SANDOZ

EU Risk Management Plan (RMP) for Denosumab 120 mg/1.7 mL, Single Use Vial (Wyost)

RMP Version to be assessed as part of this application:

RMP Version number: 1.1

Data lock point for this RMP: 21-Nov-2023

Date of final sign off: 21-Nov-2023

Rationale for submitting an updated RMP: Not applicable for this initial marketing authorization application submission.

Summary of significant changes in this RMP: Not applicable.

Other RMP versions under evaluation:

No RMP versions are currently under evaluation.

QPPV name: [redacted]Maares

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

Confidentiality Statement

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AFF	Atypical femoral fracture
ATC	Anatomical therapeutic chemical
CTCAE	Common Terminology Criteria for Adverse Events
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU-Prolia/Xgeva	EU-authorized Prolia/Xgeva
GCTB	Giant cell tumor of bone
HALT	Hormone ablation therapy
INN	International non-proprietary name
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NPM	New primary malignancy
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
PD	Pharmacodynamics
PIL	Patient Information Leaflet
PIP	Pediatric investigation plan
PK	Pharmacokinetic
PL	Package leaflet
PMGCTB	Primary malignancy in giant cell tumor of bone
PMO	Post-menopausal osteoporosis
Prolia	Amgen's Prolia®; the registered trademark sign will be omitted from all following instances of Prolia in this document
PSUR	Periodic Safety Update Report
PY	Patient year
Q4W	Once every 4 weeks
QPPV	Qualified Person for Pharmacovigilance
RANK(L)	Receptor activator of nuclear factor kappa-B (Ligand)
RANKL	Receptor activator of nuclear factor kappa-B (Ligand)

RMP	Risk Management Plan
SAE	Serious adverse event
SAF	Safety set
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SRE	Skeletal-related events
Study 101	Short key for Study CGP24112101 used in this document
Study 301	Short key for Study CGP24112301 used in this document
TP1, TP2	Treatment period 1, Treatment period 2 (of Study 301)
US-Prolia/Xgeva	US-licensed Prolia/Xgeva
Xgeva	Amgen's Xgeva®; the registered trademark sign will be omitted from all following instances of Xgeva in this document

Part I: Product(s) Overview

Table I.1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	Denosumab
Pharmacotherapeutic group(s) (ATC Code)	M05BX04
Marketing Authorization Applicant	Sandoz
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Wyost (proposed)
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Denosumab is a fully human immunoglobulin G2 (lgG) monoclonal antibody.
	Summary of mode of action: Binds to and neutralizes the activity of the human RANK ligand (RANKL). In blocking RANKL, denosumab reduces osteoclast-mediated bone resorption.
	Important information about its composition: Denosumab is derived from the Xeno-mouse™ technology and produced in genetically engineered mammalian (Chinese hamster ovary) cells.
Hyperlink to the Product Information	[Proposed SmPC] [Proposed PI]
Indication(s) in the EEA	Current: Prevention of skeletal-related events (SREs) (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone. Treatment of adults and skeletally mature adolescents with giant cell tumor of bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity.
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended dose of Wyost for prevention of SREs is 120 mg administered as a single subcutaneous (SC) injection once every 4 weeks (Q4W) into the thigh, abdomen, or upper arm. Patients must be adequately supplemented with calcium and vitamin D. The recommended dose of Wyost for treatment of adults or skeletally mature adolescents with GCTB is 120 mg Q4W administered as an SC injection, with additional 120 mg SC injections on days 8 and 15 of treatment of the first month of therapy.
	Proposed: Not applicable
Pharmaceutical form(s)	Current: Wyost is supplied in vials as a sterile, preservative-free solution intended for SC injection. The vial presentation contains 120 mg of

and strengths	denosumab in 1.7 mL of solution.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

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

As this is an application under directive article 10(4) biosimilar, modules SI is not applicable.

Part II Safety specification Module SII: Nonclinical part of the safety specification

No comparative nonclinical in vivo studies were conducted with the proposed biosimilar denosumab GP2411. This strategy is consistent with regulatory authority guidance:

- EMEA/CHMP/BMWP/42832/2005 Rev.1, Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.
- EMA/CHMP/BMWP/403543/2010, Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues.
- EMA/CHMP/CVMP/3Rs/677407/2015, Review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products –report on actions taken.
- FDA guidance for industry "Scientific considerations in demonstrating biosimilarity to a reference product" (2015).
- World Health Organization (WHO). Guidelines on evaluation of biosimilars (2022).

Since structural and functional characterization of denosumab vial (GP2411), US- and EU-Xgeva showed similarity between the products, all the nonclinical data generated for Xgeva can be extrapolated to denosumab vial, and nonclinical in vivo testing was not considered necessary to support the similarity between GP2411 and denosumab.

The findings from the originator drug (Xgeva) nonclinical studies are summarized below and are considered as relevant also for the biosimilar denosumab.

Table II.SII.1 Key safety findings from nonclinical studies and relevance to human usage

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

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

Part II Safety specification Module SIII Clinical trial exposure

GP2411 (INN: denosumab) was developed as a biosimilar to Amgen's denosumab with an adequate biosimilar clinical development program. This RMP is dedicated to GP2411 120 mg/1.7 mL, single use vial as a biosimilar to Xgeva (EMEA/H/C/002173).

Additionally, there is a separate RMP for denosumab 60 mg/mL pre-filled syringe with similar ingredients but with a different target population and dosing as a biosimilar to Prolia.

The tailored clinical development program comprised two studies:

- Study 101: a pivotal single-dose comparative PK and PD study to demonstrate PK and PD similarity between GP2411 (120 mg/1.7 mL liquid in vial), EU-Xgeva and US-Xgeva in 502 healthy male subjects (total of 39-week follow-up).
- Study 301: a pivotal integrated PK, PD, confirmatory efficacy and safety study to demonstrate similarity in efficacy, but also in PK and PD between GP2411 (denosumab 60 mg/mL syringe) and EU-Prolia in 527 female subjects with PMO, including a subgroup switching from EU-Prolia to GP2411 (three doses at 26-week interval, total follow-up of 78 weeks).

In Study 101, a total of 499 healthy subjects were treated with study medication, of which 166 subjects received GP2411 (120 mg/1.7 mL liquid in vial vial). Exposure to study drug by race in Study 101 is shown in the following table.

Table II.SIII.1 Study 101: Exposure in healthy volunteers by race (SAF)

	GP2411 (Denosumab vial) N=166 n (%)	**EU-Xgeva N=171 n (%)**	**US-Xgeva N=162 n (%)**
White	163 (98.2)	167 (97.7)	161 (99.4)
Asian	1 (0.6)	2 (1.2)	0
Black or African American	1 (0.6)	1 (0.6)	1 (0.6)
Multiple	1 (0.6)	1 (0.6)	0

In Study 301 in postmenopausal women with osteoporosis, a total of 527 subjects received at least one dose of study medication: During TP1 (up to two doses), 263 subjects were treated with GP2411 (denosumab 60 mg/mL syringe) and 264 subjects with EU-Prolia. In TP2 (week 52 to week 78), of the subjects treated with GP2411, 253 subjects received a third dose. Of the subjects treated with EU-Prolia, 124 subjects were treated with one further dose of GP2411 and 125 subjects continued EU-Prolia, in TP2 (week 52 to week 78). The exposure to study drug in Study 301 is summarized in the following tables.

Table II.SIII.2 Study 301: Exposure in postmenopausal women with osteoporosis by dose (TP1 SAF)

	GP2411 (denosumab 60 mg/mL syringe)		EU-Prolia	
	N=263		N=264	
Dose	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
Total	263 (100)	3133.4	264 (100)	3137.6
1 dose	8 (3.0)	37.1	9 (3.4)	48.4
2 doses	255 (97.0)	3096.3	255 (96.6)	3089.2

Subject-time is the sum of each subject's treatment exposure in months, derived as (date of last visit in TP1 if no TP2 or date of first dose in TP2 – date of first dose +1)/30.25.

Table II.SIII.3 Study 301: Exposure in postmenopausal women with osteoporosis by dose (TP2 SAF)

GP2411/GP2411		EU-Prolia/EU-Prolia		EU-Prolia/GP2411	
N=253		N=125		N=124	
Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
253 (100)	1537.6	125 (100)	752.6	124 (100)	752.5

Subject-time is the sum of each subject's treatment exposure in months, derived as (date of last visit – date of first dose in TP2 +1)/30.25.

GP2411: denosumab 60 mg/mL syringe.

Table II.SIII.4 Study 301: Exposure in postmenopausal women with osteoporosis by age group, during TP1 (TP1 SAF)

	GP2411 (denosumab 60 mg/mL syringe)		EU-Prolia	
	N=263		N=264	
Dose	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
<65 years				
Total	137 (52.1)	1634.7	139 (52.7)	1661.7
1 dose	4 (1.5)	19.2	5 (1.9)	33.8
2 doses	133 (50.6)	1615.4	134 (50.8)	1627.8
>=65 years				
Total	126 (47.9)	1498.7	125 (47.3)	1476.0
1 dose	4 (1.5)	17.9	4 (1.5)	14.6
2 doses	122 (46.4)	1480.9	121 (45.8)	1461.4

Subject-time is the sum of each subject's treatment exposure in months derived as (date of last visit in TP1 if no TP2 or first dose in TP2 - date of first dose + 1) / 30.25.

Table II.SIII.5 Study 301: Exposure in postmenopausal women with osteoporosis by age group, during TP2 (TP2 SAF)

	GP2411/GP2411		EU-Prolia/EU-Prolia		EU-Prolia/GP2411	
	N=253		N=125		N=124	
Pooled Age Group 1	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**
<65 years	132 (52.2)	801.4	61 (48.8)	359.9	72 (58.1)	437.6
>=65 years	121 (47.8)	736.2	64 (51.2)	392.8	52 (41.9)	314.9

Subject-time is the sum of each subject's treatment exposure in months derived as (date of last visit - date of first dose in TP2 + 1)/ 30.25.

GP2411: denosumab 60 mg/mL syringe.

Table II.SIII.6 Study 301: Exposure in postmenopausal women with osteoporosis by race during TP1 (TP1 SAF)

	GP2411 (denosumab 60 mg/mL syringe)		EU-Prolia	
	N=263		N=264	
Dose	**Subjects n (%)**	**Subject-time (months)**	**Subjects n (%)**	**Subject-time (months)**
White				
Total	239 (90.9)	2855.8	240 (90.9)	2846.0
1 dose	6 (2.3)	25.9	9 (3.4)	48.4
2 doses	233 (88.6)	2830.0	231 (87.5)	2797.6
Asian				
Total	23 (8.7)	265.4	24 (9.1)	291.6
1 dose	2 (0.8)	11.3	0	0
2 doses	21 (8.0)	254.1	24 (9.1)	291.6
Multiple				
Total	1 (0.4)	12.2	0	0
1 dose	0	0	0	0
2 doses	1 (0.4)	12.2	0	0

Subject-time is the sum of each subject's treatment exposure in months derived as (date of last visit in TP1 if no TP2 or first dose in TP2 - date of first dose + 1) / 30.25.

Table II.SIII.7 Study 301: Exposure in postmenopausal women with osteoporosis by race during TP2 (TP2 SAF)

	GP2411/GP2411		Prolia/Prolia		Prolia/GP2411	
	N=253		N=125		N=124	
Race (L)	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)	Subjects n (%)	Subject-time (months)
White	231 (91.3)	1403.3	111 (88.8)	667.3	116 (93.5)	704.2
Asian	21 (8.3)	128.3	14 (11.2)	85.4	8 (6.5)	48.4
Multiple	1 (0.4)	6.0	0	0	0	0

Subject-time is the sum of each subject's treatment exposure in months derived as (date of last visit - date of first dose in TP2 + 1)/ 30.25.

GP2411: denosumab 60 mg/mL syringe.

Part II Safety specification Module SIV: Populations not studied in clinical trials

Since this MAA has been submitted for a similar biological medicinal product under article 10(4) of Directive 2001/83/EC, as amended, a tailored clinical program was justified.

In the development of GP2411 as a similar biological medicinal product to Prolia and Xgeva, an efficacy and safety study was conducted in patients with PMO (Study 301), and a PK and PD study in healthy volunteers (Study 101).

Extensive analytical and functional comparisons between EU-Prolia/Xgeva and US-Prolia/Xgeva together with the demonstrated clinical PK and PD similarity of US-Xgeva and EU-Xgeva establish the scientific bridge between EU-Prolia/Xgeva and US- Prolia/Xgeva. This bridge allows to conclude that clinical study results obtained with one regional version (US or EU) and presentation (60 mg/mL syringe or 120 mg/1.7 mL vial) are applicable also for the other regional versions and presentations.

The safety and efficacy profile of GP2411 were shown to be similar to the originator products Xgeva and Prolia.

The exclusion criteria in the clinical studies mostly pertain to known contraindications or warnings for denosumab. These exclusion criteria do not constitute a significant lack of information for the target population of denosumab.

No GP2411 clinical study has included children. Use in pediatric patients is not considered a safety concern in this RMP, since denosumab (120 mg/1.7 mL vial presentation) is not indicated for use in pediatric patients.

Part II SIV.1. Exclusion criteria in pivotal clinical studies within the development program

Most exclusion criteria applied in the clinical studies with GP2411 aimed at optimization of study conduct and minimization of bias and confounding of study results and were not related to safety concerns.

In addition, as a standard precautionary measure to avoid potential harm to study subjects to the extent reasonably possible, patients with underlying diseases that might deteriorate during treatment with GP2411 were excluded from the clinical studies with GP2411.

Such underlying diseases leading to study exclusion included hypocalcemia, active infections, significant cardiovascular disorders, malignancies or patients who could develop fracture healing complications; please refer to the important risks in Section SVII.3 and/or appropriate warnings and recommendations which are included in the denosumab 120 mg/1.7 mL vial (Wyost) SmPC.

Part II SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Denosumab 120 mg/1.7 mL vial has been developed as a biosimilar and the safety and efficacy profile is similar to its reference product Xgeva. Therefore, a limited clinical development program as required for biosimilars was performed.

The clinical development program was conducted in patients with postmenopausal osteoporosis (PMO) and in healthy volunteers. In this setting, it is unlikely to be able to detect certain types

of adverse reactions, either because they are rare adverse reactions with a long latency, those caused by prolonged or cumulative exposure or those specific to other target populations not assessed in GP2411 pivotal trials.

However, these types of adverse reactions could be detected during the more extensive clinical development and post-marketing experience of the reference drug. The established safety profile of the originator is also applicable for the biosimilar.

Clinical trial experience with GP2411 (60 mg/mL in syringe, as biosimilar to Prolia) comprises 387 patients with postmenopausal osteoporosis (PMO) of at least 55 years. The study population had a bone mineral density (BMD) value equivalent to a T-score of ≤-2.5 at the lumbar spine, total hip, or femoral neck, as measured by dual energy X-ray absorptiometry (DXA) and received three injections of 60 mg s.c. denosumab.

In addition, GP2411 (120 mg/1.7 mL in vial, as biosimilar of Xgeva) was studied in 166 healthy volunteers that received one 35 mg dose of denosumab and were followed-up for up to 9 months.

Part II SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Children

There is no clinical trial experience with GP2411 in children.

In line with the Pediatric Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use, GP2411, as similar biological medicinal product, is exempted from the requirement to submit a Pediatric Investigational Plan (PIP).

See section 4.2 of the Xgeva SmPC for information on pediatric use:

The safety and efficacy of denosumab 120 mg/1.7 mL vial has not been established in pediatric patients (age < 18 years) other than skeletally mature adolescents (aged 12-17 years) with giant cell tumor of bone.

Denosumab 120 mg/1.7 mL, single use vial is not recommended in pediatric patients (age < 18 years) other than skeletally mature adolescents (aged 12-17 years) with giant cell tumor of bone. Treatment of skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity: the posology is the same as in adults.

There is currently an ongoing PIP for denosumab (Prolia, Xgeva) agreed upon with the EMA (EMEA-000145-PIP02-12-M04).

Elderly

Clinical trial experience with GP2411 in elderly subjects is extensive as all subjects of the confirmatory efficacy and safety study population (Study 301: GP2411 and EU-Prolia in PMO) were aged ≥55 and ≤80 years at screening. Of the treated 527 patients, 251 (47.6%) were ≥65 years at screening.

The PK properties of GP2411 and EU-Xgeva and US-Xgeva are similar. Following the information available for the reference product, no dose adjustment is required for GP2411 in elderly (≥65 years).

Pregnant or lactating women

No clinical experience with GP2411 in pregnant or lactating women is available.

There are no adequate data from the use of denosumab in pregnant or lactating women. Eight pregnancies have been reported in the clinical development program of the reference product.

Denosumab is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab 120 mg/1.7 mL, single use vial. Any effects of denosumab 120 mg/1.7 mL, single use vial is likely to be greater during the second and third trimesters of pregnancy since monoclonal IgG2 antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Renal impairment

Xgeva SmPC section 4.4: Patients with severe renal impairment (creatinine clearance <30 mL/min) or receiving dialysis are at greater risk of developing hypocalcemia. The risk of developing hypocalcemia and accompanying elevations in parathyroid hormone increases with increasing degree of renal impairment. Regular monitoring of calcium levels is especially important in these patients.

No data with GP2411 is available in patients with severe renal impairment (GFR < 30 mL/min).

Hepatic impairment

The safety and efficacy of denosumab have not been studied in patients with hepatic impairment.

Table II.SIV.1 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	In Study 101, most patients were white. Patients of different ethnic origin were Asian or Black.
Subpopulations carrying relevant genetic	Not included in the clinical development program.

Type of special population	Exposure
polymorphisms	
Other - Children - Elderly	Not included in the clinical development program. The study population in Study 301 was aged ≥55 and ≤80 years at screening. Of the treated 527 subjects, 251 (47.6%) were ≥65 years at screening.

Part II Safety specification Module SV: Post-authorization experience

Not applicable for this initial submission.

Part II Module SV.1. Post-authorization exposure

Not applicable for this initial submission.

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

Potential for misuse for illegal purposes

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

Part II Safety specification Module SVII: Identified and potential risks

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

GP2411 was developed as a biosimilar to the reference product, Xgeva. Therefore, the safety concerns of the biosimilar are expected to be the same as those for the originator Xgeva. No new safety concerns were identified in the clinical development program for GP2411.

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

Not applicable.

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

This is the first RMP for GP2411. Hence, the risks already included in this RMP are based on the originator RMP only as there is no data from the GP2411 program so far which would justify the inclusion of additional risks.

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

Not applicable for this initial submission.

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

In the following, GP2411 safety data are presented from both studies (Study 101 and Study 301).

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

Table II.SVII.1 Important identified Risk: Osteonecrosis of the jaw

Potential mechanisms	Osteonecrosis of the jaw (ONJ) appears to be of multifactorial origin. Multiple hypotheses about possible mechanisms have been postulated, including inhibition of bone remodeling, infection and/or inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. Yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact (based on Xgeva RMP).
Evidence source(s) and strength of evidence	This risk was identified in randomized, controlled phase 3 studies of the originator drug (Xgeva), and further supported by postmarketing reports.
Characterization of the risk:	**Frequency:** No cases of ONJ have been reported during Study 101 or Study 301. **Severity:** Not applicable. **Reversibility:** In general, ONJ events are clinically reversible. The majority of ONJ cases resolve with denosumab treatment interruption or discontinuation. Surgical treatment may be required; bone resection is not usually necessary. **Long-term outcomes:** No data on long-term outcomes are available. **Impact on quality of life:** Discomfort associated with ONJ lesions and/or with

	more extensive treatments may impact patient wellbeing via decreased oral intake (e.g., decreased hydration and decreased nutritional intake).
Risk factors and risk groups	Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Xgeva RMP).
Preventability	A dental examination with appropriate preventive dentistry is recommended prior to treatment with denosumab, especially in patients with risk factors. While on treatment, patients should avoid invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while on denosumab should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with denosumab, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves. Good oral hygiene practices should be maintained during treatment with denosumab and dental health should be monitored.
Impact on the benefit-risk balance of the product	The risk of ONJ has been considered in the product benefit-risk assessment. In light of the product labeling and a patient reminder card that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected based on the relative frequency observed in clinical trials and with the observations that most ONJ events appear to be moderate to severe in severity and resolve without requiring extensive surgical treatment.

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

There were no reports of osteonecrosis of the jaw in Study 101 or Study 301.

Table II.SVII.2 Important identified Risk: Atypical Femoral Fracture

Potential mechanisms	Prolonged suppression of bone turnover may be associated with increased risk of atypical femoral fracture (AFF), but the pathogenesis remains unclear and causes of AFF are likely multifactorial. Based on nonclinical studies of bisphosphonates, collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF.
Evidence source(s) and strength of evidence	This risk was identified in randomized, controlled, phase 3 clinical trials and in open-label, phase 2 clinical trials. This risk was further supported by Xgeva postmarketing reports.
Characterization of the risk:	**Frequency**: No subject experienced an atypical femur fracture during the clinical development program of GP2411 (Study 101 and Study 301) **Severity**: Not applicable. **Reversibility**: It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued. **Long-term outcomes:** No data on long-term outcomes are available.

	Impact on quality of life: As with other hip fractures, AFF can cause short-term or long-term quality of lifedisability. Some data suggests that healing of AFF may be more prolonged than a typical femoral fracture.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.
Preventability	No data are currently available on potential measures to prevent AFF. Patients using long-term antiresorptives may experience pain over the femur, which requires radiological examination if atypical fracture is suspected.
Impact on the benefit-risk balance of the product	The risk of AFF events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Based on the frequency of AFF, the size of the indicated populations, and usage patterns of denosumab in clinical practice, no significant additional public health impact is expected.

AFF = atypical femoral fracture; RA = rheumatoid arthritis

There were no reports of atypical femoral fracture in Study 101 or Study 301.

Table II.SVII.3 Important identified risk: Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons

Potential mechanisms	The mechanism(s) of hypercalcemia several months after the last dose of denosumab in patients with GCTB and in patients with a growing skeleton are not well characterized, but may be a consequence of the following, alone, or in combination: Denosumab treatment and resultant RANK/RANKL pathway inhibition in adults with giant cell containing lesions such as GCTB leads to histopathologic evidence of a dramatic decrease in osteoclast-like giant cells which is complemented by woven bone formation and calcification within the tumors and even at sites of distant metastases. It is possible this calcium could serve as a depot that is mobilized with reactivation of tumor associated, RANKL driven giant cell mediated osteolysis following cessation of denosumab. • Hypercalcemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification such as in patients with a growing skeleton. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from the skeleton either near the growth plates (as can be the case with the young adult and adolescent patients) or from the giant cell tumors themselves that have partially ossified in the cases of the adult patients with tumor recurrence via an autocrine/paracrine mechanism. • The magnitude of the resorptive response following treatment withdrawal in

	the patients with GCTB and in those with an immature skeleton could be dictated by the normal high rate of bone turnover within the GCTB lesion or in the growing skeleton of young patients. The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in young individuals or may be affected by intratumor signaling pathways (e.g., parathyroid hormone-related protein) in GCTB.
Evidence source(s) and strength of evidence	This risk was identified in phase 2 clinical trials of adolescent and adult patients with GCTB, and in postmarketing reports of pediatric patients using denosumab for unauthorized indications.
Characterization of the risk:	**Frequency:** There were no adverse events (AEs) were observed, due to the exclusion criteria in the Study 101. **Severity:** Not applicable. **Reversibility:** Hypercalcemia is reversible with appropriate supportive therapy. **Long-term outcomes:** No data on long-term outcomes are available. **Impact on quality of life:** Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury.
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of denosumab. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older. Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large amounts of calcium through dairy products or more recently liberal use of calcium supplements.
Preventability	No preventive measures are known. Monitor patients for signs and symptoms of hypercalcemia and treat appropriately. Periodic serum calcium assessments should be given to at-risk patients as clinically indicated.
Impact on the benefit-risk balance of the product	The risk of hypercalcemia events several months after the last dose patients with GCTB and in patients with growing skeletons has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	No significant public health impact is expected as hypercalcemia several months after the last dose in patients with GCTB occurs uncommonly and GCTB is a rare tumor. Off-label use of denosumab in pediatric patients appears to be limited to rare conditions for which there is significant unmet medical need.

Table II.SVII.4 Important potential risk: Cardiovascular events

Potential mechanisms	Elevated levels of osteoprotegerin (OPG) have been associated with coronary artery disease in cross-sectional studies, but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists.
Evidence source(s) and strength of evidence	The risk of cardiovascular events is a regulatory concern based on the epidemiological association between OPG levels and cardiovascular disease.

	Clinical data have not substantiated a cause-and-effect relationship between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable cardiovascular outcomes.
Characterization of the risk:	**Frequency:**In Study 101, two subjects (1.2%) in GP2411 arm, one subject (0.6%) in EU-Xgeva and two subjects (1.2%) in US-Xgeva arm experienced cardiovascular events. In Study 301, 12 (4.6%) subjects in GP2411 arm and 7 (2.7%) subjects in EU-Prolia arm experienced cardiovascular events during TP1. During TP2, one (0.4%) subject in the GP2411/GP2411 arm and one (0.8%) subject in the EU-Prolia/EU-Prolia arm experienced cardiovascular events. In the EU-Prolia/GP2411 arm no AEs were reported during TP2. **Severity:** Most cardiovascular events reported were either grade 1 or grade 2. In Study 101, one event in group GP2411 was grade 3. No AEs with grade 4 or 5 occurred during the study. There was only one SAE reported in the course of Study 101 (in treatment group GP2411). In Study 301, during TP1 there was one sudden death in a subject with underlying cardiovascular comorbidities in the GP2411 arm (no autopsy was performed and no cause of death was reported). All other AEs were graded either grade1 or grade 2. Two (0.8%) cardiovascular events in GP2411 treatment arm were classified as serious adverse events. No SAEs were reported during TP1 in EU-Prolia group. During TP2, none of the cardiovascular events were graded grade 3 or higher. There was no SAE reported during TP2. **Reversibility:** No data on reversibility are available. **Long-term outcomes:** No data on long-term outcomes are available. **Impact on quality of life:** Cardiovascular events vary greatly in severity. For some severe events, patients may be hospitalized for treatment and disability may occur.
Risk factors and risk groups	Amgen's denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular events than that of the general population. Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors.
Preventability	Based on clinical data to date, denosumab has not been associated with an increased incidence or severity of cardiovascular adverse effects; therefore, no preventive measures are defined. Patients at risk of cardiovascular events should be managed according to usual standards of care.
Impact on the benefit-risk balance of the product	The risk of cardiovascular events has been considered in the product benefit-risk risk assessment, and the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact on cardiovascular disease severity or incidence is not expected based on the information from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis (PMO)/hormone ablation therapy (HALT) settings.

The following table shows the incidence of cardiovascular events in healthy volunteers in Study 101.

Table II.SVII.5 Clinical trial data of GP2411 of cardiovascular events in healthy volunteers, (Study 101, SAF)

	GP2411 (vial)	EU-Xgeva	US-Xgeva
	N=166	**N=171**	**N=162**
	n (%)	**n (%)**	**n (%)**
Number of subjects with at least one event	2 (1.2)	1 (0.6)	2 (1.2)

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 09-May-2022

The following table shows the incidence of cardiovascular events in Study 301 during TP1.

Table II.SVII.6 Clinical trial data of GP2411 (denosumab syringe): Cardiovascular events in postmenopausal women with osteoporosis (Study 301, TP1; TP1SAF)

	GP2411 (denosumab 60 mg/mL syringe)	EU-Prolia
	N=263	**N=264**
	n (%)	**n (%)**
Number of subjects with at least one event	12 (4.6)	7 (2.7)

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.

The following table shows the incidence of cardiovascular events in Study 301 during TP2.

Table II.SVII.7 Clinical trial data of GP2411 of cardiovascular events in postmenopausal women with osteoporosis, (Study 301, TP2; TP2SAF)

	GP2411/GP2411	Prolia/Prolia	Prolia/GP2411
	N=253	N=125	N=124
	n (%)	n (%)	n (%)
Number of subjects with at least one event	1 (0.4)	1 (0.8)	0

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.
GP2411: denosumab 60 mg/mL syringe; Prolia: EU-Prolia

Table II.SVII.8 Important potential risk: Malignancy

Potential mechanisms	The risk of malignancy is a theoretical concern that RANKL inhibition may lead to an increased risk for a new primary malignancy (NPM) by impairing immune surveillance mechanisms.
Evidence source(s) and strength of evidence	Imbalance is observed in the NPM events between the zoledronic acid and Xgeva treatment groups in the pivotal clinical studies. The results of a postmarketing retrospective cohort study with Xgeva, showed NPM incidence

	rates for Xgeva were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with Xgeva.
Characterization of the risk:	**Frequency:** In study 101, only one (0.6%) AE was reported (in the EU-Xgeva arm of the trial). In Study 301, 4 (1.5%) subjects in GP2411 arm and 3 (1.1%) subjects in EU-Prolia arm experienced an AE, described as malignancy, during TP1. During TP2, two (0.8%) AEs in the GP2411/GP2411 arm were reported. **Severity:** In Study 101, one AE (which was an SAE) with grade 2 severity occurred. In TP1 of Study 301, one AE grade 1, one AE grade 2, and two AEs with grade 3 were observed in GP2411 arm of the trial. In the EU-Prolia arm, one AE grade 1, one AE grade 3, and one AE grade 4 were observed. In each treatment arm during TP1, two SAEs were reported. During TP2 of Study 301, two AEs were reported in group GP2411/2411. Both AEs were grade 3 and considered serious. **Reversibility:** No data on reversibility are available. **Long-term outcomes:** No data on long-term outcomes are available. **Impact on quality of life:** Malignancy is typically disabling and may require surgery, chemotherapy, and/or radiotherapy.
Risk factors and risk groups	General factors for increasing risk of NPM include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
Preventability	Malignant neoplasms have become increasingly recognized and current recommendations include vigilance for these cancers in adult cancer survivors.
Impact on the benefit-risk balance of the product	The risk of malignancy events has been considered in the product benefit-risk assessment. In light of the product labeling that has been proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Significant public health impact is not expected based on the information from studies in the PMO/HALT and advanced cancer settings.

The following table shows the incidence of malignancy in healthy volunteers in Study 101 and Study 301.

Table II.SVII.9 Clinical trial data of GP2411 of malignancy in healthy volunteers, (Study 101, SAF)

	GP2411 (vial)	EU-Xgeva	US-Xgeva
	N=166	N=171	N=162
	n (%)	n (%)	n (%)
Number of subjects with at least one event	0	1 (0.6)	0

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 09-May-2022

The following table shows the incidence of malignancy in study 301 during TP1.

Table II.SVII.10 Clinical trial data of GP2411 (denosumab syringe): Malignancy in postmenopausal women with osteoporosis (Study 301, TP1; TP1SAF)

	GP2411 (denosumab 60 mg/mL syringe)	EU-Prolia
	N=263	N=264
	n (%)	n (%)
Number of subjects with at least one event	4 (1.5)	3 (1.1)

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.

The following table shows the incidence of malignancy in study 301 during TP2.

Table II.SVII.11 Clinical trial data of GP2411 of malignancy in postmenopausal women with osteoporosis (Study 301, TP2; TP2SAF)

	GP2411/GP2411	Prolia/Prolia	Prolia/GP2411
	N=253	N=125	N=124
	n (%)	n (%)	n (%)
Number of subjects with at least one event	2 (0.8)	0	0

MedDRA version 25.0, CTCAE version 5.0, Case Retrieval Strategy Date: 03-May-2022.
GP2411: denosumab 60 mg/mL syringe; Prolia: EU-Prolia

Table II.SVII.12 Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumor of bone

Potential mechanisms	Due to well described sampling error at the time of GCTB diagnosis, primary malignancy in giant cell tumor of bone (PMGCTB) may be missed and benign GCTB may be presumed. Based on the mechanism of action and pathology of GCTB, denosumab is only expected to treat benign GCTB. However, there was a theoretical concern that treatment of an undiagnosed PMGCTB with denosumab could delay the diagnosis of PMGCTB.
Evidence source(s) and strength of evidence	The risk of delay in diagnosis of primary malignancy in giant cell tumor of bone is a regulatory concern based on difficulties in diagnosing primary malignancy in giant cell tumor of bone (PMGCTB). This safety concern was identified in the clinical trial setting.
Characterization of the risk:	**Frequency:** Due to the exclusion criteria of study 101, no AEs were observed. **Severity:** Not applicable. **Reversibility:** Not applicable. **Long-term outcomes:** No data on long-term outcomes are available. **Impact on quality of life:** Malignancy is typically disabling and may require surgery, chemotherapy, and /or radiotherapy.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.
Preventability	No preventive measures are known.
Impact on the benefit-risk	The risk of delay in diagnosis of PMGCTB events has been considered in the product benefit-risk assessment. In light of the product labeling that has been

balance of the product	proposed to minimize this risk, the overall benefit-risk balance is considered to be positive.
Public health impact	Given that GCTB is very rare condition, no impact on public health is expected.

Table II.SVII.13 Important potential risk: Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons

Potential mechanisms	The pathogenesis of hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in bone turnover activity. Upon cessation of denosumab, the disinhibition of RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (i.e., subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodeling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcemia in susceptible individuals if the normal homeostatic mechanism regulating serum calcium are not appropriately maintained.
Evidence source(s) and strength of evidence	Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and pediatric populations.
Characterization of the risk:	**Frequency:** Due to the exclusion criteria of Study 101, no AEs were observed. **Severity:** Not applicable. **Reversibility:** No data on reversibility are available. **Long-term outcomes:** No data on long-term outcomes are available. **Impact on quality of life:** Patients may present with severe hypercalcemia requiring hospitalization. Patients who experience hypercalcemia may develop complications such as acute renal injury.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.
Preventability	No preventive measures are known.
Impact on the benefit-risk balance of the product	The risk of hypercalcemia events following treatment discontinuation in patients other than those with GCTB or growing skeletons has been incorporated in the product benefit-risk assessment, and the overall benefit-risk balance remains positive.
Public health impact	No significant public health impact is anticipated as the potential events remain infrequent despite extensive market exposure.

SVII.3.2. Presentation of the missing information

Table II.SVII.14 Missing information: Patients with prior intravenous bisphosphonate treatment

Evidence source	The incidence of ONJ in patients with prior IV bisphosphonate use was similar to that of patients who only received denusomab in a study of the reference product Xgeva. No notable association was evident between ONJ and prior use of bisphosphonates. In study 101, due to exclusion criteria no such information was evident
Population in need of further characterization	There is information from studies in patients with cancer showing that there is no increased risk of serious complications caused by bone metastases in patients who received Xgeva following treatment with bisphosphonates. However, more information is needed.

Table II.SVII.15 Missing information: Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant tumor of bone

Evidence source	The overall safety profile of denusomab in a completed study using the reference product was similar to the safety profile of Xgeva observed in the treatment of subjects with advanced cancer andbone metastases. In study 101, due to exclusion criteria no such information was evident.
Population in need of further characterization	Information on safety with long-term treatment and with long-term follow-up in adults or adolescents with GCTB will be monitored by routine pharmacovigilance activities.

Table II.SVII.16 Missing information: Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity

Evidence source	No formal studies have been completed to determine denosumab's effect on off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity. In study 101, due to exclusion criteria no such information was evident.
Population in need of further characterization	Information is not available on safety in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Part II Safety specification Module SVIII: Summary of the safety concerns

Table II.SVIII.1 Summary of safety concerns

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

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

Part III.1. Routine pharmacovigilance activities

No special important risks have been identified for denosumab which require additional pharmacovigilance activities other than routine pharmacovigilance.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists

Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

Table III.1 Specific adverse reaction follow-up questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Osteonecrosis of the jaw	Osteonecrosis of the jaw	To monitor the nature of ONJ in patients treated with Wyost in the post-marketing environment.
Atypical fracture	Atypical femoral fracture	To monitor the nature of AFF reportedin patients treated with Wyost in the post-marketing environment.

The forms have been appended in Annex 4 of the RMP.

Part III.2. Additional pharmacovigilance activities

Not applicable as no additional pharmacovigilance activities are proposed for denosumab.

Part III.3 Summary Table of additional pharmacovigilance activities

Not applicable as no additional pharmacovigilance activities are proposed for denosumab.

Part IV: Plans for post-authorization efficacy studies

No post-authorization efficacy studies are in place or planned.

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

Risk Minimization Plan

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

Part V.1. Routine risk minimization measures

Routine risk minimization measures are aligned to the reference medicinal product.

Table V.1 Routine risk minimization activities

Safety concern	Routine risk minimization activities
Important identified risk	
Osteonecrosis of the jaw	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Routine risk minimization activities recommending specific clinicalmeasures to address the risk: • Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC.
Atypical femoral fracture	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC.
Hypercalcemia several months afterthe last dose in patients with giant cell tumor of bone and in patients with growing skeletons	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2

Safety concern	Routine risk minimization activities
	• PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for monitoring the patients for signs and symptoms of hypercalcemia after discontinuation of denosumab treatment are included in Section 4.4 of SmPC and Section 2 of the PIL.
Important potential risks	
Cardiovascularevents	Routine risk communication: • None
Malignancy	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for monitoring the patients for radiological signs of malignancy, new malignancy, or osteolysis are included in Section 4.4 of SmPC.
Delay in diagnosis of primary malignancy in giant cell tumor of bone	Routine risk communication: • None
Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons	Routine risk communication: • None
Missing information	
Patients with prior intravenous treatment with bisphosphonate treatment	Routine risk communication: • SmPC Section 4.5 • PIL Section 2
Safety with long-termtreatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with GCTB	Routine risk communication: • None
Off-label use in patients with GCTBthat is resectable where resection is unlikely to result in severe morbidity	Routine risk communication: • None

Part V.2. Additional Risk minimization measures

Osteonecrosis of the jaw is the only risk requiring additional risk minimization measures; this in order to prevent the occurrence of this risk.

Patient Reminder Card for Osteonecrosis of the jaw (ONJ)

Objectives:

To minimize the risk for the side effect "Osteonecrosis of the jaw (ONJ)".

Rationale for the additional risk minimization activity:

To reduce the risk of ONJ in patients treated with GP2411.

Target audience and planned distribution path:

Patient reminder cards are provided to GP2411-prescribing physicians for distribution to patients receiving GP2411.

Routine pharmacovigilance activities will be performed to identify new safety signals and monitor reporting trends.

The complete patient reminder card can be found in Annex 6.

Part V.3. Summary of risk minimization measures

Table V.3 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Osteonecrosis of the jaw	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • Patient Information Leaflet (PIL) Section 2 • PIL Section 4 Additional risk minimization measures: • Patient reminder cards	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None
Atypical femoral fracture	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important potential risks		
Cardiovascular events	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Malignancy	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Delay in diagnosis of primary malignancy in giant cell tumor of bone	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing information		
Patients with prior intravenous bisphosphonate treatment	Routine risk minimization measures: • SmPC Sections 4.5 • PIL Section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Safety with long-term treatment and with	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and

Safety concern	Risk minimization measures	Pharmacovigilance activities
long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	• None Additional risk minimization measures: • None	signal detection: • None Additional pharmacovigilance activities: • None
Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Part VI: Summary of the risk management plan for Wyost (INN: denosumab)

This is a summary of the risk management plan (RMP) for Wyost (denosumab 120 mg/1.7 mL, single use vial), a biosimilar to Xgeva. The RMP details important risks of Wyost, how these risks can be minimized, and how more information will be obtained about Wyost risks and uncertainties (missing information).

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

This summary of the RMP for Wyost should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Wyost's RMP.

Part VI: I. The medicine and what it is used for

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

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

https://www.ema.europa.eu/en/medicines/human/EPAR/Wyost.

Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

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

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

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

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

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

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

Part VI – II.A: List of important risks and missing information

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

Table VI.II.1 List of important risks and missing information

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

Part VI – II.B: Summary of important risks

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

Table VI.II.2 Important identified risk: Osteonecrosis of the jaw

Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase 3 clinical trials of the reference drug Xgeva. This risk was further supported by Xgeva postmarketing reports.
Risk factors and risk groups	Risk factors associated with osteonecrosis of the jaw (ONJ) include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • Patient Information Leaflet (PIL) Section 2 • PIL Section 4 Additional risk minimization measures: • Patient reminder cards

Table VI.II.3 Important identified risk: Atypical femoral fracture

Evidence for linking the risk to the medicine	This risk was identified in randomized, controlled, phase 3 clinical trials and in open-label phase 2 clinical trial of the reference drug Xgeva. This risk was further supported by Xgeva postmarketing reports.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture (AFF). Corticosteroids have also been reported in the literature to potentially be associated with AFF. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • None

Table VI.II.4 Important identified risk: Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons

Evidence for linking the risk to the medicine	This risk was identified in Xgeva phase 2 clinical trials of adolescent and adult patients with giant cell tumor of bone (GCTB), and in postmarketing reports of pediatric patients using denosumab for unauthorized indications.
Risk factors and risk groups	Patients with GCTB and young patients with growing skeletons following discontinuation of denusomab. In general, the most common cause of hypercalcemia in humans is hyperparathyroidism, particularly among women and individuals aged 65 years or older. Hyperthyroidism and rhabdomyolysis associated with renal failure also increase the risk of hypercalcemia, as does the ingestion of large of amounts of calcium through dairy products or more recently liberal use of calcium supplements.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Additional risk minimization measures: • None

Table VI.II.5 Important potential risk: Cardiovascular events

Evidence for linking the risk to the medicine	The risk of cardiovascular events is a regulatory concern based on the epidemiological association between osteoprotegerin (OPG) levels and cardiovascular disease in man. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of receptor activator of nuclear factor kappa B-ligand (RANKL) and undesirable cardiovascular outcomes.
Risk factors and risk groups	The denosumab development program comprised Xgeva studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population. Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None.

Table VI.II.6 Important potential risk: Malignancy

Evidence for linking the risk to the medicine	Imbalance is observed in the new primary malignancy (NPM) events between the zoledronic acid and Xgeva treatment groups in the pivotal clinical studies. The results of a postmarketing retrospective cohort study, showed NPM incidence rates for Xgeva were generally lower than those for zoledronic acid in unadjusted analyses, suggesting no obvious excess risk associated with Xgeva.
Risk factors and risk groups	General factors for increasing risk of new primary malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, advanced cancer populations are at increased risk for NPM because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 4 Additional risk minimization measures: • None

Table VI.II.7 Important potential risk: Delay in diagnosis of primary malignancy in giant cell tumor of bone

Evidence for linking the risk to the medicine	The risk of delay in diagnosis of primary malignancy in giant cell tumor of bone is a regulatory concern based on difficulties in diagnosing primary malignancy in giant cell tumor of bone (PMGCTB). This safety concern was identified in the clinical trial setting of the reference product.
Risk factors and risk groups	Patients with GCTB are known to be at risk for PMGCTB.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Table VI.II.8 Important potential risk: Hypercalcemia several months after the last dose in patients other than those with giant cell tumor of bone or growing skeletons

Evidence for linking the risk to the medicine	Hypercalcemia several months after the last dose in patients other than those with GCTB or growing skeletons is a theoretical concern based on the identified risk in other specific populations, GCTB, and pediatric populations.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.
Risk minimization measures	Routine risk minimization measures:

	• None Additional risk minimization measures: • None

Table VI.II.9 Missing information: Patients with prior intravenous bisphosphonate treatment

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.5 • PIL Section 2 Additional risk minimization measures: • None

Table VI.II.10 Missing information: Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone

Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Table VI.II.11 Missing information: Off-label use in patients with giant cell tumor of bone that is resectable where resection is unlikely to result in severe morbidity

Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

Part VI – II.C: Post-authorization development plan

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

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

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

There are no studies required for Wyost.

Part VII: Annexes

Annex 4 – Specific adverse drug reaction follow-up forms

- Annex 4.1 - Follow-up form: Potential ONJ
  (Version 1.0/Dec-2021)
- Annex 4.2 - Follow-up form: Potential atypical fracture
  (Version 1.0/Dec-2021)

Annex 4.1 – Follow-up form: Potential ONJ

(Version 1.0/Dec-2021)

Annex 4.2 – Follow-up form: Atypical fracture

(Version 1.0/Dec-2021)

Annex 6 – Details of proposed additional risk minimization activities

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

The MAH shall ensure that in each Member State where denosumab is marketed, all healthcare professionals and patients/carers who are expected to prescribe and dispense denosumab have access to/are provided with the following educational package to be disseminated through professional bodies:

The Summary of Product Characteristics

Patient Reminder Card

Key messages of Patient Reminder Card:

- Patient reminder cards for osteonecrosis of the jaw (ONJ) will be distributed to prescribers for denosumab with background information of the purpose of the patient reminder card and instructions to provide it to patients.
- The patient reminder card will remind patients about important safety information that they need to be aware of before and during treatment with denosumab injections for osteonecrosis and bone loss, including:
  - The risk of osteonecrosis of the jaw during treatment with denosumab.
  - The need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment.
  - The need to ensure good oral hygiene during treatment.
  - The need to inform their dentist of treatment with denosumab and to contact their doctor and dentist if problems with the mouth or teeth occur during treatment.

The patient reminder card will be distributed by mail and prescribers will be provided with contact details to request additional copies of the card.