.0)	0 (0.0)	1 (0.2)
Ethnicity, n (%)					
Hispanic or Latino	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Other	225 (100.0)	231 (99.6)	100 (100.0)	101 (100.0)	456 (99.8)

[a] Based on subjects who had re-randomisation at Month 12, PROLIA+ OBODENCE and PROLIA+PROLIA may not add up to PROLIA overall.
Note: Percentages were based on the number of subjects in the Randomised Set.

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

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

The summary of important exclusion criteria presented in this section is based on the exclusion criteria in the comparative Phase III study SB16-3001 in postmenopausal women with osteoporosis. However, any limitations of the populations not studied in clinical trials are solely based on the data available for the reference product PROLIA [9, 10].

Uncorrected vitamin D deficiency (defined as serum 25-hydroxyvitamin D level < 20 ng/mL [50 nmol/L])

Not able to tolerate long-term calcium or vitamin D supplementation or had malabsorption of calcium or vitamin D supplements

Reason for exclusion	These exclusion criteria were selected to minimise the risk to participants enrolled in the comparative study. Patients with uncorrected vitamin D deficiency or patients unable to tolerate long-term calcium and/or vitamin D supplementation are at increased risk of developing hypocalcaemia during denosumab therapy.
Is it considered to be included as missing information?	No
Rationale	Patients treated with denosumab must be adequately supplemented with calcium and vitamin D during therapy with denosumab. As such, the excluded population is not expected to be treated in clinical practice.

Hypercalcaemia or hypocalcaemia (defined as albumin-adjusted serum calcium for hypocalcaemia < 2.1 mmol/L [8.4 mg/dL] or for hypercalcaemia > 2.62 mmol/L [10.5 mg/dL])

Reason for exclusion	These exclusion criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants in the comparative study.
Is it considered to be included as missing information?	No

Rationale	Hypocalcaemia represents a contraindication for use of denosumab and an important identified risk of denosumab therapy (refer to Part II: Module SVII). The exclusion of patients with pre-existing hypercalcaemia from the comparative study has no impact on the safety in this patient population, if treated in clinical practice.

History of osteonecrosis of jaw, osteonecrosis of external auditory canal, or atypical femoral fracture at Screening or related risk based on the physical examination including oral

History of active periodontal disease or invasive dental procedure within 6 months prior to Screening or planned to have invasive dental procedures (e.g., tooth extraction, dental implants, or oral surgery) during the study period

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	Special precautions are needed during treatment of patients with risk factors for the development of osteonecrosis of jaw, osteonecrosis of external auditory canal, or atypical femoral fractures.

Fracture (except atypical femoral fracture and hip fracture) that had been actively healing within 12 months prior to Screening

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of denosumab is not expected to differ in patients with a history of (typical) fractures.

History of clinically significant active infection within 2 weeks prior to Randomisation, and for cellulitis, erysipelas, or infections that required hospitalisation or intravenous antibiotics, within 8 weeks prior to Randomisation

Reason for exclusion	These criteria were selected to minimise potential bias in collected data and to minimise potential risks to study participants.
Is it considered to be included as missing information?	No
Rationale	The safety profile of denosumab is not expected to differ in patients with a history of infection.

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.

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

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	Not included in the clinical development programme or not specifically studied.
Population with relevant different ethnic origin	Refer to Table SIII.2 and Table SIII.3.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.

Part II: Module SV - Post-authorisation experience

OBODENCE has not yet been approved for marketing in any country.

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

Potential for misuse for illegal purposes

The potential for misuse for illegal purposes is considered negligible, given the mechanism of action of denosumab.

Part II: Module SVII - Identified and potential risks

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

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

There are currently no risks considered as not important for inclusion in the list of safety concerns in respect to this RMP.

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

The safety concerns in the RMP for OBODENCE are aligned with the safety concerns for the reference product PROLIA [9], taking into account findings from the comparative studies SB16-1001 and SB16-3001 and potential unique characteristics of the OBODENCE biosimilar medicinal product.

Important identified risk(s):

- **Hypocalcaemia**

Risk-benefit impact:

Hypocalcaemia is relatively rare but significant adverse effect of denosumab therapy. While usually asymptomatic, severe symptomatic cases with fatal outcome were reported in post-marketing setting, mainly in patients at risk of hypocalcaemia. Considering the characteristics of the target population, the risk minimisation measures in place, and the infrequent occurrence of this event in clinical practice, the impact of this risk on the benefit-risk balance of denosumab is considered acceptable.

- **Skin infection leading to hospitalisation**

Risk-benefit impact:

Serious skin infections requiring hospitalisation were reported in patients treated with denosumab. Considering the effective antibiotic treatment in affected patients and the overall characteristics of this risk, the benefits of denosumab therapy outweigh this risk.

- **Osteonecrosis of the jaw**

Risk-benefit impact:

Osteonecrosis of the jaw is a rare but serious and potentially life-threatening adverse effect associated with denosumab therapy. Considering the infrequent occurrence, benefits of denosumab therapy and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

- **Hypersensitivity reactions**

Risk-benefit impact:

Hypersensitivity reactions, including anaphylaxis, represent potentially serious, albeit rare adverse effects of therapy with denosumab. Considering the rarity of occurrence and benefits of denosumab therapy, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

- **Atypical femoral fractures**

Risk-benefit impact:

Atypical femoral fractures represent serious adverse effects associated with antiresorptive medication, including denosumab. Given the relative rarity of these effects, the benefits of denosumab treatment fully outweigh this risk.

- **Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation**

Risk-benefit impact:

Hypercalcaemia in paediatric population following discontinuation of off-label use of denosumab is a serious and potentially life-threatening complication, requiring intensive treatment. Considering the infrequent occurrence of this event, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

Important potential risk(s):

- **Fracture healing complications**

Risk-benefit impact:

Fracture healing complications represent a theoretical risk associated with denosumab mechanism of action. Neither non-clinical nor clinical data showed any adverse effects of denosumab on fracture healing. Therefore, the impact of this potential risk on the benefit-risk balance of denosumab is acceptable.

- **Infection**

Risk-benefit impact:

Infections represent a potential risk of denosumab treatment, based on denosumab mechanism of action. However, a causal association between infections and denosumab has not yet been clearly established. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

- **Cardiovascular events**

Risk-benefit impact:

Although a plausible biological link exists between denosumab and cardiovascular disease, there is no evidence from human trials to support a positive or negative effect on cardiovascular risk. Therefore, cardiovascular events represent a theoretical risk associated with denosumab. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

- **Malignancy**

Risk-benefit impact:

Malignancy represents a theoretical risk of denosumab treatment, based on denosumab immunomodulatory effects. However, no evidence for the association between the onset of malignancy and denosumab treatment was collected to date. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

Missing information:

None.

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

Not applicable.

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

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

Important identified risk 1: Hypocalcaemia

Potential mechanisms:

Denosumab inhibits osteoclastic bone resorption, leading to hypocalcaemia by reducing calcium mobilisation from the bone into the bloodstream [11].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of hypocalcaemia in association with denosumab is 'rare' (i.e., ≥1 in 10,000 to <1 in 1,000), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

The incidence of hypocalcaemia was comparable between the OBODENCE and PROLIA Overall treatment groups within the comparative Phase III study SB16-3001 and the overall incidence was 10.2% (23/225 subjects) for OBODENCE and 11.7% (27/231 subjects) for the PROLIA Overall treatment groups within the Overall Study Period (Safety Set 1).

While the randomised controlled trials have reported a rate of 0.05% to 1.7% in denosumab-treated postmenopausal women with osteoporosis, retrospective analysis from 2,005 osteoporotic patients treated with denosumab in real-world setting showed a 7.4% rate of hypocalcaemia [11].

The events of hypocalcaemia were usually asymptomatic. Symptoms of hypocalcaemia in denosumab clinical studies included paraesthesia or muscle stiffness, twitching, spasms, and muscle cramps.

In the post-marketing setting, severe symptomatic hypocalcaemia (including fatal cases) was reported, with most cases occurring in the first weeks of initiating therapy. However, the literature from the real-world experience with denosumab showed that hypocalcaemia may occur after each dose [11].

The post-marketing cases predominantly involved patients at increased risk of hypocalcaemia. The clinical manifestations of severe symptomatic hypocalcaemia included QT interval prolongation, tetany, seizures, and altered mental status.

Among patients who developed hypocalcaemia during denosumab treatment, the median time to serum calcium nadir after denosumab administration was 3 weeks, in general approximately 1 to 2 weeks, and median time to correction of hypocalcaemia was by 4 weeks [12].

Risk factors and risk groups:

The known 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 mL/min), dialysis, and some medications (e.g., glucocorticoids, bisphosphonates) [12, 13].

Preventability:

It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Hypocalcaemia represents a contraindication for use of denosumab. Adequate intake of calcium and vitamin D during denosumab treatment is important in all patients.

Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose.

If any patient presents with suspected symptoms of hypocalcaemia during treatment, calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.

Impact on the risk-benefit balance of the product:

Hypocalcaemia is a relatively rare but significant adverse effect of denosumab therapy. While usually asymptomatic, severe symptomatic cases with fatal outcome were reported in post-marketing setting, mainly in patients at risk of hypocalcaemia. Considering the characteristics of the target population, the risk minimisation measures in place, and the infrequent occurrence of this event in clinical practice, the impact of this risk on the benefit-risk balance of denosumab is considered acceptable.

Public health impact:

No impact on public health is expected.

Important identified risk 2: Skin infection leading to hospitalisation

Potential mechanisms:

The mechanism for denosumab-induced skin infections has not yet been elucidated.

Since RANKL and RANK are expressed by immune cells (e.g., activated T cells, B cells, dendritic cells), it has been theorised that inhibition of RANKL might increase the risk of infections and/or malignancy [14].

However, it has been hypothesised that the inhibition of RANKL in keratinocytes may decrease the number of regulatory T cells, leading to an increased inflammatory response in the skin [15], which may be responsible for skin presentations observed n patients treated with denosumab.

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation. The frequency of cellulitis in association with denosumab is 'uncommon' (i.e., ≥1 in 1,000 to <1 in 100), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

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 denosumab. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the denosumab (0.6%, 5 out of 860) groups in the breast and prostate cancer studies [10].

The incidence of skin infection was comparable between the OBODENCE and PROLIA Overall treatment groups within the comparative Phase III study SB16-3001 and the overall incidence was 0.4% (1/225 subjects) for Obodence and 0.4% (1/231 subjects) for the PROLIA Overall treatment groups within the Overall Study Period (Safety Set 1). However, any of skin infection events occurred in the Phase III study SB16-3001 were not serious adverse events.

An increased incidence of hospitalisation for cellulitis was observed in subjects in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial who were treated with denosumab [16]. However, there was no significant difference in the overall incidence of cellulitis between the two groups (denosumab versus placebo).

Most of skin infections reported in association with denosumab were cellulitis or clinically diagnosed erysipelas, involving the lower extremities. Cellulitis and erysipelas are usually caused by *Streptococcus pyogenes*, *Staphylococcus aureus*, and other gram-positive bacterial infections [15].

Serious events of cellulitis and erysipelas resulting in hospitalisation occurred more frequently in the FREEDOM trial with denosumab in comparison with placebo, although the number of events was overall low [15].

There was no temporal association between the onset of serious events of cellulitis and erysipelas and duration of treatment or time since last dose of investigational product. The median duration of hospitalisation for denosumab subjects was 5.5 days (range 1 to 17 days). The skin infections resolved with the treatment with common antibiotics [15].

A fatal event was reported in a patient with neuroendocrine carcinoma of pancreas who experienced a fatal cellulitis of the right leg, complicated by sepsis, shock, and multiple organ failure [15].

Risk factors and risk groups:

The specific risk factors or risk groups for denosumab-associated serious skin infection have not yet been established.

The general risk factors for the skin infections include venous ulcers and skin wounds.

The general risk factors for development of infections include increasing age, immunosuppression associated with cancer, diabetes mellitus, HIV/AIDS, immunosuppressive

drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.

Preventability:

The preventability measures have not yet been established for denosumab.

Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Impact on the risk-benefit balance of the product:

Serious skin infections requiring hospitalisation were reported in patients treated with denosumab. Considering the effective antibiotic treatment in affected patients and the overall characteristics of this risk, the benefits of denosumab therapy outweigh this risk.

Public health impact:

No impact on public health is expected.

Important identified risk 3: Osteonecrosis of the jaw

Potential mechanisms:

The mechanism for denosumab-induced osteonecrosis of the jaw has not yet been elucidated but appears to be multi-factorial.

Several potential mechanisms have been hypothesised, including over suppression of bone remodelling, local infection, inhibition of angiogenesis, soft tissue toxicity, and immune dysfunction [17].

Inhibition of osteoclastic activity, mediated by denosumab, has also been hypothesised as a potential mechanism for the development of osteonecrosis of the jaw [18].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of osteonecrosis of the jaw in association with denosumab is ‘rare’ (i.e., ≥ 1 in 10,000 to < 1 in 1,000), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

No events of osteonecrosis of the jaw were reported in the comparative Phase III study SB16-3001 in either treatment group in the Overall Study Period (Safety Set 1).

The observational study, analysing real-world data from 3,068 patients receiving bisphosphonates and/or denosumab therapy for osteoporosis, showed the incidence rate of denosumab-associated osteonecrosis of the jaw to be 28.3 per 10,000 patient-years (12 cases), in comparison to 4.5 per 10,000 patients-years for bisphosphonates (5 cases). Nine of the 12 patients who developed the osteonecrosis of the jaw under denosumab had undergone prior therapy with bisphosphonates [17]. The risk of osteonecrosis of the jaw associated with

denosumab is significantly higher than in association with bisphosphonates (up to 0.3% for denosumab versus up to 0.05% for bisphosphonates) [19, 20].

Osteonecrosis of the jaw is a serious complication of denosumab therapy, characterised by persistent, often painful necrosis of bone in the maxillofacial region, which reduces quality of life and is associated with significant morbidity [17]. Osteonecrosis of the jaw may lead to jawbone infections, chronic pain, and tooth loss and compromised function [21].

While moderate to severe cases are the most frequent, life-threatening cases complicated by sepsis were also reported [22, 23].

Denosumab-associated osteonecrosis of the jaw was shown to be reversible in some cases upon denosumab discontinuation [24, 25]. Other reports showed more complete healing only following a major surgery, with no effect of denosumab discontinuation on healing [26].

The literature further reports that the success rate of conservative treatment regimens range from less than 20% to above 50%, although some cases become chronic and develop complications [25]. There is no consensus on the treatment of denosumab-associated osteonecrosis of the jaw but surgery indicated as an early treatment was shown to prevent complications and the progression of the lesions [23].

No data on the long-term outcomes are available. However, the incidence of denosumab-related osteonecrosis of the jaw reported in clinical practice is higher in comparison to clinical trial data, suggesting a potential impact of cumulative doses and/or prolonged exposure on development of this event [27].

Risk factors and risk groups:

The following risk factors should be considered when evaluating a patient's risk of developing osteonecrosis of the jaw:

- potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy
- cancer, co-morbid conditions (e.g., anaemia, coagulopathies, diabetes mellitus, infection), smoking
- concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck
- poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures (e.g., tooth extractions).

The general risk factors for the development of osteonecrosis of the jaw associated with anti-osteoporotic medication include [17, 28, 29]:

- 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
- vascular insufficiency due to thrombosis

Preventability:

The start of treatment/new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab in patients with concomitant risk factors.

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab.

While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.

The management plan of the patients who develop osteonecrosis of the jaw should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in osteonecrosis of the jaw.

Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Refer to Part V.2, detailing the additional risk minimisation measures in place for this risk.

Impact on the risk-benefit balance of the product:

Osteonecrosis of the jaw is a rare but serious and potentially life-threatening adverse effect associated with denosumab therapy. Considering the infrequent occurrence, benefits of denosumab therapy and risk minimisation measures in place, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

Public health impact:

No impact on public health is expected.

Important identified risk 4: Hypersensitivity reactions

Potential mechanisms:

The exact mechanism for development of denosumab-associated hypersensitivity reactions remains unclear.

The general hypersensitivity reactions to monoclonal antibodies are classified as type β reactions, including IgE-, IgG-, and T cell-mediated reactions [30, 31].

The IgE-mediated reactions can cause a local wheal and flare reaction at the injection site, if administered subcutaneously, but may also cause urticaria and anaphylaxis [30].

Acute infusion reactions are mostly not IgE-mediated [30]. Their mechanism for development is unclear but may be related to activation of cells or of the complement system via immune complexes.

Delayed reactions appear more than 6 hours after the administration. They can be subdivided in Ig- and T cell-mediated reactions [30]. The normal physiological immune response to a foreign, soluble protein is Ig-mediated. Thus, the development of IgG antibodies directed to the biological agent is by far the most frequent reaction. These antibodies are not necessarily associated with symptoms. The most frequent effect is inactivation of the biological agent.

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of anaphylactic reaction and drug hypersensitivity in association with denosumab is ‘rare’ (i.e., ≥ 1 in 10,000 to < 1 in 1,000), while the frequency of rash is ‘common’ (i.e., ≥ 1 in 100 to < 1 in 10), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

The incidence of hypersensitivity to investigational product was comparable between the OBODENCE and PROLIA Overall treatment groups within the comparative Phase III study SB16-3001 and the overall incidence was 0.4% (1/225 subjects) for OBODENCE and 1.3% (3/231 subjects) for the PROLIA Overall treatment groups within the Overall Study Period (Safety Set 1).

In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving denosumab.

Subcutaneous administration of monoclonal antibodies is often associated with local reactions at the site of administration, including erythema, oedema, pruritus, induration, ecchymosis, and pain that usually occur in the first month of treatment and remit within a few days of subcutaneous administration. These are generally not followed by systemic reactions but anaphylactic reactions and other systemic hypersensitivity reactions have been described [30, 31].

Hypersensitivity reactions usually become more severe with subsequent exposures [31].

Various desensitisation protocols in patients experiencing hypersensitivity reactions associated with denosumab were published in the literature with favourable results [32, 33].

Risk factors and risk groups:

Besides the known hypersensitivity to denosumab and/or any of component of OBODENCE, which represents a standard contraindication for use, the risk factors or risk groups for hypersensitivity reactions associated with denosumab therapy have not yet been established.

Preventability:

Patients with a known hypersensitivity to denosumab or any component of OBODENCE cannot receive denosumab therapy.

Impact on the risk-benefit balance of the product:

Hypersensitivity reactions, including anaphylaxis, represent potentially serious, albeit rare adverse effects of therapy with denosumab. Considering the rarity of occurrence and benefits of denosumab therapy, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

Public health impact:

No impact on public health is expected.

Important identified risk 5: Atypical femoral fracture

Potential mechanisms:

The mechanism for development of atypical femoral fractures remains poorly understood, although a number of mechanisms have been proposed [34].

Radiologic features seen in atypical femoral fractures are consistent with stress fractures, which occur when bones are subjected to repetitive loading that overwhelms the capacity for bone repair. Antiresorptive medications, including denosumab, which suppress bone remodelling, may result in accumulation of micro-damage which is not repaired, thus leading to the development of stress fractures [34].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency of atypical femoral fractures in association with denosumab is ‘rare’ (i.e., ≥ 1 in 10,000 to < 1 in 1,000), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

No events of atypical femoral fractures were reported in the comparative Phase III study SB16-3001 in either treatment group in the Overall Study Period (Safety Set 1).

Atypical femoral fractures associated with denosumab may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur and have specific radiographic findings [34]. Similar fractures reported in association with bisphosphonates are often bilateral.

A high percentage of patients affected with atypical femoral fractures experience prodromal thigh/groin pain [35, 36].

Atypical femoral fractures are serious events, usually requiring medical interventions, including surgery and ongoing monitoring. Appropriate exercise guidance is important for patients affected with atypical femoral fractures, because repetitive stress to the lower limbs can cause further bone damage and slow fracture healing [34].

No data on the reversibility of the pathophysiological mechanism upon denosumab discontinuation or on the long-term outcomes are available. However, available data suggest that healing of atypical femoral fractures can be prolonged in comparison to the typical fractures [35, 36]. Because of the propensity for delayed healing, the morbidity of these fractures is particularly high [36].

Atypical femoral fractures have a potentially significant impact on patients quality of life, leading to short- or long-term disability.

Risk factors and risk groups:

The risk of atypical femoral fractures seems to increase with the duration of therapy [34, 36].

Observational studies showed that women are at increased risk compared to men and Asian women are more prone to atypical femoral fractures compared to White women [34].

The presence of a genetic metabolic bone disorder may be an important risk factor for developing atypical femoral fractures [34].

Atypical femoral fractures have been reported in patients with certain co-morbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain medicinal products (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors) [34, 36, 37]. These events have also occurred without antiresorptive therapy.

Preventability:

Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit-risk assessment.

Similar fractures reported in association with bisphosphonates are often bilateral. Therefore, the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture.

During denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.

Impact on the risk-benefit balance of the product:

Atypical femoral fractures represent serious adverse effects associated with antiresorptive medication, including denosumab. Given the relative rarity of these effects, the benefits of denosumab treatment fully outweigh this risk.

Public health impact:

No impact on public health is expected.

Important identified risk 5: Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation

Potential mechanisms:

The mechanism for development of hypercalcaemia after treatment discontinuation has not yet been fully elucidated but is most likely caused by the rapid recovery of osteoclastic activity, triggering the surge of bone resorption and the release of calcium from the calcified tissue into the circulation [38]. This concept indicates that bone turnover rate and the amount of overstored calcium determine the severity of the increase in serum calcium following denosumab discontinuation.

The published literature indicates that hypercalcemia occurs even in skeletally mature patients, although rarely, if they are treated with denosumab long enough to reach the potential threshold [38]. Rebound hypercalcaemia was reported in adult patients with giant cell tumour of bone treated with denosumab 120 mg (XGEVA®) [27, 38, 39].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

Serious and life-threatening hypercalcaemia, requiring hospitalisation and complicated by acute renal injury, has been reported in association with denosumab use in children and adolescents (denosumab 60 mg) in clinical trials and during off-label use in the post-marketing setting [39].

There are currently no approved indications for use of denosumab 60 mg in the paediatric population. However, denosumab 120 mg (XGEVA) is authorised for the treatment in skeletally mature adolescents with giant cell tumour of bone. Denosumab 60 mg (PROLIA) is used in paediatric population in clinical trials or as an off-label treatment in post-marketing setting for several indications, including certain forms of osteogenesis imperfecta, fibrous dysplasia, juvenile Paget's disease, giant cell tumours, aneurysmatic bone cysts, and others [40].

Worldwide, about 20 suspected reports of (rebound) hypercalcaemia were reported (up to 26 August 2021), during off-label treatment with denosumab 60 mg (PROLIA) in paediatric population. Reports included cases in paediatric patients with osteogenesis imperfecta, as well as in those with various other conditions [39].

General symptoms of hypercalcaemia include excessive thirst, excessive urination, drowsiness, confusion, loss of concentration, feeling or being sick, constipation, and muscle weakness. Severe hypercalcaemia can cause serious kidney problems (acute renal injury), coma, heart rhythm abnormalities, and cardiac arrest [39].

The symptoms of rebound hypercalcaemia reported in paediatric patients in association with denosumab included fatigue, nausea, vomiting, constipation, abdominal pain, weight loss, polyuria, dehydration, renal failure, and sinus bradycardia, which often developed within a few days [40].

The mean half-life of denosumab after cessation is reported to be 29 days (range: 25 to 35 days). However, the clearance is likely to be longer in individuals with accumulated doses, hence the occurrence of rebound hypercalcaemia as late as 7 months from treatment cessation [27].

Given the current state of knowledge, the exact timing of onset of hypercalcemia cannot be anticipated [40]. The literature shows that rebound hypercalcaemia often occurs in children and adolescents within 3 months after the last dose of denosumab [38].

Rebound hypercalcaemia is often intractable and requires intensive treatment as it usually responds poorly to hydration alone and the literature described the administration of diuretics, corticosteroids, and/or calcitonin. In severe cases, repeated use of bisphosphonates (zoledronate, pamidronate, ibandronate) or reinjection of denosumab was often required to repress the surge of calcium released into the circulation [27, 38]. Although the prolonged antiresorptive action of bisphosphonates is an effective treatment of hypercalcaemia in the context of hypercalcaemia, the presence of acute kidney injury increases the risk of bisphosphonate-induced renal failure [27].

Risk factors and risk groups:

The specific risk factors or risk groups for rebound hypercalcaemia associated with denosumab have not yet been established.

The literature shows that the individual vitamin D level can represent additional influencing factor [27]. In general, paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta) represent a risk group for rebound hypercalcaemia.

The literature further shows potential male predisposition to rebound hypercalcaemia in children and adolescents, which is in line with the proposed pathophysiology and fact that males tend to have higher bone mass than females [38].

The correlation between the treatment duration and patient age described in the literature indicates that rebound hypercalcemia occurs following a relatively short treatment duration in juveniles and adolescents compared with adults [38].

Preventability:

No specific preventive measures have yet been established for denosumab. Denosumab 60 mg is not approved for use in paediatric population and should not be used in paediatric patients.

Precautions should be taken when denosumab therapy is interrupted and gradual decrease of dose and/or timing of treatment should be considered [41]. However, clinical benefits of this approach are currently unknown [38].

Impact on the risk-benefit balance of the product:

Hypercalcaemia in paediatric population following discontinuation of denosumab is a serious and potentially life-threatening complication, requiring intensive treatment. Considering the infrequent occurrence of this event, the impact of this risk on the benefit-risk balance of denosumab is acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 1: Fracture healing complications

Potential mechanisms:

This is a theoretical risk based on the denosumab mechanism of action, potentially negatively impacting bone healing.

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency and the nature of this risk has not yet been established.

Denosumab does not appear to impair fracture healing in animal studies. In a study conducted in male human RANKL knock-in mice, there was no effect of denosumab on fracture union or initial callus formation. Denosumab (as well as bisphosphonates) was found to delay callus remodelling, though callus strength and stiffness were greater in treated animals than in controls [2, 42].

Denosumab was not associated with delayed healing or healing complications, following fracture or surgical management in the pre-planned analysis of the FREEDOM trial [43], providing further evidence that antiresorptive treatment does not interfere with fracture healing [42, 44]. A total of 667 subjects of the FREEDOM trial (303 in the denosumab group and 364 in the placebo group) experienced 851 nonvertebral fractures (386 in the denosumab group and 465 in the placebo group). Seven patients experienced delayed healing (two in the denosumab group and five in the placebo group). In this analysis, delayed healing or non-union was not observed in any subject who received denosumab within 6 weeks preceding or following the fracture. Fracture healing seemed to be unaffected in patients treated with denosumab, even when administered within a day of the fracture [43].

Risk factors and risk groups:

The specific risk factors or risk groups for fracture healing complications potentially associated with denosumab have not yet been established.

The general risk factors for fracture healing complications include older age, diabetes mellitus, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition [45-47].

Preventability:

There are no specific preventability measures established for denosumab.

Impact on the risk-benefit balance of the product:

Fracture healing complications represent an theoretical risk associated with denosumab mechanism of action. Neither non-clinical nor clinical data showed any adverse effects of denosumab on fracture healing. Therefore, the impact of this potential risk on the benefit-risk balance of denosumab is acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 2: Infection

Potential mechanisms:

Since RANKL and RANK are expressed by immune cells (e.g., activated T cells, B cells, dendritic cells), it has been theorised that inhibition of RANKL might increase the risk of infections and/or malignancy [14, 48].

Gene ablation studies in mice have shown that complete absence of RANKL during embryogenesis is followed by total absence of lymph nodes [3, 49] and as such, a theoretical concern exists that denosumab might adversely impact the immune system in humans [50], i.e., increase a potential for development of infections. However, investigations of RANKL inhibition in rodents, cynomolgus monkeys, and humans have found no significant impairment of immune function [15, 50-52].

RANKL mutation reported in 6 humans with autosomal recessive osteoporosis showed no apparent immunological abnormalities [53].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The causal association of infections reported in patient treated with denosumab and denosumab's mode of action has not yet been clearly established.

The frequency of urinary tract infection and upper respiratory tract infection in association with denosumab is 'common' (i.e., ≥ 1 in 100 to < 1 in 10), while the frequency of diverticulitis, cellulitis, or ear infection is 'uncommon' (i.e., ≥ 1 in 1,000 to < 1 in 100), based on the overall experience with denosumab from Phase II and Phase III clinical studies and the post-marketing experience [10].

The incidence of infections was comparable between the OBODENCE and PROLIA Overall treatment groups within the comparative Phase III study SB16-3001 and the overall incidence was 35.1% (79/225 subjects) for OBODENCE and 36.8% (85/231 subjects) for the PROLIA Overall treatment groups within the Overall Study Period (Safety Set 1).

In the FREEDOM trial, no significant differences in the overall incidence of (serious) adverse events of infection, including opportunistic infection, were noted during the 3-year treatment period [16] and subsequent 7-year Extension period, remaining low and stable in the year-by-year analysis [54].

A population-based cohort study conducted in Taiwan found that denosumab therapy was associated with a higher risk of infection at the early periods of treatment. The risk attenuates significantly after the second year of therapy [55].

Two systemic reviews and meta-analyses of randomised clinical trials showed a higher incidence of serious infections in patients treated with denosumab when compared to placebo but not compared to bisphosphonates [56, 57]. However, there was no change in the risk for any infection or for infection-related mortality and the overall risk for any infection or related mortality in patients treated with denosumab was similar to comparator groups [57].

Risk factors and risk groups:

The specific risk factors or risk groups for infections potentially associated with denosumab have not yet been established.

The general risk factors for infections include increasing age, immunosuppression associated with cancer, diabetes mellitus, HIV/AIDS, immunosuppressive drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.

Preventability:

No specific preventability measures have been established for denosumab.

Impact on the risk-benefit balance of the product:

Infections represent a potential risk of denosumab treatment, based on denosumab mechanism of action. However, a causal association between infections and denosumab has not yet been clearly established. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 3: Cardiovascular events

Potential mechanisms:

Denosumab mimics the natural action of osteoprotegerin (OPG) [48, 58]. OPG is a soluble decoy receptor of RANKL, preventing RANKL from binding to RANK on osteoclast and osteoclasts precursors and inhibiting bone resorption [14, 59]. The increased RANKL/OPG ratio is described among the inflammatory mechanisms associated with atherosclerosis [60].

RANKL is produced by the main cells involved in the atherosclerotic process in response to inflammatory stimuli (activated T lymphocytes, endothelial and vascular smooth muscle cells), while studies in mice have demonstrated that OPG has protective role in vascular calcification [60, 61].

Genetically modified animals that lack the gene for OPG have increased vascular calcification and osteoporosis, indicating a potential protective role of OPG. Moreover, exogenous OPG has been shown to have mitigating effects on vascular calcification in animal models of atherosclerosis and calcific arteriopathy [59].

However, the exact role of RANKL and OPG in the vascular compartment is unclear, because preclinical findings are not consistent with human epidemiological observations [59].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency and nature of risk of cardiovascular events potentially associated with denosumab has not yet been established, since no significant differences in the overall incidence of cardiovascular events were noted during the 3-year treatment period and subsequent 7-year Extension period of the FREEDOM trial [16, 54] as well as in the post-marketing setting.

The incidence of cardiovascular event was comparable between the OBODENCE and PROLIA. Overall treatment groups within the comparative Phase III study SB16-3001 and the overall incidence was 2.2% (5/225 subjects) for OBODENCE and 3.0% (7/231 subjects) for the PROLIA Overall treatment groups within the Overall Study Period (Safety Set 1). Reported cardiovascular events included coronary artery disease, acute myocardial infarction, atrial fibrillation, chronic cardiac failure, myocardial ischemia, carotid artery stenosis, cerebral small vessel disease, intracranial aneurysm and transient ischemic attack. One subject (0.4%) in OBODENCE and two subjects (0.8%) in PROLIA Overall treatment groups experienced serious events of cardiovascular events.

Although a plausible biological link exists between denosumab and cardiovascular disease, there is no evidence from clinical trials to support a positive or negative effect on cardiovascular risk, at least at the dose used in osteoporosis therapy [62].

A further analysis of a subset of 2,363 women (1,142 placebo, 1,221 denosumab) from the FREEDOM trial who were at high risk of cardiovascular disease was conducted [59]. In this study, aortic calcification and progression was assessed using a semi-quantitative method from lateral spine radiographs. There was no significant difference in aortic calcification progression over the 3 years of the trial between the placebo (22%) and denosumab (22%) groups and no difference in cardiovascular risk across the two groups (in the high cardiovascular risk population) [59].

Risk factors and risk groups:

The specific risk factors or risk groups for cardiovascular events potentially associated with denosumab have not yet been established.

The general risk factor for cardiovascular events and atherosclerosis include older age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes mellitus, and medications, including antipsychotics or cyclooxygenase-2 inhibitors.

Preventability:

No specific preventability measures have been established for denosumab.

Impact on the risk-benefit balance of the product:

Although a plausible biological link exists between denosumab and cardiovascular disease, there is no evidence from human trials to support a positive or negative effect on cardiovascular risk. Therefore, cardiovascular events represent a theoretical risk associated with denosumab. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

Public health impact:

No impact on public health is expected.

Important potential risk 4: Malignancy

Potential mechanisms:

Since denosumab possesses immunomodulatory effect, a concerns exists about its potential to cause malignancy [48]. RANKL and RANK are expressed by immune cells (e.g., activated

T cells, B cells, dendritic cells) and it has. therefore, been theorised that inhibition of RANKL might increase the risk of infections and/or malignancy [14].

It should be noted that one of the mechanisms of enhancing tumour cell survival by OPG is inhibition of tumour necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL)-induced apoptosis; yet, an in vitro observation showed that denosumab differs from OPG since it binds only to human and nonhuman primate RANKL and not to any other member of the TNF family including human TRAIL [48].

Evidence source(s) and strength of evidence:

This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA [9, 10].

Characterisation of the risk:

Frequency, severity, and nature of the risk (including reversibility and long-term outcomes)

The frequency and nature of risk of malignancy potentially associated with denosumab has not yet been established, since no significant differences in the overall incidence of malignancy were noted during the 3-year treatment period and subsequent 7-year Extension period of the FREEDOM trial [16, 54] as well as in the post-marketing setting.

The incidence of malignancies was comparable between the OBODENCE and PROLIA Overall treatment groups within the comparative Phase III study SB16-3001 and the overall incidence was 0.4% (1/225 subjects) for OBODENCE and 0.9% (2/231 subjects) for the PROLIA Overall treatment groups within the Overall Study Period (Safety Set 1).

A meta-analysis of 25 randomised clinical trials with denosumab 60 mg, including 21,523 patients (10,721 treated with denosumab) and up to 48 months of exposure, demonstrated that denosumab therapy in an osteoporosis dosage is not associated with an increased risk of malignancy with drug exposure of up to 48 months [48]. The finding of a similar risk of malignancy in denosumab and a comparator group was consistent throughout the subgroup analyses, including all treatment comparators, all indications for treatment, and ethnicity.

The long-term post-marketing surveillance is needed to collected data on potential cumulative effects or outcomes of long-term exposure. In the 7-year Extension period of the FREEDOM trial, the risk of malignancy remained low as in the original trial. However, all subjects that were included in the long-term extension of the FREEDOM trial received denosumab for a total of 7 to 10 years in the absence of a control group [48, 54].

Risk factors and risk groups:

The specific risk factors or risk groups for the onset of malignancy potentially associated with denosumab have not yet been established.

The general factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins.

Preventability:

No specific preventability measures have been established for denosumab.

Impact on the risk-benefit balance of the product:

Malignancy represents a theoretical risk of denosumab treatment, based on denosumab's immunomodulatory effects. However, no evidence for the association between the onset of malignancy and denosumab treatment was collected to date. Considering the benefits of therapy, the impact of this potential risk on the benefit-risk balance of denosumab remains acceptable.

Public health impact:

No impact on public health is expected.

SVII.3.2 Presentation of the missing information

None.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaire for hypocalcaemia**

This questionnaire is designed to monitor the nature of hypocalcaemia in patients treated with OBODENCE in the post-marketing environment.

- **Specific adverse reaction follow-up questionnaire for skin infection leading to hospitalisation and infection**

This questionnaire is designed to monitor the nature of skin infection leading to hospitalisation and infections of any type reported in patients treated with OBODENCE in the post-marketing environment.

- **Specific adverse reaction follow-up questionnaire for osteonecrosis of the jaw**

This questionnaire is designed to monitor the nature of osteonecrosis of the jaw in patients treated with OBODENCE in the post-marketing environment.

- **Specific adverse reaction follow-up questionnaire for hypersensitivity reactions**

This questionnaire is designed to monitor the nature of hypersensitivity reaction reported in patients treated with OBODENCE in the post-marketing environment.

- **Specific adverse reaction follow-up questionnaire for atypical femoral fracture**

This questionnaire is designed to monitor the nature of atypical femoral fracture reported in patients treated with OBODENCE in the post-marketing environment.

- **Specific adverse reaction follow-up questionnaire for fracture healing complications**

This questionnaire is designed to monitor the nature of fracture healing complications reported in patients treated with OBODENCE in the post-marketing environment.

- **Specific adverse reaction follow-up questionnaire for malignancy**

This questionnaire is designed to monitor the nature of malignancy adverse events reported in patients treated with OBODENCE in the post-marketing environment.

The respective questionnaires are provided in Annex 4.

III.2 Additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hypocalcaemia	Routine risk communication SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Adequate supplementation with calcium and vitamin D is stressed in the SmPC section 4.2. Clinical monitoring of calcium levels before each dose, in predisposed patients within 2 weeks of initial dose, and in case of suspected symptoms is recommended in the SmPC section 4.4. Patients should be instructed to report any symptoms suggestive of low calcium levels per the SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Subject to medical prescription
Skin infections leading to hospitalisation	Routine risk communication SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients should be instructed to seek prompt medical attention if they develop signs or symptoms of cellulitis per the SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Subject to medical prescription

Safety concern	Routine risk minimisation activities
Osteonecrosis of the jaw	Routine risk communication SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: The risk factors to consider before treatment are listed in SmPC section 4.4. Patients should be instructed to maintain oral hygiene and immediately report any oral symptoms per the SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Subject to medical prescription
Hypersensitivity reactions	Routine risk communication SmPC sections 4.3 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Subject to medical prescription
Atypical femoral fracture	Routine risk communication SmPC sections 4.4 and 4.8 PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Patients should be advised to report any new or unusual thigh, hip, or groin pain per the SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Subject to medical prescription
Hypercalcaemia in paediatric patients receiving denosumab and after	Routine risk communication SmPC sections 4.2, 4.4, and 4.8 PL section 2

Safety concern	Routine risk minimisation activities
treatment discontinuation	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to medical prescription
Fracture healing complications	Routine risk communication SmPC section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to restricted medical prescription
Infection	Routine risk communication SmPC section 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to medical prescription
Cardiovascular events	Routine risk communication None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to medical prescription
Malignancy	Routine risk communication None

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Subject to medical prescription

PL = Package Leaflet; SmPC = Summary of Product Characteristics.

V.2 Additional risk minimisation measures

Patient reminder card

Objectives:

The objective of the patient reminder card is to remind patients about the risk of osteonecrosis of the jaw that they need to be aware of before and during the treatment with denosumab injections for osteoporosis and bone loss, including:

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

List of addressed safety concern(s):

- Osteonecrosis of the jaw

Rationale for the additional risk minimisation activity:

Osteonecrosis of the jaw is a rare but serious adverse effect associated with denosumab therapy. The patient reminder card was designed to provide patients with important safety information that they need to be aware before and during treatment with denosumab.

Target audience and planned distribution path:

The target audience for this card is represented by patients treated with OBODENCE.

These cards are distributed to the prescribers with instructions to provide these to patients or as agreed on a national level. Some national plans include making the patient reminder card available on a website.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypocalcaemia	Routine risk minimisation SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, and 4 Adequate supplementation with calcium and vitamin D is stressed in the SmPC section 4.2. Clinical monitoring of calcium levels before each dose, in predisposed patients within 2 weeks of initial dose, and in case of suspected symptoms is recommended in the SmPC section 4.4. Patients should be instructed to report any symptoms suggestive low calcium levels per the SmPC section 4.2 and 4.4. Subject to medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Follow-up questionnaire for hypocalcaemia Additional pharmacovigilance activities None
Skin infection leading to hospitalisation	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Patients should be instructed to seek prompt medical attention if they develop signs or symptoms of cellulitis per the SmPC section 4.4. Subject to medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Follow-up questionnaire for infection Additional pharmacovigilance activities None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Osteonecrosis of the jaw	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 The risk factors to consider before treatment are listed in SmPC section 4.4. Patients should be instructed to maintain oral hygiene and immediately report any oral symptoms per the SmPC section 4.4. Subject to medical prescription Additional risk minimisation Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Follow-up questionnaire for osteonecrosis of the jaw Additional pharmacovigilance activities None
Hypersensitivity reactions	Routine risk minimisation SmPC sections 4.3 and 4.8 PL sections 2 and 4 Subject to medical prescription Additional risk minimisation 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 minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Patients should be advised to report any new or unusual thigh, hip, or groin pain per the SmPC section 4.4. Subject to medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Follow-up questionnaire for atypical femoral fracture Additional pharmacovigilance activities None
Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimisation SmPC sections 4.2, 4.4, and 4.8 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Subject to medical prescription Additional risk minimisation None	None Additional pharmacovigilance activities None
Fracture healing complications	Routine risk minimisation SmPC section 5.3 Subject to medical prescription Additional risk minimisation 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 minimisation SmPC section 4.8 PL section 4 Subject to medical prescription Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Follow-up questionnaire for infection Additional pharmacovigilance activities None
Cardiovascular events	Routine risk minimisation None Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignancy	Routine risk minimisation None Additional risk minimisation None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Follow-up questionnaire for malignancy Additional pharmacovigilance activities None

PL = Package Leaflet; SmPC = Summary of Product Characteristics.

Part VI: Summary of the risk management plan

Summary of risk management plan for Obodence (denosumab)

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

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

This summary of the RMP for Obodence should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Obodence is authorised for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, 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 fractures (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous injection.

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

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

Important risks of Obodence, together with measures to minimise such risks and the proposed studies for learning more about Obodence's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Obodence, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken, as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Obodence are risks that need special risk management activities to further investigate or minimise 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 Obodence. 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);

List of important risks and missing information	
Important identified risks	Hypocalcaemia Skin infection leading to hospitalisation Osteonecrosis of the jaw Hypersensitivity reactions Atypical femoral fracture Hypercalcaemia in paediatric 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

Important identified risk: Hypocalcaemia	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).

Important identified risk: Hypocalcaemia	
Risk factors and risk groups	The known 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 mL/min), dialysis, and some medications (e.g., glucocorticoids, bisphosphonates) (Ishikawa et al. 2018; Kim 2022).
Risk minimisation measures	<u>Routine risk minimisation</u> SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2 and 4 Adequate supplementation with calcium and vitamin D is stressed in the SmPC section 4.2. Clinical monitoring of calcium levels before each dose, in predisposed patients within 2 weeks of initial dose, and in case of suspected symptoms is recommended in the SmPC section 4.4. Patients should be instructed to report any symptoms suggestive low calcium levels per the SmPC section 4.2 and 4.4. Subject to medical prescription <u>Additional risk minimisation</u> None

Ishikawa K, Nagai T, Tsuchiya K, Oshita Y, Kuroda T, Ito H, et al. High bone turnover status as a risk factor in symptomatic hypocalcemia following denosumab treatment in a male patient with osteoporosis. Clin Interv Aging. 2018; 13: 1929-34.
Kim D. Hypocalcemia After the Administration of Denosumab in a Patient With Osteoporotic Fracture and Vitamin D Deficiency2022.

Important identified risk: Skin infection leading to hospitalisation	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).

Important identified risk: Skin infection leading to hospitalisation	
Risk factors and risk groups	The specific risk factors or risk groups for denosumab associated serious skin infection have not yet been established. The general risk factors for the skin infections include venous ulcers and skin wounds. The general risk factors for development of infections include increasing age, immunosuppression associated with cancer, diabetes mellitus, HIV/AIDS, immunosuppressive drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimisation measures	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Patients should be instructed to seek prompt medical attention if they develop signs or symptoms of cellulitis per the SmPC section 4.4. Subject to medical prescription Additional risk minimisation None

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).
Risk factors and risk groups	The following risk factors should be considered when evaluating a patient's risk of developing osteonecrosis of the jaw: • potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy • cancer, co-morbid conditions (e.g., anaemia, coagulopathies, diabetes mellitus, infection), smoking • concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck

Important identified risk: Osteonecrosis of the jaw	
	• poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures (e.g., tooth extractions). The general risk factors for the development of osteonecrosis of the jaw associated with anti-osteoporotic medication include (Mehrotra and Ruggiero 2006; Tofé et al. 2020; Everts-Graber et al. 2022): • 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 • vascular insufficiency due to thrombosis
Risk minimisation measures	<u>Routine risk minimisation</u> SmPC sections 4.4 and 4.8 PL sections 2 and 4 The risk factors to consider before treatment are listed in SmPC section 4.4. Patients should be instructed to maintain oral hygiene and immediately report any oral symptoms per the SmPC section 4.4. Subject to medical prescription <u>Additional risk minimisation</u> Patient reminder card

Everts-Graber J, Lehmann D, Burkard J-P, Schaller B, Gahl B, Häuselmann H, et al. Risk of Osteonecrosis of the Jaw Under Denosumab Compared to Bisphosphonates in Patients With Osteoporosis. J Bone Miner Res. 2022; 37(2): 340-8.
Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaw. Hematology Am Soc Hematol Educ Program. 2006: 356-60, 515.

Important identified risk: Osteonecrosis of the jaw

Tofé VI, Bagán L, Bagán JV. Osteonecrosis of the jaws associated with denosumab: Study of clinical and radiographic characteristics in a series of clinical cases. J Clin Exp Dent. 2020; 12(7): e676-e81.

Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).
Risk factors and risk groups	Besides the known hypersensitivity to denosumab and/or any of component of Obodence, which represents a standard contraindication for use, the risk factors or risk groups for hypersensitivity reactions associated with denosumab therapy have not yet been established.
Risk minimisation measures	<u>Routine risk minimisation</u> SmPC sections 4.3 and 4.8 PL sections 2 and 4 Subject to medical prescription <u>Additional risk minimisation</u> None

Important identified risk: Atypical femoral fractures	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).

Important identified risk: Atypical femoral fractures	
Risk factors and risk groups	The risk of atypical femoral fractures seems to increase with the duration of therapy (Shane et al. 2010; Tile and Cheung 2020). Observational studies showed that women are at increased risk compared to men and Asian women are more prone to atypical femoral fractures compared to White women (Tile and Cheung 2020). The presence of a genetic metabolic bone disorder may be an important risk factor for developing atypical femoral fractures (Tile and Cheung 2020). Atypical femoral fractures have been reported in patients with certain co-morbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain medicinal products (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors) (Shane et al. 2010; Meier et al. 2012; Tile and Cheung 2020). These events have also occurred without antiresorptive therapy.
Risk minimisation measures	Routine risk minimisation SmPC sections 4.4 and 4.8 PL sections 2 and 4 Patients should be advised to report any new or unusual thigh, hip, or groin pain per the SmPC section 4.4. Subject to medical prescription Additional risk minimisation None

Meier RP, Perneger TV, Stern R, Rizzoli R, Peter RE. Increasing occurrence of atypical femoral fractures associated with bisphosphonate use. Arch Intern Med. 2012; 172(12): 930-6.
Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010; 25(11): 2267-94.
Tile L, Cheung AM. Atypical femur fractures: current understanding and approach to management. Ther Adv Musculoskelet Dis. 2020; 12: 1759720x20916983.

Important identified risk: Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).

Important identified risk: Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	
Risk factors and risk groups	The specific risk factors or risk groups for rebound hypercalcaemia associated with denosumab have not yet been established. The literature shows that the individual vitamin D level can represent additional influencing factor (Uday et al. 2018). In general, paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta) represent a risk group for rebound hypercalcaemia. The literature further shows potential male predisposition to rebound hypercalcaemia in children and adolescents, which is in line with the proposed pathophysiology and fact that males tend to have higher bone mass than females (Horiuchi et al. 2021). The correlation between the treatment duration and patient age described in the literature indicates that rebound hypercalcemia occurs following a relatively short treatment duration in juveniles and adolescents compared with adults (Horiuchi et al. 2021).
Risk minimisation measures	<u>Routine risk minimisation</u> SmPC sections 4.2, 4.4, and 4.8 PL section 2 Subject to medical prescription <u>Additional risk minimisation</u> None

Horiuchi K, Kobayashi E, Mizuno T, Susa M, Chiba K. Hypercalcemia following discontinuation of denosumab therapy: A systematic review. Bone Reports. 2021; 15: 101148.
Uday S, Gaston CL, Rogers L, Parry M, Joffe J, Pearson J, et al. Osteonecrosis of the Jaw and Rebound Hypercalcemia in Young People Treated With Denosumab for Giant Cell Tumor of Bone. J Clin Endocrinol Metab. 2018; 103(2): 596-603.

Important potential risk: Fracture healing complications	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).

Important potential risk: Fracture healing complications	
Risk factors and risk groups	The specific risk factors or risk groups for fracture healing complications potentially associated with denosumab have not yet been established. The general risk factors for fracture healing complications include older age, diabetes mellitus, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition (Aspenberg 2005; Gaston and Simpson 2007; Hernandez et al. 2012)
Risk minimisation measures	Routine risk minimisation SmPC section 5.3 Subject to medical prescription Additional risk minimisation None

Aspenberg P. Drugs and fracture repair. Acta Orthop. 2005; 76(6): 741-8.
Gaston MS, Simpson AH. Inhibition of fracture healing. J Bone Joint Surg Br. 2007; 89(12): 1553-60.
Hernandez RK, Do TP, Critchlow CW, Dent RE, Jick SS. Patient-related risk factors for fracture-healing complications in the United Kingdom General Practice Research Database. Acta Orthop. 2012; 83(6): 653-60.

Important potential risk: Infection	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).
Risk factors and risk groups	The specific risk factors or risk groups for infections potentially associated with denosumab have not yet been established. The general risk factors for infections include increasing age, immunosuppression associated with cancer, diabetes mellitus, HIV/AIDS, immunosuppressive drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimisation measures	Routine risk minimisation SmPC sections 4.8 PL sections 4 Subject to medical prescription Additional risk minimisation None

Important potential risk: Cardiovascular events	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).
Risk factors and risk groups	The specific risk factors or risk groups for cardiovascular events potentially associated with denosumab have not yet been established. The general risk factor for cardiovascular events and atherosclerosis include older age, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes mellitus, and medications, including antipsychotics or cyclooxygenase-2 inhibitors.
Risk minimisation measures	Routine risk minimisation Subject to medical prescription Additional risk minimisation None

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	This risk is based on the safety profile of denosumab as reflected in the Product Information and the summary of safety concerns for the reference product PROLIA (denosumab).
Risk factors and risk groups	The specific risk factors or risk groups for the onset of malignancy potentially associated with denosumab have not yet been established. The general factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins.
Risk minimisation measures	Routine risk minimisation Subject to medical prescription Additional risk minimisation 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 authorisation or specific obligation of Obodence.

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

There are no studies required for Obodence.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Hypocalcaemia targeted follow-up questionnaire

Skin infection leading to hospitalisation and infection targeted follow-up questionnaire

Osteonecrosis of the jaw targeted follow-up questionnaire

Hypersensitivity reactions targeted follow-up questionnaire

Atypical femoral fracture targeted follow-up questionnaire

Fracture healing complications targeted follow-up questionnaire

Malignancy targeted follow-up questionnaire

Questionnaire: Hypocalcemia

This form is subject to applicable governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Samsung Bioepis Ltd., does not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

Patient / Case Administrative Information (Please indicate dates as Mmm DD, YYYY)					
Patient Identifier		**Patient initial**		**Gender**	☐ Male ☐ Female
Date of Event Onset				**Date of this Report**	
Weight		lb _____ kg		**Age at time of event**	
Event Reported term					
Study No. *(if applicable)*			**Safety Database case No.**		

Denosumab Administration / Information (Please indicate dates as Mmm DD, YYYY)

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

☐ 60mg SC every 6 months
☐ 120mg 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 were skipped
☐Yes ☐No ☐Unknown
If yes, date of first dose following start of event_____

Signs and Symptoms (Check all that apply)

☐Numbness
(Specify if involving digits and/or peri oral region) _____
☐Convulsions
☐Muscle cramping
☐Syncope
☐None
☐Muscle twitching_
☐Paresthesia
☐Tetany
☐Other_____

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 was > 2.0 X times upper limit of normal?
(Please provide result)_____☐Yes ☐No ☐Unknown
Hypocalcemia induced EKG changes (QT prolongation)? ☐Yes ☐No ☐Unknown

Treatment

Treated 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

Anti arrhythmic medications?
☐Yes ☐No ☐Unknown
If yes, please provide the details such as names and dates of treatment
Anti arrhythmic medications_____

Questionnaire: Hypocalcemia

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

Other treatment? ☐Yes ☐No ☐Unknown
If yes, specify:_____

RISK FACTORS (Check all that apply)

Medical History Risk Factors
Does the patient have any of the following risk factors: ☐Yes ☐No
If yes, please provide dates and details:

☐Acute pancreatitis
☐History of parathyroid disease
☐History of malignancy (please specify)
☐Hyperphosphatemia
☐Recent surgery
☐History of chronic renal disease
☐History of hypoalbuminemia
☐Hypoproteinemia
☐Magnesium deficiency
☐Sepsis

☐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 lime of the hypocalcemia event _____

☐Prior hypocalcemia event (before denosumab treatment)
Please provide dales and details of prior hypocalcemia event _____

Medication Risk Factors
Antineoplastic agents? (Check which apply):☐ cisplatin ☐ cytosine arabinoside ☐ Other_____ ☐ None
Antimicrobials? (Check which apply):☐ pentamidine ☐ ketoconazole ☐ 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)_____
Other concomitant medications _____

Hypocalcemic Event Resolved ☐Yes ☐No ☐Unknown
If yes, what date? (Mmm DD, YYYY) _____

Reporter

Name:
Address:
City:
Email:
Phone: (include country code)
State/Province:
Postal Code:

Signature _____

Date _____

Questionnaire: Infection

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Patient / Case Administrative Information (Please indicate dates as Mmm DD, YYYY)					
Patient Identifier		**Patient Initial**		**Gender**	☐ Male ☐ Female
Date of Event Onset				**Date of this Report**	
Weight		_____lb _____ kg		**Age at Time of Event**	
Event Reported Term					
Study Number *(if applicable)*				**Safety DB case No.**	

Denosumab Administration / Information (Please indicate dates as Mmm DD, YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify diagnosis _____

_____

☐ Other (please specify) _____

_____

☐ Don't know_____

Denosumab Dose

☐ 60mg SC every 6 months

☐ 120mg 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_____

Questionnaire: Infection

Signs and Symptoms (Check all that apply, provide dates of inset, 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_____
_____

Evaluations, Diagnosis & Laboratory Measures (Please attach copy of report)

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N	Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N

Questionnaire: Infection

Reports/Relevant Findings (Please provide dates, baseline information and indicate attachments if available)

Questionnaire: Infection

CHECK WHICH INFECTION APPLIES

☐ 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
- ☐ Lung abscess
- ☐ Legionella pneumonia
- ☐ Mycoplasma pneumonia

☐ 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 _____
- ☐ Coccidioidemycosis 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:_____

Questionnaire: Infection

☐ Other, please specify:_____

☐ Kidney and genito-urinary tract infections

☐ Cystitis _____

☐ Pyelonephritis _____

☐ Urinary tract infection _____

☐ Other, please specify:_____

☐ Systemic infections

☐ Bacteremia _____

☐ Sepsis _____

☐ Toxic shock syndrome _____

☐ Other, please specify:_____

_____

☐ Other infections, please specify:_____

_____

☐ Parasitic evaluation (ova, etc.) _____

_____

DIAGNOSTICS

☐Cultures done
☐No ☐Yes ☐Unknown

If yes, check which apply:

☐ Blood culture _____

☐Culture positive ☐No ☐Yes ☐ Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

☐Urine culture_____

☐Culture positive ☐No ☐Yes ☐ Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

☐Sputum culture _____

☐Culture positive ☐No ☐Yes ☐ Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

☐Synovial culture_____

☐Culture positive ☐No ☐Yes ☐ Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐ Cerebrospinal fluid culture

☐Culture positive ☐No ☐Yes ☐ Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

☐ Tissue culture _____ _

If yes, specify: ☐Brain ☐Lung ☐ Liver ☐Kidney ☐Skin ☐Bone ☐ Other

☐Culture positive ☐No ☐Yes ☐ Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

☐Catheter Tip/Line _____

☐Culture positive ☐No ☐Yes ☐ Unknown

If yes, which ☐Bacterial ☐Fungal ☐Viral

☐Pathogen identified:_____

☐PPD placement ☐No ☐Yes ☐ Unknown

If yes, PPD positive ☐No ☐Yes

☐Unknown

_____

_____

☐Parasitic evaluation (ova, etc.)_____

_____

☐X-ray ☐No ☐Yes ☐Unknown

☐MRI ☐No ☐Yes ☐Unknown

☐CT scan ☐No ☐Yes ☐Unknown

_____

☐Bone scan ☐No ☐Yes ☐Unknown

_____

☐Other_____

☐Rapid test_____

☐Serum titres_____

☐Hospital discharge report_____

_____

☐Other consult report_____

_____

☐Provide final diagnosis and treatment,

if available (please specify)_____

_____

☐Outcome and resolution date_____

Questionnaire: Infection

☐Pathogen identified:_____

Treatment

☐ER antibiotics ☐No ☐Yes ☐ Unknown

If yes,

☐IV ☐Oral ☐SC ☐Both oral and IV

☐Required hospital admission

☐No ☐Yes ☐Unknown

☐ICU admission ☐No ☐Yes ☐ Unknown

If yes, reason for ICU admission_____

_____

Overall length of hospital stay

☐≤1 day ☐> 1 day or ≤ 7 days ☐>7 days

_____

☐In-hospital antibiotics

☐No ☐Yes ☐Unknown

☐If yes, route of administration

☐IV ☐Oral ☐Both oral and IV

☐Other in-hospital treatment

☐Antivirals ☐No ☐Yes ☐Unknown

If yes, route of administration ☐IV ☐ Oral

☐Antifungals ☐No ☐Yes ☐Unknown

If yes, route of administration ☐IV ☐ Oral

☐Surgery ☐No ☐Yes ☐Unknown

☐Hyperbaric oxygen ☐No ☐Yes ☐ Unknown

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 infections/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_____

Exposure to infectious agents (continued)

☐Hospital acquired_____

☐Other_____

☐Steroid exposure_____

☐Insect/tick bite_____

☐Drug or IV drug abuse: Type_____

Amount_____

Frequency_____

☐Alcohol/tobacco use: Type_____

Amount_____

Frequency_____

☐Indwelling catheters_____

☐Recent skin injury_____

_____

☐Recent travel (specify)_____

_____

☐Exposure to animals/zoonotic diseases

(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_____

_____

Questionnaire: Infection

☐ Share personal items (razor, needles, etc)_____

☐ Potentially contaminated food/ liquid_____

Reporter	
Name:	
Address:	
City:	State/Province:
Email:	Postal Code:
Phone: (include country code)	
Signature _____	
Date _____	

Questionnaire: Osteonecrosis of the Jaw

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Patient / Case Administrative Information (Please indicate dates as Mmm DD, YYYY)					
Patient Identifier		**Patient Initials**		**Gender**	☐ Male ☐ Female
Date of Event Onset				**Date of this Report**	
Weight		_____lb _____kg		**Age at Time of Event**	
Event Reported Term					
Study Number *(if applicable)*				**Safety DB Case No.**	

Denosumab Administration / Information (Please indicate dates as Mmm DD, YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify diagnosis _____

_____

☐ Other (please specify) _____

_____

☐ Don't know

Denosumab Dose

☐ 60mg SC every 6 months

☐ 120mg 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

☐ No ☐ Yes ☐ Unknown

If yes, please specify_____

☐ Doses of denosumab given after event began ☐ No ☐ Yes ☐ Unknown

If yes, date of first dose following start of event

_____

Questionnaire: Osteonecrosis of the Jaw

Evidence of Exposed Bone (Please indicate dates as Mmm DD, YYYY)

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

☐ No ☐ Yes ☐ Unknown; please describe _____

Date exposed bone was first visualized/probed:_____

Exposed bone or probed bone that has persisted for more than eight weeks:
☐ No ☐ Yes ☐ Unknown, _____

Prior history of radiation therapy to jaw:

☐ No ☐ Yes ☐ Unknown _____

Prior history of metastatic disease to jaw:

☐ No ☐ Yes ☐ Unknown

Describe:_____

Please describe location(s):

- ☐ Right maxilla (**upper** part), teeth and lateral jaw
- ☐ Left maxilla (**upper** part), teeth and lateral jaw
- ☐ Right maxilla (**upper** part), medial jaw
- ☐ Left maxilla (**upper** part), medial jaw
- ☐ Right mandible (**lower** part) teeth and lateral jaw
- ☐ Left mandible (**lower** part) teeth and lateral jaw
- ☐ Right mandible (**lower** part), medial jaw
- ☐ Left mandible (**lower** part), medial jaw
- ☐ Maxilla hard palate
- ☐ Other (specify) _____

Oral Findings

Evidence of infection: ☐ No ☐ Yes ☐ Unknown

Please describe _____

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

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

If yes, date of complete mucosal coverage _____

Questionnaire: Osteonecrosis of the Jaw

Clinical Symptoms (Please indicate dates as Mmm DD, YYYY)

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

_____

Please describe the clinical signs/symptoms/location:

_____

_____

_____

_____

Consultations (Please indicate all dates as Mmm DD, YYYY)

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

If yes, please give date of examination _____

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

_____

Treatment Information (Please indicate what treatments were administered and indicate dates as Mmm DD, YYYY)

Antibiotics ☐ No ☐ Yes ☐ Unknown

If yes, agent(s)/route/dose _____

Start date _____ Stop date _____

Please describe outcomes of treatment _____

Oral rinses ☐ No ☐ Yes ☐ Unknown

If yes, agent(s)/dose _____

Start date _____ Stop date _____

Please describe outcomes of treatment _____

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

Start date _____ Stop date _____

Please describe outcomes of treatment _____

Hospitalizations ☐ No ☐ Yes ☐ Unknown

If yes, reason for hospitalization _____

Hospitalization begin date _____ Hospitalization end date _____

Please describe outcomes of treatment _____

Questionnaire: Osteonecrosis of the Jaw

Dental History (Please indicate all dates as Mmm DD, YYYY)

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

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

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

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

Start date _____Stop date _____

Draining fistula in affected area ☐ No ☐ Yes ☐ Unknown, Start date _____Stop date _____

Dental abscess in affected area ☐ No ☐ Yes ☐ Unknown, Start date _____Stop date _____

Osteomyelitis in affected area ☐ No ☐ Yes ☐ Unknown, Start date _____Stop date _____

Root-canal treatment near affected area ☐ No ☐ Yes ☐ 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 ☐ No ☐ Yes ☐ Unknown

History of dentures / dental appliance / implant ☐ No ☐ Yes ☐ Unknown
If yes, please specify ☐ Upper ☐ Lower

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

Medications (Please indicate all dates as Mmm DD, YYYY)

PO bisphosphate ☐ No ☐ Yes ☐ Unknown

If yes, agent(s) / dose_____

Start date _____Stop date_____

IV bisphosphate ☐ No ☐ Yes ☐ Unknown

If yes, agent(s) / dose_____

Start date _____Stop date_____

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

If yes, agent(s) / dose_____

Start date _____Stop date_____

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

If yes, agent(s) / dose_____

Start date _____Stop date_____

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

If yes, agent(s) / dose_____

Start date _____Stop date_____

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

Questionnaire: Osteonecrosis of the Jaw

If yes, agent(s) / dose_____

Start date _____Stop date_____

Other History (Please indicate all dates as Mmm DD, YYYY)

Current smoker ☐ No ☐ Yes ☐ Unknown

If yes, estimated number of pack-years_____

If past smoker, stop date_____

Alcohol consumption ☐ No ☐ Yes ☐ Unknown

If yes, estimated of drinks per week_____

Diabetes ☐ No ☐ Yes ☐ Unknown If yes, ☐ Type I ☐ Type II

Patient Reminder Card Status (For EU Patients)

Received a patient reminder card prior to the ONJ event ☐ Yes ☐ No ☐ Unknown

_____

_____

Reporter

Name:

Address:

City: State/Province:

Email: Postal Code:

Phone: (include country code)

Signature _____

Date _____

Questionnaire: Hypersensitivity

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Patient / Case Administrative Information (Please indicate dates as Mmm DD, YYYY)					
Patient Identifier		**Patient Initial**		**Gender**	☐ Male ☐ Female
Date of Event Onset				**Date of this Report**	
Weight		_____lb _____kg		**Age at Time of Event**	
Event Reported team					
Study Number *(if applicable)*				**Safety DB Case No.**	

Denosumab Administration / Information (Please indicate dates as Mmm DD, YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify diagnosis _____

_____

☐ Other (please specify) _____

_____

☐ Don't know

Denosumab Dose

☐ 60mg SC every 6 months

☐ 120mg 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

_____

Questionnaire: Hypersensitivity

Signs and Symptoms (Check all that apply)

☐ Anaphylaxis ☐ Angioneurotic edema ☐ Colic
☐ Facial edema ☐ Hypotension ☐ Laryngeal edema
☐ Rash ☐ Shortness of breath ☐ Strider
☐ Diarrhea ☐ Pruritis ☐ Swelling
☐ Tachycardia ☐ Urticaria ☐ Wheezing ☐ Other (specify) _____

Evaluations, Diagnosis & Laboratory Measures (Please indicate and attach copy of report if available)

Diagnostic	Results/ Units	Reference Range/ Units	Date	Report Attached Y	Report Attached N
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 Y	Report Attached N
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					

Treatments (Please provide dates and indicate attachments if available

☐ ER corticosteroids
Route: ☐ IV ☐ oral

☐ ER anti-histamines
Route: ☐ IV only ☐ oral only ☐ 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 only ☐ oral only ☐ both oral and IV

In-hospital an!i-histaminics
Route: ☐ IV only ☐ oral only ☐ both oral and IV

☐ Other in-hospital treatment
☐ IV vasopressors ☐ Yes ☐ No ☐ Unknown

CONCOMITANT MEDICATIONS

☐ 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
☐ Quinolones

☐ Hypersensitivity event resolved ☐ Yes ☐ No
☐ Unknown
If yes, date (Mmm DD, YYYY):_____

Questionnaire: Hypersensitivity

☐ Intubation/mechanical ventilation ☐ Yes ☐ No ☐ Unknown ☐ Hospital admissions/discharge report (please attach if available) _____ _____ _____ _____ _____	☐ Final diagnosis or etiology (incl. start date). Please send supporting documents for diagnosis _____ _____ ☐ Other consult report (please indicate any attachments) _____ _____ _____ _____

Reporter	
Name:	
Address:	
City:	State/Province:
Email:	Postal Code:
Phone: (include country code)	
Signature _____	
Date _____	

Questionnaire: Postmarketing Reports of Potential Atypical Fracture (low energy, subtrochanteric/femoral shaft fractures)

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Patient / Case Administrative Information (Please indicate dates as Mmm DD, YYYY)					
Patient identifier		**Patient initial**		**Gender**	☐ Male ☐ Female
Date of Event Onset			**Date of this Report**		
Weight	_____lb _____kg		**Age at time of event**		
Event					
Study Number (if applicable)					

Denosumab Administration / Information (Please indicate dates as Mmm DD, YYYY)

Denosumab Indication Drug

☐ Postmenopausal osteoporosis
☐ Bone loss from hormone ablation therapy
Please specify diagnosis _____
_____
☐ Advanced cancer with bone materials
Please specify diagnosis _____
_____
☐ Other (please specify) _____
_____
☐ Don't know_____

Denosumab Dose

☐ 60mg SC every 6 months
☐ 120mg 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 were skipped ☐ Yes ☐ No ☐ Unknown
If yes, date of first dose following start of event_____
_____

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

Type of trauma reported at 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 higher 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

Questionnaire: Postmarketing Reports of Potential Atypical Fracture (low energy, subtrochanteric/femoral shaft fractures)

Date of imaging at time of femur fracture (Mmm DD, YYYY): _____

☐ **Please attach a copy of applicable radiology report(s).**

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
☐ Spiral
☐ Not reported

Fracture radiology report includes:
Simple transverse or oblique (30°) fracture with breaking of the cortex:
☐ Yes ☐ No ☐ Not reported
Diffuse cortical thickening of the proximal femoral shaft:
☐ Yes ☐ No ☐ Not reported

Early symptom of pain over fracture site:
☐ Pain at site at rest
☐ Pain at site with weight bearing
☐ None

Fracture healed (union) within 6 months ☐ Yes ☐ No ☐ Unknown
If yes:
☐ Date of fracture union (Mmm DD, YYYY): _____
☐ Patient able to walk without assistance:
☐ Yes ☐ No ☐ Unknown
☐ Fracture union confirmed through imaging:
☐ Yes ☐ No ☐ Unknown
If yes, check all diagnostic imaging that applies:
☐ X-ray ☐ CT scan ☐ MRI

Treatment Information (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 _____
_____

Medical History/Risk Factors (Check all that 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

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

Prior osteoporosis therapy:
☐ Estrogen
☐ Selective estrogen receptor modulator (SERM)
☐ Bisphosphonate (please indicate)
☐ Intravenous ☐ Oral
If yes, how long has therapy been received? (months, years) _____
☐ Parathyroid hormone

Past medical and surgical history: _____
_____
_____

Questionnaire: Postmarketing Reports of Potential Atypical Fracture (low energy, subtrochanteric/femoral shaft fractures)

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

_____

_____

_____

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

_____

_____

_____

Reporter
Name: Address: City: State/Province: Email: Postal Code: Phone: (include country code) **Signature** _____ **Date** _____

Questionnaire: Fracture Healing

This form is subject to applicable governing laws the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Samsung Bioepis Ltd., does not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

Patient / Case Administrative Information (Please indicate dates as Mmm DD, YYYY)					
Patient Identifier		**Patient Initial**		**Gender**	☐ Male ☐ Female
Date of Event Onset				**Date of this Report**	
Weight		_____lb _____kg		**Age at Time of Event**	
Event Reported Term					
Study Number *(if applicable)*				**Safety DB Case No.**	

Denosumab Administration / Information (Please indicate dates as Mmm DD, YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify diagnosis _____

_____

☐ Other (please specify) _____

_____

☐ Don't know

Denosumab Dose

☐ 60mg SC every 6 months

☐ 120mg 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

_____

Questionnaire: Fracture Healing

Diagnosis (Check all that apply, please indicate dates as Mmm DD, YYYY)

Date of fracture: _____ Date of fracture delayed healing: _____ Date of fracture non-healing:_____

☐ Fracture to upper body (i.e., above waist)

Specify location (check all that apply):

- ☐ Cervical spine
- ☐ Clavicle
- ☐ Hand/metacarpal/phalange
- ☐ Head/face/skull
- ☐ Humerus
- ☐ Olecranon
- ☐ Radius
- ☐ Rib
- ☐ Scapula
- ☐ Shoulder
- ☐ Sternum
- ☐ Ulna
- ☐ Wrist/carpal
- ☐ Other_____

☐ Fracture to lower body (i.e., below waist)

Specify location (check all that 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 that apply):

- ☐ Comminuted
- ☐ Compound
- ☐ Pathologic
- ☐ Poor alignment
- ☐ Poor immobilization of segments
- ☐ Soft tissue injury
- ☐ Unknown

Treatments (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture (check all that apply):

- ☐ Casting _____
- ☐ Non-surgical reduction _____
- ☐ Revision surgery (2nd surgery) _____
- ☐ Surgery _____
- ☐ Traction _____
- ☐ Other _____

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

If yes, provide dale of union (Mmm DD,YYYY):_____

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

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

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

Medical History/Risk Factors (Check all that apply, provide dates and attach relevant reports)

- ☐ Current smoker/tobacco use_____
- ☐ History or current corticosteroid use_____
- ☐ Prior fracture history_____
- ☐ Diabetes_____

Reporter

Name:

Address:

City: State/Province:

Email: Postal Code:

Phone: (include country code)

Questionnaire: Fracture Healing

Signature _____

Date _____

Questionnaire: Malignancy Adverse Events

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Office Patient Identifier:

Patient Initials:

Date of event onset (Mmm DD, 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 (Mmm DD, YYYY):

Tumor stage, if known:_____

Primary site of malignancy:_____

Denosumab Administration / Information (Please indicate dates as Mmm DD, YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy

Please specify diagnosis _____

_____

☐ Advanced cancer with bone metastasis

Please specify diagnosis _____

_____

☐ Other (please specify) _____

_____

☐ Don't know

Denosumab Dose

☐ 60mg SC every 6 months

☐ 120mg 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

Questionnaire: Malignancy Adverse Events

☐ Yes ☐ No ☐ Unknown

If yes, date of first dose following start of event

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 ≤7 days ☐>7 days

Surgical treatment? ☐Yes ☐No ☐Unknown

Chemotherapy (includes biologics)? ☐Yes ☐No ☐Unknown

Hormonal treatment? ☐Yes ☐No ☐Unknown

Radiation treatment? ☐Yes ☐No ☐Unknown

Bone marrow transplant? ☐Yes ☐No ☐Unknown

If yes, ☐autologous ☐heterologous

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 ☐

Questionnaire: Malignancy Adverse Events

Specify:_____

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

Draft Key Messages of the Additional Risk Minimisation Measures

Prior to the launch of OBODENCE in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programmes, with the National Competent Authority.

The educational programme is aimed at reminding to patients about the risk of osteonecrosis of the jaw associated with denosumab therapy.

The MAH shall ensure that in each Member State where OBODENCE is marketed, all healthcare professionals who are expected to prescribe OBODENCE have access to/are provided with the following educational package:

- Patient reminder card.

Patient reminder cards for osteonecrosis of the jaw will be distributed to prescribers of OBODENCE with background information on the purpose of the patient reminder card and instructions to provide it to patients.

Patient reminder card

The patient reminder card is intended to remind patients about the risk of osteonecrosis of the jaw that they need to be aware of before and during the treatment with denosumab injections for osteoporosis and bone loss, including:

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