EU Risk Management Plan
For
Osenvelt
(CT-P41 120 mg vial, denosumab biosimilar)

RMP version to be assessed as part of this application:	
RMP Version number:	2.1
Data lock point for this RMP:	31 March 2026
Date of final sign off:	20 July 2026
Rationale for submitting an updated RMP	The Risk Management Plan (RMP) has been updated to harmonise the safety concerns in line with the reference product, Xgeva.
Summary of significant changes in this RMP	Part II: Safety Specification - Updated the clinical trial exposure data - Updated the post marketing exposure data to a data lock point of 31 March 2026 - Removed the following safety concerns: • Important identified risk of 'Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons' • Important potential risks of 'Malignancy' and 'Delay in diagnosis of primary

	malignancy in giant cell tumor of bone' • Missing information of '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'
Other RMP versions under evaluation	
RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP	
Version number:	1.0
Approved with procedure:	EMEA/H/C/006157/0000
Date of approval (opinion date):	12 December 2024
QPPV name:	**Oliver Wiedemann**
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

Note: Throughout this document, symbols indicating proprietary names (®, ™) are not displayed. The appearance of product names without these symbols does not imply that these names are not protected.

Table of content

List of Tables

List of Abbreviations

Term	Explanation
AFF	Atypical Femoral Fractures
ADR	Adverse Drug Reaction
CI	Confidence Interval
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EOS	End-of study
EPAR	European Public Assessment Report
EU	European Union
GCTB	Giant Cell Tumour of Bone
GVP	Good pharmacovigilance practice
HIV	Human Immunodeficiency Virus
IgG	Immunoglobulin G
MAH	Marketing Authorisation Holder
NYHA	New York Heart Association
ONJ	Osteonecrosis of the jaw
RANK	Receptor Activator of Nuclear factor kappa b
RANKL	RANK ligand
RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SRE	Skeletal-related event
TEAE	Treatment Emergent Adverse Event
PD	Pharmacodynamics
PL	Package Leaflet
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PY	Patient-year

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Denosumab
Pharmacotherapeutic group(s) (ATC Code)	Drugs for treatment of bone diseases, drugs affecting bone structure and mineralisation, other drugs affecting bone structure and mineralisation (M05BX04)
Marketing Authorisation Holder or Applicant	Celltrion Healthcare Hungary Kft.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Osenvelt
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Fully human monoclonal antibody of the immunoglobulin G (IgG) subclass.
	Summary of mode of action Denosumab binds to and neutralizes the activity of the human RANK ligand (RANKL), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. By blocking RANKL, denosumab prevents activation its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing osteoclast-mediated bone resorption and increasing bone mass and strength in both cortical and trabecular bone.
	Important information about its composition The antibody is produced in a Chinese hamster ovary mammalian cell line by recombinant DNA technology.
Hyperlink to the Product Information	CTD Module 1.3.1
Indication(s) in the EEA	**Current:** Prevention of skeletal-related events (SREs) (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone.

	Treatment of adults and skeletally mature adolescents with giant cell tumour of bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity.
Dosage in the EEA	**Current:** The recommended dose for prevention of SREs is 120 mg administered as a single subcutaneous (SC) injection once every 4 weeks into the thigh, abdomen or upper arm. The recommended dose for treatment of adults or skeletally mature adolescents with GCTB is 120 mg administered as a single SC injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on day 8 and 15 of treatment of the first month of therapy.
Pharmaceutical form(s) and strengths	**Current:** Denosumab is supplied in vials intended for SC injection. Each vial contains 120 mg of denosumab in 1.7 mL solution (70 mg/mL)
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Osenvelt, biosimilar denosumab and CT-P41 may be used interchangeably in this document to describe the investigational product to which this application refers.

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

According to the Guideline on Good Pharmacovigilance Practices (GVP) Module V (EMA/838713/2011 Rev 2) this part of the Risk Management Plan (RMP) is not required for biosimilar medicinal products.

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

The reference medicinal product for Osenvelt (CT-P41, biosimilar denosumab) is the innovator product Xgeva, which contains denosumab. The Marketing Authorisation Holder (MAH) for the reference medicinal product also holds a separate marketing authorisation in the EU for denosumab under the brand name Prolia. The authorised indications for Prolia are not the same as those for Xgeva and there are separate Risk Management Plans for the authorised reference products Xgeva and Prolia, although the active substances are the same in both products.

Table 2: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies) of CT-P41 (denosumab biosimilar)	Relevance to human usage
Repeat-dose toxicity of CT-P41 Toxicity studies comparing CT-P41 with Xgeva have not been performed because toxicity study comparing CT-P41 with Prolia has been performed. *In vitro* physicochemical and biological assessments between CT-P41 and Xgeva negated the need of the *in vivo* toxicity study as both Prolia and Xgeva have an identical drug substance, denosumab. Also, both Prolia and Xgeva have the same route of administration and the excipients selected for the drug product were not regarded to be of toxicological interest. Accordingly, it was considered that Prolia and Xgeva would present comparable risks and thus no *in vivo* comparative toxicity study between CT-P41 and Xgeva has been performed. **Repeat-dose toxicity of Xgeva (European Public Assessment Report [EPAR])** In monkey, subcutaneous doses up to 10 mg/kg once weekly and 50 mg/kg given once per month were administered for durations up to 12 months. No specific single dose toxicity studies were conducted, but no remarkable observations were recorded after the first dose in the repeated dose toxicity studies. The intended human dose is 120 mg given subcutaneously every 4 weeks corresponding to an AUC 0-4 weeks of 752 µg*day/ml and in most cases, doses used in toxicology studies represented high multiples of expected human exposure. However, the development of neutralising and/or binding antibodies in subsets of animals, resulting in greatly reduced exposure, was a confounding factor. There were no remarkable changes in clinical parameters, serum biochemistry, or histopathological effects in any of the studies, but bone turnover markers in serum and urine were decreased as were calcium levels (in males). Clinical data indicate cataracts as common eye disorders, but no treatment related ocular changes were reported after ophthalmological examinations in monkey. In the 12-month monkey study, 2 deaths at the high dose occurred. The overall conclusion was that deaths were not related to treatment, one diagnosed with possibly cardiac inflammation and the other death linked to acute exacerbation of pre-existing parasitic intestinal infection. However, it does not seem completely justified to exclude a possibility of involvement of an induced dysregulation of immune function in these findings. Of note is that the 2 deaths were both males. No deaths were recorded in the 16-month bone study that utilized female animals only.	No direct safety concern for the use of denosumab in the target population.

Key Safety findings (from non-clinical studies) of CT-P41 (denosumab biosimilar)	Relevance to human usage
Reproductive/Developmental toxicity of CT-P41 Reproductive toxicology studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Reproductive/Developmental toxicity of Xgeva (RMP)** 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 foetal harm. In this study, foetal lymph nodes were not examined. In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AAC exposures 12-fold higher than the human dose (120 mg every 4-weeks), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal. 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 haematopoiesis, 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.	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. The safety and efficacy of denosumab have not been established in paediatric patients other than skeletally mature paediatric patients with GCTB. Treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. .

Key Safety findings (from non-clinical studies) of CT-P41 (denosumab biosimilar)	Relevance to human usage
Genotoxicity/Carcinogenicity of CT-P41 Genotoxicity/carcinogenicity studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Genotoxicity/Carcinogenicity of Xgeva (EPAR)** No studies were conducted. Denosumab is a recombinant protein and contains no inorganic or synthetic organic linkages or other non-protein portions. Regulatory guidance is consistent with studies on genotoxicity not being necessary for this type of product. No carcinogenicity studies were conducted in accordance with available regulatory guidance. Ovariectomized monkey 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. 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.	Not applicable

Key Safety findings (from non-clinical studies) of CT-P41 (denosumab biosimilar)	Relevance to human usage
General Safety Pharmacology of CT-P41 No specific safety pharmacology studies were performed. Safety end-points were incorporated into the monkey repeat-dose toxicity study. No CT-P41- or Prolia-related clinical observations and changes to ECG parameters were noted. This approach is compatible with the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **General Safety Pharmacology of Xgeva (EPAR)** The safety pharmacology package included two studies; one of these was incorporated in a toxicology study in accordance with ICH S6 and ICH S7A. According to the guideline, clinical observation of animals is generally not adequate to assess respiratory function. However, since no indication of denosumab to affect respiratory function were noted, the assessment in toxicology study is considered sufficient. There was no ECG evidence of cardiotoxicity after 53 weeks of treatment with denosumab. Isolated cases of slight bradycardia, fused P-T wave or slight tachycardia were observed in single animals. These findings were not considered to be related to the administration of the test material. Two male animals died in the high dose group. According to the Applicant these deaths were not related to treatment. In other study, one animal (3 mg/kg) had a run of four ventricular premature complexes (VPCs) approximately 45 minutes following administration of the test article. This episode was not considered to be related to treatment with denosumab. No treatment related changes in respiration rate were observed. No treatment related cage side observations were observed.	Not applicable
Mechanisms for Drug Interactions of CT-P41 Drug Interactions studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Mechanisms for Drug Interactions of Xgeva (EPAR)** No specific preclinical studies have been conducted addressing drug interactions. In the switch study performed in ovariectomized cynomolgus monkeys with 6 months pretreatment of alendronate before 6 months treatment of denosumab (report 106564) no adverse effects on the pharmacodynamic activity of either alendronate or denosumab were noted. The absence of pharmacodynamic drug interaction studies is considered acceptable.	Not applicable

Key Safety findings (from non-clinical studies) of CT-P41 (denosumab biosimilar)	Relevance to human usage
Juvenile Toxicity Studies of CT-P41 Juvenile toxicity studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Juvenile Toxicity Studies of Xgeva (EPAR)** No specific studies were conducted.	Not applicable

Conclusion on Non-Clinical Data

Non-clinical investigations comparing CT-P41 with the reference product have not shown them to behave differently from one another in any relevant respects when administered by subcutaneous injection. No unexpected safety findings or signals were identified in the non-clinical programme for CT-P41.

Part II: Module SIII - Clinical trial exposure

The terms Osenvelt and CT-P41 may be used interchangeably in this document.

The clinical development programme for Osenvelt (CT-P41) includes three completed Phase 1 clinical studies in healthy male subjects (Studies CT-P41 1.1, 1.2 and 1.3) and one completed Phase 3 study in postmenopausal women with osteoporosis (Study CT-P41 3.1).

Osenvelt (CT-P41, biosimilar denosumab) has been developed as a biosimilar of Xgeva, which contains denosumab. The MAH for the reference medicinal product also holds a separate marketing authorisation in the EU for denosumab under the name Prolia. The indications for Prolia authorised in the EU are as follows: osteoporosis in postmenopausal women and in men at increased risk of fractures, bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture. The active substances are the same in Xgeva and Prolia, but the indications, the populations affected by the indications, the posology and the risks for Xgeva and Prolia are substantially different. The clinical development programme for CT-P41 set out to establish therapeutic equivalence between CT-P41 and the reference medicinal product Prolia, as a model for the expected therapeutic equivalence for all indications, including osteoporosis and malignancy. There have been no studies conducted with CT-P41 in patients with oncological indications. In order to document the exposure to CT-P41 in clinical development studies, exposure data derived from clinical trial in postmenopausal women with osteoporosis is presented in this RMP for Osenvelt.

- **Study CT-P41 1.1** (Pilot study): A phase 1, randomised, double-blind, two-arm, parallel group, single-dose study to evaluate the safety and Pharmacokinetic (PK) of CT-P41 and EU-approved Prolia in healthy male subjects. Thirty-two (32) subjects were randomised, of whom 30 received the allocated treatment. Fifteen (15) subjects received CT-P41, and 15 received EU-approved Prolia.

- **Study CT-P41 1.2** (Pivotal PK study for biosimilarity): A phase 1, randomised, double-blind, two-arm, parallel group, single-dose study to compare the PK, pharmacodynamics (PD), and safety between CT-P41 and US-licensed Prolia in healthy male subjects. One hundred fifty-four (154) subjects were randomised, of whom 151 received the allocated treatment. Seventy-four (74) subjects received CT-P41, and 77 subjects received US-licensed Prolia.

- **Study CT-P41 1.3:** A phase 1, randomised, double-blind, two-arm, parallel group, single-dose study to compare the PK, PD, safety and immunogenicity between CT-P41 and US-licensed Xgeva in healthy male subjects. One hundred fifty-seven (157) subjects were randomized, of whom 151 subjects received the allocated treatment. Seventy-three (73) subjects received CT-P41, and 78 subjects received US-licensed Xgeva.

- **Study CT-P41 3.1**: A phase 3, double-blind, randomised, active-controlled study to compare efficacy, PK, PD and safety of CT-P41 and US-licensed Prolia in postmenopausal women with osteoporosis. This study consists of 479 patients with postmenopausal osteoporosis, aged between 50 and 80 years, randomly assigned to receive 60 mg of CT-P41 or US-licensed Prolia. All patients also received daily supplementation containing at least 1,000 mg of elemental calcium and at least 400 IU vitamin D from randomisation to end-of-study (EOS). This study comprised 4 study periods (Screening Period, Treatment Period I, Treatment Period II, and

EOS visit). The maximum duration of the study per patient was 82 weeks: a Screening Period of 4 weeks, Treatment Period I of 52 weeks, and Treatment Period II of 26 weeks including EOS visit. All patients who completed the Treatment Period I underwent a second randomisation process prior to study drug administration at Week 52 to ensure blinding and entered Treatment Period II to receive an additional 1 dose of study drug. During Treatment Period II, patients who were initially randomised to US-licensed Prolia in Treatment Period I were re-randomised in a 1:1 ratio to switching arm (CT-P41) or non-switching arm (US-licensed Prolia). The patients who were initially randomised to CT-P41 in Treatment Period I continued to receive CT-P41. The study drug during the Treatment Period II was given at Week 52 visit and EOS visit was performed at Week 78 including assessment of efficacy, PK, PD, and safety including immunogenicity data.

Estimates of the patient exposure up to Week 52 visit from the completed pivotal study CT-P41 3.1 are presented in the following tables.

The following tables include data from study CT-P41 3.1 conducted in postmenopausal women with osteoporosis; no clinical trials in patients with malignancies involving bone have been conducted in the clinical development of CT-P41.

The recommended dose of denosumab for the management of osteoporosis in postmenopausal women is 60 mg administered as a single subcutaneous injection once every 6 months. Denosumab is administered intermittently. Exposure to denosumab has been estimated without taking into account the duration of action of the last administered dose of denosumab. The duration of exposure underestimates the exposure to risk because exposure estimates do not take account of the duration of action of the last administered dose.

Table 3 provides exposure by the duration of exposure. Table 4 shows exposure by age group. Table 5 shows exposure by the number of doses administered and summary of total cumulative dose. Table 6 displays exposure by the ethnicity of the participants in study CT-P41 3.1. Data on race are not presented because all participants were Caucasian.

Table 3: Exposure by duration

INDICATION: Postmenopausal osteoporosis (CT-P41 3.1)								
Duration of exposure	**CT-P41**						**Denosumab reference product****	
	CT-P41 only		**Switched from Denosumab reference product***		**Total**			
	Patients (n)	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
Duration < 1 week	14	14	101	101	115	115	24	24
1 week ≤ Duration < 25 weeks	0	0	0	0	0	0	0	0
25 weeks ≤ Duration < 51 weeks	8	2,012	0	0	8	2,012	23	5,945
51 weeks ≤ Duration	217	79,716	0	0	217	79,716	191	70,359
Total	239	81,742	101	101	340	81,843	238	76,328

* Exposure to CT-P41 during the Treatment Period II in the switching arm is included in this column and these patients received only one single additional dose of CT-P41.
** Exposure to reference product during Treatment Period I (52 weeks; from Week 0 to Week 52 pre-dose) in the switching arm is included in this column.
Person time (days) is the sum of each patient's duration of exposure. The duration is calculated as follows.
CT-P41 only: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1)
Switched from Denosumab reference product: ([Date of Last Exposure to Switched Treatment] – [Date of First Exposure of Switched Treatment] + 1)
CT-P41 Total: Duration from 'CT-P41 only' and 'Switched from Denosumab reference product
Denosumab reference product: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or ([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)
1 Week = 7.024 Days
Protocol Number: CT-P41 3.1

Table 4: Exposure by age group

INDICATION: Postmenopausal osteoporosis (CT-P41 3.1)								
Age group (years)	**CT-P41**						**Denosumab reference product****	
	CT-P41 only		**Switched from Denosumab reference product***		**Total**			
	Patients (n)	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
50 - 64	101	34,856	44	44	145	34,900	101	32,426
65 - 74	116	39,930	45	45	161	39,975	113	36,486
≥ 75	22	6,956	12	12	34	6,968	24	7,416
Total	239	81,742	101	101	340	81,843	238	76,328

Only female patients were included in the CT-P41 3.1, due to the nature of indication.
* Exposure to CT-P41 during the Treatment Period II in the switching arm is included in this column and these patients received only one single additional dose of CT-P41.
** Exposure to reference product during Treatment Period I (52 weeks; from Week 0 to Week 52 pre-dose) in the switching arm is included in this column.
Person time (days) is the sum of each patient's duration of exposure. The duration is calculated as follows.
CT-P41 only: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1)
Switched from Denosumab reference product: ([Date of Last Exposure to Switched Treatment] – [Date of First Exposure of Switch] + 1)
Total: Duration from 'CT-P41 only' and 'Switched from Denosumab reference product'
Denosumab reference product: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or ([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)
Protocol Number: CT-P41 3.1

Table 5: Exposure by number of treatments received

INDICATION: Postmenopausal osteoporosis (CT-P41 3.1)								
	CT-P41						Denosumab reference product**	
	CT-P41 only		Switched from Denosumab reference product*		Total			
	Patients (n)	Person time (days)	Patients (n)	Person time (days)	Patients (n)	Person time (days)	Patients (n)	Person time (days)
Number of treatment administration								
1	14	14	101	101	115	115	24	24
2	5	941	0	0	5	941	114	39,436
3	220	80,787	0	0	220	80,787	100	36,868
Total	239	81,742	101	101	340	81,843	238	76,328
Total Cumulative Dose (mg)								
Mean	171.7	-	60.0	-	138.5	-	139.2	-
Minimum	60	-	60	-	60	-	60	-
Median	180.0	-	60.0	-	180.0	-	120.0	-
Maximum	180	-	60	-	180	-	180	-

* Exposure to CT-P41 during the Treatment Period II in the switching arm is included in this column and these patients received only one single additional dose of CT-P41.
** Exposure to reference product during Treatment Period I (52 weeks; from Week 0 to Week 52 pre-dose) in the switching arm is included in this column.
Person time (days) is the sum of each patient's duration of exposure. The duration is calculated as follows.
CT-P41 only: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1)
Switched from Denosumab reference product: ([Date of Last Exposure to Switched Treatment] – [Date of First Exposure of Switched Treatment] + 1)
CT-P41 Total: Duration from 'CT-P41 only' and 'Switched from Denosumab reference product
Denosumab reference product: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or ([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)
Protocol Number: CT-P41 3.1

Table 6: Exposure by ethnicity

INDICATION: Postmenopausal osteoporosis (CT-P41 3.1)								
Ethnicity	**CT-P41**						**Denosumab reference product****	
	CT-P41 only		**Switched from Denosumab reference product***		**Total**			
	Patients (n)	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
Hispanic or Latino	0	0	2	2	2	2	3	737
Non-Hispanic or Non-Latino	239	81,742	99	99	338	81,841	235	75,591
Unknown	0	0	0	0	0	0	0	0
Total	239	81,742	101	101	340	81,843	238	76,328

* Exposure to CT-P41 during the Treatment Period II in the switching arm is included in this column and these patients received only one single additional dose of CT-P41.
** Exposure to reference product during Treatment Period I (52 weeks; from Week 0 to Week 52 pre-dose) in the switching arm is included in this column.
Person time (days) is the sum of each patient's duration of exposure. The duration is calculated as follows.
CT-P41 only: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1)
Switched from Denosumab reference product: ([Date of Last Exposure to Switched Treatment] – [Date of First Exposure of Switched Treatment] + 1)
CT-P41 Total: Duration from 'CT-P41 only' and 'Switched from Denosumab reference product
Denosumab reference product: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or ([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)
Protocol Number: CT-P41 3.1

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

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

The important exclusion criteria from the pivotal clinical study, CT-P41 3.1, are presented below.

Patient who has previously received denosumab (Prolia, Xgeva, or biosimilar denosumab), any other monoclonal antibodies (e.g., romosozumab), or biologic agents for osteoporosis.

Receipt of any investigational drug within 4 weeks or five half-lives (whichever is longer) prior to the first administration of the study drug

Reason for exclusion: The above-mentioned exclusion criteria were applied to prevent misinterpreting observations about study-related treatment that were actually received due to prior therapies.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned criteria were excluded to prevent interference with efficacy and safety study endpoints.

Patient with a hypersensitivity to any component of denosumab or dry natural rubber (a derivative of latex).

Reason for exclusion: Patients with hypersensitivity to any component of the medicinal products were excluded from the clinical development programme for safety reasons. Patients with a known hypersensitivity would be at a higher risk of subsequent serious systemic, potentially life-threatening hypersensitivity reactions with re-exposure.

Is it considered to be included as missing information?: No

Rationale: The use of denosumab is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients. This is adequately described in the SmPC of Osenvelt (Section 4.3 [Contraindication] and Section 4.8 [Undesirable effects]).

Patient who is confirmed or suspected with infection of COVID-19 at Screening, or has contact with COVID-19 patient within 14 days from Screening.

Reason for exclusion: These are precautionary measures applied to clinical trial subjects to reduce the risk of premature discontinuation from the study.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned conditions were excluded to prevent interference with efficacy and safety study endpoints.

Patient has one of the following laboratory test results at Screening:

a) Serum 25-OH vitamin D < 20 ng/mL (if vitamin D deficiency has been supplemented at the Investigator's discretion, and retest result shows the level above 20 ng/mL within the Screening period, the patient can be enrolled in the study. The retest is limited up to twice within the Screening period)

b) Estimated glomerular filtration rate < 30 mL/min/1.73 m^2

Reason for exclusion: Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients receiving denosumab must have adequate intake of calcium and vitamin D to prevent hypocalcaemia. The rationale for exclusion of patients with severe renal dysfunction is because these patients have disordered calcium metabolism, and are at risk of early termination.

Is it considered to be included as missing information?: No

Rationale: The use of denosumab is contraindicated in patients with hypocalcaemia. This is adequately described in the SmPC of Osenvelt (Section 4.3 [Contraindication] and Section 4.8 [Undesirable effects]).

Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risk of developing hypocalcaemia and accompanying elevations in parathyroid hormone increases with increasing degree of renal impairment. Regular monitoring of calcium levels is especially important in these patients. This is adequately described in the SmPC of Osenvelt (Section 4.4 [Special warnings and precautions for use]).

Concurrent or past history of infection with active hepatitis B or hepatitis C or human immunodeficiency virus (HIV). However, a patient with past hepatitis B was allowed if resolved.

Concurrent or past history of severe or active infection requiring hospitalisation or parenteral antibiotics within 4 weeks prior to the first administration of the study drug, or oral antibiotics within 2 weeks prior to the first administration of the study drug.

Reason for exclusion: Treatment with immunomodulatory agents may increase the risk of infection or worsen an existing infection. Such infections may confound safety evaluation. Moreover, infectious disease may lead to increased risk of dropout.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned conditions were excluded to prevent interference with efficacy and safety study endpoints.

Patient who has a medical history of and/or current disease including any of the following(s):

a) One severe or > 2 moderate vertebral fractures (severe fracture is defined as > 40% vertebral height loss and moderate fracture is defined as 25% to 40% vertebral height loss [Genant et al., 1993]) as determined by central reading of lateral spine X-ray

b) Hip fracture

Reason for exclusion: The exclusion criteria for previous vertebral and hip fractures are based on technical requirements for the reduction of confounding factor impact on efficacy measurements in clinical studies.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned exclusion criteria were excluded to prevent interference with efficacy and safety study endpoints.

Patients with history of hyperparathyroidism or hypoparathyroidism, irrespective of current controlled or uncontrolled status; Current hyperthyroidism (unless well controlled on stable antithyroid therapy); Current hypothyroidism (unless well controlled on stable thyroid replacement therapy)

Reason for exclusion: Parathyroid hormone plays an important role in bone mineral homeostasis and bone density. Both hyperthyroidism and to some extent, hypothyroidism are associated with altered bone mineral density, which may increase fracture risk. Pre-existing hypocalcaemia must be corrected prior to initiating therapy with Osenvelt.

Is it considered to be included as missing information?: No

Rationale: Denosumab, parathyroid hormone and thyroid hormone all have an effect on bone metabolism and calcium homeostasis. Parathyroid pathology and thyroid abnormalities would potentially have confounded the interpretation of efficacy results in clinical studies. Patients with above mentioned exclusion criteria were excluded to prevent confounding the interpretation of study results of efficacy endpoints.

History of bone disease and metabolic disease (except for osteoporosis) that may interfere with the interpretation of the results including osteomalacia, osteogenesis imperfecta, Paget's disease, rheumatoid arthritis, ankylosing spondylitis, osteopetrosis, fibrous dysplasia, an elevation of ALP at the Investigator's discretion, Cushing's disease, hyperprolactinemia, malabsorption syndrome, advanced scoliosis or extensive lumbar fusion

Reason for exclusion: Patients with other bone diseases (as mentioned in the above exclusion criterion) were excluded from the pivotal study because other bone diseases could confound the efficacy results.

Is it considered to be included as missing information?: No

Rationale: Denosumab is not indicated for use in the patient populations with these types of bone disease.

New York Heart Association (NYHA) Class III or IV chronic heart failure, any unstable cardiovascular disease, pulmonary disease, autoimmune disease or electrocardiogram (ECG) abnormalities which can be judged as clinically significant at the Investigator's discretion

Reason for exclusion: Clinically significant cardiac, pulmonary, or autoimmune disease may complicate the interpretation of safety endpoints. These co-morbidities may also increase risk of hospitalisation and patient dropout.

Is it considered to be included as missing information?: No

Rationale: 'Cardiovascular events' are an important potential risk for denosumab. Patients with above mentioned exclusion criteria were excluded to prevent confounding the interpretation of safety study endpoints.

History and/or current oral or dental conditions including osteomyelitis or osteonecrosis of the jaw (ONJ); active dental or jaw condition which requires oral surgery; planned invasive dental procedure (e.g., tooth extraction, dental implants, oral surgery); unhealed dental oral surgery

Reason for exclusion: While on treatment, invasive dental procedures should be performed only

after careful consideration and be avoided in close proximity to denosumab administration.

Is it considered to be included as missing information?: No

Rationale: 'ONJ' is an important identified risk of denosumab (SmPC Section 4.8 [Undesirable effects]). The use of denosumab is contraindicated in patients with unhealed lesions from dental or oral surgery (Section 4.3 [Contraindication]). Routine risk minimisation activities recommending specific clinical measures to address the risk before and during treatment have been adequately described in Osenvelt SmPC (Section 4.4 [Special warnings and precautions for use]).

History of any malignancy within 5 years prior to the first administration of the study drug except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ. Any history of bone metastases, implant radiation involving the skeleton, or skeletal malignancies are exclusionary.

Reason for exclusion: Use of any other giant cell tumour of bone-specific treatment would interfere with the ability to assess denosumab's efficacy. Also, the presence of osteosarcoma or other bone tumours could interfere with the ability to assess denosumab's efficacy on giant cell tumour of bone. Additionally, treatment with an immunomodulatory agent may theoretically increase the risk of developing a malignancy. Concurrent or recent malignancy may complicate the interpretation of efficacy and safety endpoints. Moreover, patients with history of past or concurrent malignancy are prone to frequent hospitalisation, hence an increased risk of dropout.

Is it considered to be included as missing information?: No

Rationale: Malignancy is an important potential risk for denosumab (SmPC Section 4.8 [Undesirable effects]), based on theoretical concerns, and have not been substantiated in the extensive clinical study programme or in the postmarketing experience with the reference product Xgeva. Recommendations for monitoring radiological signs of malignancy, new radiolucency or osteolysis are included in SmPC of Osenvelt (Section 4.4 [Special warnings and precautions for use]).

Patient who has a history of and/or concurrent use of medications including any of the following:

Receipt of intravenous bisphosphonates, fluoride, and strontium for osteoporosis within the last 5 years prior to the first administration of the study drug

Receipt of oral bisphosphonates ≥3 years cumulatively prior to Screening or receipt of any dose of oral bisphosphonates within 12 months prior to Screening

History of severe skeletal pain with bisphosphonates

Reason for exclusion: Patients who received prior treatment with above mentioned medicinal products were excluded as such treatments could confound the determination of efficacy and safety in clinical studies. Bisphosphonates incorporate into bone and long-term use of bisphosphonates is associated with continued and prolonged activity after the treatment has stopped.

Is it considered to be included as missing information?: Yes (for prior IV bisphosphonate use only)

Rationale: In clinical trials performed with the reference product, denosumab has been administered in combination with standard anti-cancer treatment and in subjects previously receiving bisphosphonates. There were no clinically-relevant alterations in trough serum

concentration and pharmacodynamics of denosumab (creatinine adjusted urinary N-telopeptide, uNTx/Cr) with previous intravenous bisphosphonate exposure.

The efficacy and safety of denosumab in patients treated with fluoride, or strontium for osteoporosis have not been established. In clinical trials performed with the reference product, data are available for 795 subjects in advanced cancer settings and an additional 19 subjects that received denosumab from the multiple myeloma pivotal study who had previously received bisphosphonates. A denosumab study was also conducted in cynomolgus monkeys transitioned from bisphosphonate therapy and two clinical studies of bisphosphonate-transition in bone loss settings. Results from these studies did not demonstrate an increased risk of skeletal adverse effects over the period exposed in patients who received denosumab following bisphosphonate use.

Patient who has a history of and/or concurrent use of medications including any of the following:

Use of parathyroid hormone (PTH) or its derivatives, systemic hormone-replacement therapy (estrogen with or without progestogen), selective estrogen-receptor modulator, tibolone, calcitonin, or calcitriol within 12 months prior to the first administration of the study drug

Use of other bone active drugs including heparin, anticonvulsives (except benzodiazepines), systemic ketoconazole, anabolic steroids, testosterone, androgens, adrenocorticotropic hormone, cinacalcet, aluminum, lithium, protease inhibitors, methotrexate, or gonadotropin-releasing hormone agonists within 3 months prior to the first administration of the study drug

Use of oral or parenteral glucocorticosteroids (> 5 mg/prednisone daily or equivalent for > 10 days) within 3 months prior to the first administration of the study drug

Reason for exclusion: The medications listed may affect bone turnover, and/or bone density that could interfere with the interpretation of both efficacy and safety outcomes in clinical studies.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned received drugs were excluded to prevent interference with efficacy and safety study endpoints.

Patient who has evidence of any other coexisting disease or medical or psychological condition, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational product (IP) or could have interfere with the interpretation of study results, or patient is at high risk for treatment complication in the opinion of the Investigator.

Reason for exclusion: Coexisting conditions may complicate the interpretation of efficacy endpoints and safety results.

Is it considered to be included as missing information?: No

Rationale: The patients were excluded to prevent confounding of efficacy and safety results and to reduce the risk of premature termination of treatment in the study. There are no specific safety concerns associated with this exclusion criterion.

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, or adverse reactions with a long latency or those caused by prolonged or cumulative exposure.

CT-P41 has been studied in healthy males and postmenopausal women with osteoporosis. Up to the data lock point of this RMP, 162 healthy volunteers in phase I studies (CT-P41 1.1, 1.2 and 1.3) and 340 postmenopausal women with osteoporosis (study CT-P41 3.1) have been treated with CT-P41 in the clinical development programme.

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

Table 7: 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 of CT-P41.
Breastfeeding women	Not included in the clinical development programme of CT-P41.
Patients with relevant comorbidities	
Patients with hepatic impairment	Patients with hepatic impairment were not studied in the clinical development programme of CT-P41. None of the patients entered into study CT-P41 3.1 had evidence of hepatic impairment. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics (PK) of denosumab is not expected to be affected by hepatic impairment.
Patients with renal impairment	Patients with renal impairment were not studied in the clinical development programme of CT-P41. None of the patients entered into study CT-P41 3.1 had evidence of renal impairment. In a study of 32 patients without advanced cancer but with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the PK of denosumab; this study was conducted with the reference medicinal product. Since Osenvelt is a biosimilar, based on the safety profile of the reference product Xgeva, no dose adjustment is required in patients with renal impairment.
Patients with cardiovascular impairment	Patients with cardiovascular impairment were not studied in the clinical development programme of CT-P41.

Type of special population	Exposure
Immunocompromised patients	Immunocompromised patients were not studied in the clinical development programme of CT-P41.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme of CT-P41.
Population with relevant different ethnic origin	All of patients who received CT-P41 were Caucasians (340 patients) in study CT-P41 3.1. Ethnic origin is not known to be relevant to the response to treatment with denosumab.
Subpopulations carrying relevant genetic polymorphisms	There are no known relevant genetic polymorphisms.
Other	
Paediatric patients	Not included in the clinical development programme of CT-P41.
Geriatric patients	This population has not been underrepresented in the clinical development programme. Overall, 138 female patients aged ≥ 65 years received CT-P41 in the study CT-P41 3.1 (see Table 4).

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Post-authorisation exposure to Osenvelt (denosumab 120 mg) was estimated based on the approved standard dosing regimen. Osenvelt is administered as a maintenance dose of 120 mg once every 4 weeks. Based on this posology, the annual exposure per patient corresponds to 13 administrations per year, resulting in a total annual dose of 1,560 mg per patient.

Cumulative post-marketing exposure was estimated using aggregated global sales data, divided by the calculated annual dose per patient. The formula used by Celltrion for estimating the patient exposure is as described below:

$$\text{Patient exposure (patient-years)} = \frac{\text{Number of dosage forms sold} \times \text{dosage form strength in mg}}{\text{Standard annual dose per patient in mg}}$$

SV.1.2 Exposure

The total cumulative exposure was approximately 3,025 patient-year (PY) based upon Celltrion sales data available by Mar 31, 2026.

Table 8: SV.1: Cumulative Patient Exposure from Marketing Experience[#]

Country	Total number of vials sold	Total units sold (mg)	Estimated exposure (Patient-Years)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	3,025

[#]The cumulative patient exposure is based on sales data from 21 Nov 2024 to 31 Mar 2026.
[redacted]

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

Potential for misuse for illegal purposes

Based on the given mechanism of action of Osenvelt and its indications, the potential for misuse or abuse for illegal purposes is considered negligible.

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

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

1. **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**

   None.

2. **Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:**

   None.

3. **Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):**

   In accordance with the EU requirements, Osenvelt has been shown to have quality, safety and efficacy comparable to the reference product Xgeva, in the indication studied in study CT-P41 3.1. The safety profile of Osenvelt has been adequately described in the product information.

   The following risks are labelled in the product information for the reference product. They require no further characterisation and are not important safety concerns for either Osenvelt or Xgeva:

   Drug hypersensitivity, anaphylactic reaction, hypocalcaemia, hypophosphataemia, dyspnoea, diarrhoea, tooth extraction, hyperhidrosis, lichenoid drug eruptions, musculoskeletal pain and osteonecrosis of the external auditory canal.

4. **Known risks that do not impact the risk-benefit profile:**

   None.

5. **Other reasons for considering the risks not important:**

   None.

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

Important identified risk: Osteonecrosis of the Jaw

Risk-benefit impact:

Osteonecrosis of the Jaw (ONJ) is a multifactorial disease in patients with primary or metastatic bone malignancy or osteoporosis undergoing systemic antiresorptive therapy, where pathophysiology has not yet been fully determined. The staging of ONJ is based on severity of symptoms and extent of clinical and radiographic findings. Treatment strategies range from conservative local wound care to aggressive resective surgery of all necrotic bone (Aghaloo et al., 2015).

In the clinical development programme of the reference product Xgeva, the subject incidence of positively adjudicated adverse events of ONJ ranged from 1.8%-4.1% in the denosumab group. The incidence of ONJ was higher with longer duration of exposure. In a non-interventional postmarketing observational study of the reference product Xgeva, the incidence rates (95% Confidence Interval [CI]) of medically confirmed ONJ per 100 person-years (PY) were 3.0 (2.3, 3.7) in the Xgeva inception cohort, 1.0 (0.6, 1.5) in the zoledronic acid inception cohort, and 4.3 (2.8, 6.3) in the Xgeva-switch cohort (this cohort included patients who switched to Xgeva after having started antiresorptive therapy with bisphosphonates for skeletal-related event prevention of no more than 2 years' net duration) (Xgeva RMP version 36.0).

According to the SmPC of Osenvelt and the reference product Xgeva, the frequency of denosumab induced ONJ is 'common'.

Patients should maintain good oral hygiene, get regular dental check-ups, and report any mouth issues like dental mobility, pain, swelling, or slow-healing sores. During denosumab treatment, patients should avoid invasive dental procedures near the time of denosumab administration.

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

Important identified risk: Atypical Femoral Fracture

Risk-benefit impact:

Atypical Femoral Fractures (AFF) have been reported in patients receiving denosumab. AFF may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterise these events. AFFs have also been reported in patients with certain co-morbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. 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.

In the clinical trial programme of the reference product Xgeva, AFF has been reported uncommonly in patients treated with denosumab 120 mg and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued.

According to the SmPC of Osenvelt and the reference product Xgeva, the frequency of denosumab induced AFF is 'Uncommon'. The risk of AFF can be minimised by reporting new or unusual thigh, hip, or groin pain, during denosumab treatment. Discontinuation of Osenvelt therapy in patients suspected to have an AFF should be considered pending evaluation of the patient based on an individual benefit-risk assessment.

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

Important identified risk: Hypercalcemia Several Months After the Last Dose in Patients With Giant Cell Tumour of Bone and in Patients With Growing Skeletons

Risk-benefit impact:

Clinically significant hypercalcaemia requiring hospitalisation that may be complicated by acute renal injury has been reported in denosumab-treated patients with giant cell tumour of bone weeks to months following treatment discontinuation.

In the clinical development programme of the reference product Xgeva, the frequency of hypercalcaemia in patients with Giant Cell Tumour of Bone (GCTB) following discontinuation of Xgeva was 0.8 events per 100 subjects (Xgeva RMP version 36.0).

After treatment discontinuation, the patients should be monitored for signs and symptoms of hypercalcaemia, periodic assessment of serum calcium and re-evaluation of the patient's calcium and vitamin D supplementation requirements should be performed.

As per the SmPC of Osenvelt, it is not recommended in patients with growing skeletons. Clinically significant hypercalcaemia has also been reported in this patient group weeks to months following treatment discontinuation.

The risk of hypercalcaemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall risk-benefit balance is considered to be favourable.

Important potential risk: Cardiovascular Events

Risk-benefit impact:

A cardiovascular event, commonly known as heart disease, encompasses four main conditions: Coronary Artery Disease (CAD), also referred to as Coronary Heart Disease (CHD), cerebrovascular disease, Peripheral Artery Disease, and aortic atherosclerosis. CAD, in particular, arises from reduced blood flow to the heart, leading to angina due to ischaemia and potentially resulting in Myocardial Infarction (MI) or heart failure (Olvera et al., 2023). The risk of cardiovascular events is based on the epidemiological association with elevated levels of Osteoprotegerin (OPG), which has been associated with CAD in cross-sectional studies.

In the pooled pivotal SRE Solid Tumour studies of the reference product Xgeva, subject incidence of Cardiovascular adverse events was 29.7% in patients exposed to denosumab and the comparator.

In a pivotal study with denosumab 120 mg Q4W in subjects with castration-resistant prostate cancer (Study 20050147), the subject incidence of Cardiovascular (CV) adverse events was 33.1% in the denosumab group (Xgeva RMP version 36.0).

Although, the majority of CV events were mild to moderate, life-threatening and fatal events have been reported. Based on clinical data to date, denosumab has not been shown to be associated with an increased incidence or severity of CV adverse effects; therefore, no preventive measures are defined. Patients with potential CV events should be managed according to usual standards of care.

The risk of CV events has been considered in the product benefit-risk assessment, and the overall risk-benefit balance is considered to be favourable.

Important potential risk: Malignancy

Risk-benefit impact:

Denosumab may have immunosuppressant effects. Immunosuppressants have the potential to increase the risk of malignancy. Malignant cells tend to have fast, uncontrolled growth and do not undergo normal programmed cell death (apoptosis) due to their genetic makeup.

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 (Xgeva RMP version 36.0).

In the clinical trials for the reference product Xgeva in patients with advanced malignancies involving bone, new primary malignancy was reported in 54/3691 (1.5%) of patients treated with Xgeva (median exposure of 13.8 months; range: 1.0–51.7). The cumulative incidence at one year was 1.1 % for denosumab.

Second malignant neoplasms have become increasingly recognised and current recommendations include vigilance for these cancers in adult cancer survivors.

The risk of malignancy has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimise this risk, the overall risk-benefit balance is considered to be favourable.

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

Risk-benefit impact:

At the time of GCTB diagnosis, Primary Malignancy in Giant Cell Tumour of Bone (PMGCTB) may be missed and benign GCTB may be presumed.

In clinical studies for the reference product Xgeva in GCTB, based on medical review, 11 subjects (2.1%; N = 523) had GCTB bone malignancies. Of these, 5 subjects (1.0%) had PMGCTB. Patients with GCTB are known to be at risk for PMGCTB.

The risk of delay in diagnosis of PMGCTB events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimise this risk, the overall risk-benefit balance is considered to be favourable.

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

Risk-benefit impact:

The pathogenesis of hypercalcaemia 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. Patients who experience hypercalcaemia may develop complications such as acute renal injury (Xgeva RMP version 36.0).

As per the RMP of the reference product Xgeva, cases of hypercalcaemia in the off-treatment period have been reported in subjects exposed to denosumab in clinical studies for Xgeva, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcaemia in patients other than those with GCTB or with growing skeletons could not be definitively attributed to discontinuation of denosumab based on available information.

The risk of hypercalcaemia 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 risk-benefit balance remains favourable.

Missing information: Use in Patients With Prior Intravenous Bisphosphonate Treatment

Risk-benefit impact:

In clinical trials for the reference product Xgeva, denosumab has been administered in subjects previously receiving bisphosphonates. There were no clinically-relevant alterations in trough serum concentration and pharmacodynamics of denosumab by previous intravenous bisphosphonate exposure.

There is information from clinical studies of the reference product Xgeva in patients with cancer showing that there is no increased risk of serious complications caused by bone metastases in patients who received denosumab following treatment with bisphosphonates. The use of denosumab in patients previously treated with intravenous bisphosphonates has not, however, been systematically studied. This is an area of missing information that requires further characterisation.

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

Risk-benefit impact:

The overall safety profile of Xgeva in the completed Study 20062004 was similar to the safety profile of Xgeva observed in the treatment of subjects with advanced cancer and bone metastases.

The safety of long-term treatment has not been systematically studied and will be monitored by long-term follow-up in adults or adolescents with GCTB by routine pharmacovigilance activities.

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

Risk-benefit impact:

No formal studies have been completed to determine the effect of denosumab off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Information is not available on specific risks that may be associated with off label use in this patient population.

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

The following safety concerns have been removed from the RMP to be aligned with the reference product, Xgeva.

- Important identified risk of 'Hypercalcemia several months after the last dose in patients with giant cell tumour of bone and in patients with growing skeletons'
- Important potential risks of 'Malignancy' and 'Delay in diagnosis of primary malignancy in giant cell tumour of bone'
- Missing information of 'Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumour of bone'

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

Since Osenvelt is a biosimilar medicine, all risks have been included based on the safety profile of the reference product Xgeva for all indications.

Osenvelt (CT-P41, biosimilar denosumab) has been developed as a biosimilar of Xgeva, which contains denosumab. The MAH for the reference medicinal product also holds a separate marketing authorisation in the EU for denosumab under the name Prolia. The indications for Prolia authorised in the EU are as follows: osteoporosis in postmenopausal women and in men at increased risk of fractures, bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

The active substances are the same in Xgeva and Prolia, but the indications, the populations affected by the indications, the posology and the risks for Xgeva and Prolia are substantially different. The clinical development programme for CT-P41 set out to establish therapeutic equivalence between CT-P41 and the reference medicinal product Prolia, as a model for the expected therapeutic equivalence for all indications, including osteoporosis and malignancy. There have been no studies conducted with CT-P41 in patients with oncological indications. The details of important safety concerns for CT-P41 are derived from clinical trial exposure involving postmenopausal women with osteoporosis.

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

Important identified risk: Osteonecrosis of the jaw_(Medical Dictionary for Regulatory Activities (MedDRA) PT Osteonecrosis of jaw)

Potential mechanisms:

ONJ appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodelling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence

supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact (Fassio et al., 2017; Aghaloo et al., 2015).

Evidence source(s) and strength of evidence:

ONJ is a condition where the jawbone is not covered by the gums and is exposed. It can be caused by two types of medicines: Antiresorptive medicines (including bisphosphonates (BPs) and receptor activator of nuclear factor kappa-B ligand [RANK-L] inhibitors) and antiangiogenic medicines (Rosella et al., 2016).

In the clinical development programme of the reference product, the subject incidence of ONJ was 1.8% in the denosumab group. In a multiple myeloma study, the subject incidence of ONJ was 4.1% in the denosumab group. The incidence of ONJ increased with longer duration of treatment with denosumab (Xgeva RMP version 37.1).

In a post-marketing study with the reference product, the incidence of ONJ per 100 person-years was 3.0 (2.3, 3.7) in patients that started treatment with denosumab, and 4.3 (2.8, 6.3) in patients who switched to denosumab from alternative treatment.

Characterisation of the risk:

In study CT-P41 3.1, there were no Treatment Emergent Adverse Events (TEAEs) reported for osteonecrosis of the jaw in the CT-P41 only group (239 patients), and switched from reference product group (101 patients). One single case of ONJ was reported in the denosumab reference product group (238 patients).

Risk factors and risk groups:

Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis (Almazrooa et al., 2009; Estilo et al., 2008; Mehrotra et al., 2006; Ruggiero et al., 2006).

Preventability:

A dental examination with appropriate preventive dentistry is recommended prior to treatment with Osenvelt, especially in patients with risk factors. The 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 Osenvelt administration.

Patients who are suspected of having, or who develop ONJ while on Osenvelt should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with Osenvelt, a temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Impact on the risk-benefit balance of the product:

The risk of ONJ events has been considered in the product benefit-risk assessment. In light of the product labelling and a patient reminder card that has been proposed to minimise this risk, the overall benefit-risk balance is considered to be favourable.

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.

Important identified risk: Atypical femoral fracture (MedDRA PT Atypical femur fracture)

Potential mechanisms:

Prolonged suppression of bone turnover may be associated with increased risk of 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 micro damage and advanced glycation end products, mineralisation, remodelling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF (Ismail et al., 2018; Shane et al., 2010).

Evidence source(s) and strength of evidence:

In the clinical development programme of the reference product, 0.2% (15 of 8342) of all subjects who received at least one dose of denosumab experienced AFF. AFF has been reported uncommonly in patients treated with denosumab and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued.

Characterisation of the risk:

There were no TEAEs reported for atypical femoral fracture in the CT-P41 only group (239 patients), switched from reference product group (101 patients), and the reference product group (238 patients) in Study CT-P41 3.1.

Risk factors and risk groups:

Long-term anti-resorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF (Meier et al., 2012, Giusti et al., 2011). AFFs have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors (Shane et al., 2010).

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 risk-benefit balance of the product:

The risk of AFF events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimise this risk, the overall benefit-risk balance is considered to be favourable.

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.

Important potential risk: Cardiovascular events (MedDRA SOC Cardiac disorders)

Potential mechanisms:

Elevated levels of OPG have been associated with coronary artery disease in cross-sectional studies, but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists.

Evidence source(s) and strength of evidence:

The risk of cardiovascular events is a regulatory concern based on the epidemiological association between OPG levels and cardiovascular disease in humans. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable cardiovascular outcomes.

In pooled pivotal solid tumour studies with the reference product, subject incidence of cardiovascular adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% CI: 0.89, 1.08). In a study with denosumab 120 mg Q4W in subjects with castration-resistant prostate cancer (Study 20050147), the subject incidence of cardiovascular adverse events was 33.1% in the denosumab group. In a multiple myeloma study, the subject incidence of adverse events of cardiac disorders was 11.6% and vascular disorder was 20.9% in the denosumab group.

Characterisation of the risk:

Frequency with 95% CI for Incidence per 100 PY

INDICATION: Postmenopausal Osteoporosis (CT-P41 3.1)				
	CT-P41			**Denosumab Reference Product** (N=238)**
	CT-P41 only (N=239)	**Switched from Denosumab Reference Product* (N=101)**	**Total (N=340)**	
Total Number of TEAEs	26	3	29	15
Number of Patients with TEAEs [1]	15 (6.3%)	2 (2.0%)	17 (5.0%)	14 (5.9%)
Incidence of TEAEs per 100 PYs	11.618	1084.901	12.942	7.178
95% CI for Incidence of TEAEs per 100 PYs	(7.589, 17.023)	(223.733, 3170.541)	(8.668, 18.587)	(4.017, 11.839)

INDICATION: Postmenopausal Osteoporosis (CT-P41 3.1)				
	CT-P41			
	CT-P41 only (N=239)	Switched from Denosumab Reference Product* (N=101)	Total (N=340)	Denosumab Reference Product** (N=238)
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk. The subject is counted only once regardless of the number of events or occurrences.				
From the MedDRA dictionary, version 26.0.				
* Exposure to CT-P41 during the Treatment Period II in the switching arm is included in this column and these patients received only one single additional dose of CT-P41.				
** TEAEs occurred during Treatment Period I (52 weeks; from Week 0 to Week 52 pre-dose) in the switching arm are included in this column.				
Patient Year is the sum of each patient's duration of exposure. The duration is calculated as follows.				
CT-P41 only: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) /365.25				
Switched from Denosumab reference product: ([Date of Last Exposure to Switched Treatment] – [Date of First Exposure of Switched Treatment] + 1) /365.25				
CT-P41 Total: Duration from 'CT-P41 only' and 'Switched from Denosumab reference product'				
Denosumab reference product: ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) /365.25 or ([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25				
Abbreviation: CI = Confidence Interval; N = Number of patients in each treatment group; NE = Not estimated; PY = Patient Year; TEAE = Treatment Emergent Adverse Event				
Exact confidence interval for incidence of TEAEs per 100PY is calculated using chi-squared distribution.				
TEAEs indicate the applicable risks in relevant tables.				
Protocol Number: CT-P41 3.1				

CT-P41 is administered intermittently. The recommended dose in postmenopausal osteoporosis is 60 mg administered as a single subcutaneous injection once every 6 months.

Exposure-adjusted incidences of TEAEs are based on exposure that has been estimated without taking into account the duration of action of the last administered dose of denosumab. Exposure-adjusted incidences of TEAEs underestimate the exposure to risk, because they do not take into account the exposure to the effects of the last administered dose of denosumab. This has the greatest impact on the estimated incidence of TEAEs per 100 patient-years for patients that were switched from the denosumab reference product to CT-P41 in study CT-P41 3.1 because these patients received only a single dose of CT-P41 after switching treatment at Week 52.

In the table below, exposure-adjusted incidences of TEAEs have been corrected to take account of the duration of action of the last dose of trials treatment received. This has been calculated by adding 182 days to the actual estimated duration of exposure, to account for the exposure that would have accrued had the patient continued treatment and received the next scheduled six-monthly dose of denosumab.

INDICATION: Postmenopausal Osteoporosis (CT-P41 3.1)				
	CT-P41			
	CT-P41 only (N=239)	Switched from Denosumab Reference Product* (N=101)	Total (N=340)	Denosumab Reference Product** (N=238)
Total Number of TEAEs	26	3	29	15
Number of Patients with TEAEs [1]	15 (6.3%)	2 (2.0%)	17 (5.0%)	14 (5.9%)
Incidence of TEAEs per 100 PYs	7.583	5.928	7.370	5.410

INDICATION: Postmenopausal Osteoporosis (CT-P41 3.1)				
	CT-P41			
	CT-P41 only (N=239)	Switched from Denosumab Reference Product* (N=101)	Total (N=340)	Denosumab Reference Product** (N=238)
95% CI for Incidence of TEAEs per 100 PYs	(4.953, 11.110)	(1.223, 17.325)	(4.936, 10.584)	(3.028, 8.924)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk. The subject is counted only once regardless of the number of events or occurrences.

From the MedDRA dictionary, version 26.0.

* Exposure to CT-P41 during the Treatment Period II in the switching arm is included in this column and these patients received only one single additional dose of CT-P41.

** TEAEs occurred during Treatment Period I (52 weeks; from Week 0 to Week 52 pre-dose) in the switching arm are included in this column.

Patient Year is the sum of each patient's duration of exposure. The duration is calculated as follows.

CT-P41 only: ([Date of Last Exposure to Treatment] + 182 days (Planned Dosing Interval) – [Date of First Exposure to Treatment] + 1) /365.25

Switched from Denosumab reference product: ([Date of Last Exposure to Switched Treatment] + 182 days (Planned Dosing Interval) – [Date of First Exposure of Switched Treatment] + 1) /365.25

CT-P41 Total: Duration from 'CT-P41 only' and 'Switched from Denosumab reference product'

Denosumab reference product: ([Date of Last Exposure to Treatment] + 182 days (Planned Dosing Interval) – [Date of First Exposure to Treatment] + 1) /365.25 or ([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25

Abbreviation: CI = Confidence Interval; N = Number of patients in each treatment group; NE = Not estimated; PY = Patient Year; TEAE = Treatment Emergent Adverse Event

Exact confidence interval for incidence of TEAEs per 100PY is calculated using chi-squared distribution.

TEAEs indicate the applicable risks in relevant tables.

Protocol Number: CT-P41 3.1

Frequency with Severity, Seriousness and Outcome

INDICATION: Postmenopausal Osteoporosis (CT-P41 3.1)				
	CT-P41			
	CT-P41 only (N=239)	Switched from Denosumab Reference Product* (N=101)	Total (N=340)	Denosumab Reference Product** (N=238)
Total Number of TEAEs	26	3	29	15
Number of Patients with TEAEs [1]	15 (6.3%)	2 (2.0%)	17 (5.0%)	14 (5.9%)
95% CI for Proportion of Patients with TEAEs	(3.55, 10.14)	(0.24, 6.97)	(2.94, 7.88)	(3.25, 9.67)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	5 (2.1%)	1 (1.0%)	6 (1.8%)	9 (3.8%)
Grade 2	6 (2.5%)	1 (1.0%)	7 (2.1%)	4 (1.7%)
Grade 3	2 (0.8%)	0	2 (0.6%)	1 (0.4%)
Grade 4	1 (0.4%)	0	1 (0.3%)	0
Grade 5	1 (0.4%)	0	1 (0.3%)	0
Seriousness [3]				
Non-serious	11 (4.6%)	2 (2.0%)	13 (3.8%)	13 (5.5%)
Serious	4 (1.7%)	0	4 (1.2%)	1 (0.4%)
Outcomes [4]				

INDICATION: Postmenopausal Osteoporosis (CT-P41 3.1)				
	CT-P41			Denosumab Reference Product** (N=238)
	CT-P41 only (N=239)	Switched from Denosumab Reference Product* (N=101)	Total (N=340)	
Missing/Unknown	0	0	0	0
Recovered/Resolved	3 (1.3%)	1 (1.0%)	4 (1.2%)	5 (2.1%)
Recovered/Resolved with Sequelae	0	0	0	1 (0.4%)
Recovering/Resolving	2 (0.8%)	1 (1.0%)	3 (0.9%)	3 (1.3%)
Not recovered/Not resolved	9 (3.8%)	0	9 (2.6%)	5 (2.1%)
Fatal	1 (0.4%)	0	1 (0.3%)	0

* TEAEs occurred during the Treatment Period II in the switching arm are included in this column and these patients received only one single additional dose of CT-P41.
** TEAEs occurred during Treatment Period I (52 weeks; from Week 0 to Week 52 pre-dose) in the switching arm are included in this column.
Abbreviations: CI = Confidence Interval; N = Number of patients in each treatment group; TEAE = Treatment Emergent Adverse Event
Confidence interval for proportion of patients with TEAEs is calculated using the Clopper-Pearson method.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk. The subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Severity of outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown + Missing
From the MedDRA dictionary, version 26.0.
TEAEs indicate the applicable risks in relevant tables.
Protocol Number: CT-P41 3.1

Overall, there were 44 TEAEs in 31 patients related to cardiovascular events; 26 in the CT-P41 only group, three (3) in the switched from reference product group, and 15 in the reference product group. The incidence of TEAEs per 100 patient-years in CT-P41 only group was 11.618 (95% CI: 7.589, 17.023), in the switched from reference product group was 1084.901 (95% CI: 223.733, 3170.541), and in the reference product group was 7.178 (95% CI: 4.017, 11.839).

The apparent high incidence of cardiovascular events in the group that switched from the reference product to receive a single further dose of CT-P41 at Week 52 is an artefact produced by the method of estimation of exposure to the trial treatments, which assumes exposure to risk stops on the day following administration of the last dose of trial treatment. Based on the duration of action of denosumab, the corrected incidence of TEAEs per 100 patient-years in CT-P41 only group was 7.583 (95% CI: 4.953, 11.110), in the switched from reference product group was 5.928 (95% CI: 1.223, 17.325), and in the reference product group was 5.410 (95% CI: 3.028, 8.924).

Of the 31 patients, 11 patients (4.6%) in the CT-P41 only group, two (2) patients (2.0%) in the switched from reference product group and 13 patients (5.5%) in the reference product group were categorised as experiencing non-serious events. Four (4) patients (1.7%) in the CT-P41 only group and one (1) patient (0.4%) in the reference product group were categorised as experiencing serious event.

Five (5) patients from CT-P41 only group, one (1) patient switched from reference product group and nine (9) patients from reference product group reported Grade 1 events. Six (6) patients from CT-P41 only group, one (1) patient switched from reference product group and four (4) patients from reference product group reported Grade 2 events. Two (2) patients from CT-P41 only group and one (1) patient from reference product group reported Grade 3 events. One (1) patient from CT-P41 only group reported Grade 4 event. One (1) patient from CT-P41 group reported Grade 5 event.

In nine (9) patients TEAEs related to cardiovascular events were reported as "recovered", in six (6) patients they were reported as "recovering", in one (1) patient it was reported as "recovered with sequelae", in 14 patients they were reported as "not recovered" and in one (1) patient it was reported as "fatal" at the end of the trial period.

The proportion of patients with TEAEs in the CT-P41 only group was 6.3% (95% CI: 3.55, 10.14) in the switched from reference product group was 2.0% (95% CI: 0.24, 6.97), and in the reference product group was 5.9% (95% CI: 3.25, 9.67).

Risk factors and risk groups:

The denosumab development programme comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population (Schulz et al., 2004; Hak et al., 2000).

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

Preventability:

Based on clinical data to date, denosumab has not been categorically associated with an increased incidence or severity of cardiovascular adverse effects; therefore, no preventive measures are defined.

Impact on the risk-benefit balance of the product:

The risk of cardiovascular events has been considered in the product benefit-risk assessment, and the overall benefit-risk balance is favourable.

Public health impact:

Significant public health impact on cardiovascular disease severity or incidence is not expected based on the evidence from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis/hormone ablation therapy settings.

Important potential risk: Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons (MedDRA PT Hypercalcaemia)

Potential mechanisms:

The pathogenesis of hypercalcaemia 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 remodelling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcaemia in susceptible individuals if the normal homeostatic mechanisms regulating serum calcium are not appropriately maintained.

Evidence source(s) and strength of evidence:

Hypercalcaemia after several months of 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 paediatric populations.

Cases of hypercalcaemia in the off-treatment period have been reported in clinical studies of the reference product, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcaemia in patients other than those with GCTB or with growing skeletons could not be attributed to discontinuation of denosumab based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups.

Characterisation of the risk:

There are no data for the important potential risk of hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons were not included in the study CT-P41 3.1.

Risk factors and risk groups:

Patients other than those with GCTB or growing skeletons following cessation of denosumab.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The risk of hypercalcaemia 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 favourable.

Public health impact:

No significant public health impact is expected as the potential events remain infrequent despite extensive market exposure.

SVII.3.2. Presentation of the missing information

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 denosumab in the clinical study for the reference product (Study 20101363). No notable association was evident between ONJ and prior use of bisphosphonates.

Population in need of further characterisation:

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 the reference product following treatment with bisphosphonates. However, more information is needed in this population.

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

Evidence source:

No specific risks associated with off-label use of denosumab have been identified.

Off-label use is the therapeutic use of a medicinal product for indications other than the approved indications. As with other drugs, denosumab might intentionally be used off-label. Since the clinical experience with the reference product as off-label use is limited (in particular in terms of efficacy and safety), it is considered missing information.

No formal studies have been performed to determine the effect of denosumab during off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Population in need of further characterisation:

Information is not available on safety in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Part II: Module SVIII - Summary of the safety concerns

Table 9: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Osteonecrosis of the jaw • Atypical femoral fracture
Important potential risks	• Cardiovascular events • Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	• Patients with prior intravenous bisphosphonate treatment • Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Targeted follow-up questionnaires will be used for serious adverse events of the risks listed below (Annex 4):

- Osteonecrosis of the jaw
- Atypical femoral fracture

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

Not applicable as there are no additional pharmacovigilance activities planned for Osenvelt.

III.3 Summary Table of additional Pharmacovigilance activities

Table 10: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

Not applicable, since there are no post authorisation efficacy studies planned for Osenvelt.

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

V.1. Routine Risk Minimisation Measures

Table 11: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified risk - Osteonecrosis of the jaw	Routine risk communication: SmPC sections 4.3, 4.4, 4.8 and 5.1 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for dental examination prior to/during treatment, maintenance of good oral hygiene during treatment, immediate report of any oral symptoms, and management plan if osteonecrosis of the jaw occurs are included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine).
Important Identified risk - Atypical femoral fracture	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: Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine).
Important Potential risk - 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: *Legal status*: Restricted medical prescription (Prescription only medicine).
Important Potential risk - Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	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: *Legal status*: Restricted medical prescription (Prescription only medicine).
Missing Information - Patients with prior intravenous bisphosphonate treatment	Routine risk communication: SmPC sections 4.5 and 5.1 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine).
Missing Information - Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	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: *Legal status*: Restricted medical prescription (Prescription only medicine).

V.2. Additional Risk Minimisation Measures

Patient reminder card – Osteonecrosis of the jaw (ONJ)

Objectives:

To remind the patient to tell his/her doctor of important symptoms that may suggest that he/she may have developed ONJ on the reminder card.

To provide the patient with a document that he/she can show to any health professional that may not be familiar with the treatment he/she is receiving.

Patients are to be provided with the patient reminder card for the following risk:

- Osteonecrosis of the jaw

Rationale for the additional risk minimisation activity:

The patient reminder card is to remind patients about important safety information that they need to be aware of before and during treatment with Osenvelt injections for cancer-related conditions. Also, to ensure that the patient is aware that regular dental examination and good oral hygiene should be maintained during treatment and that he/she should contact the relevant healthcare professional quickly for problems that may arise with the teeth and gums.

Target audience and planned distribution path:

Patients who receive Osenvelt must be given a patient reminder card that summarises the safety information about the medicine. The patient reminder card is distributed to healthcare professionals with instruction to provide it to patients.

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

Signal detection will be performed on the reports consistent with ONJ that are received from postmarketing experience. A trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. The occurrence of ONJ will be monitored by routine pharmacovigilance activities.

Effectiveness will be assessed using frequencies of ONJ in postmarketing experience as an outcome indicator. Data on the effectiveness of the additional risk minimisation activity will be presented in each scheduled PSUR for denosumab.

V.3 Summary of risk minimisation measures

Table 12: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Osteonecrosis of the jaw (Important identified risk)	Routine risk minimisation measures: • *SmPC sections 4.3, 4.8 and 5.1* • *SmPC section 4.4 where maintenance of oral hygiene, regular dental management and potential oral symptoms of ONJ are included* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: Patient reminder card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Atypical femoral fracture (Important identified risk)	Routine risk minimisation measures: • *SmPC section 4.8* • *SmPC section 4.4 where recommendations for monitoring patients for signs and symptoms of hypercalcaemia after discontinuation of treatment are included* • *PL section 2 where recommendations for reporting new or unusual pain in hip, groin, or thigh are included* • *PL section 4 where possible signs of thigh bone fracture are included* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Cardiovascular events (Important potential risk)	Routine risk minimisation measures: *None* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons (Important potential risk)	Routine risk minimisation measures: None Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with prior intravenous bisphosphonate treatment (Missing information)	Routine risk minimisation measures: • *SmPC sections 4.5 and 5.1* • *PL section 2* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity (Missing information)	Routine risk minimisation measures: None Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation 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

Summary of risk management plan for Osenvelt (denosumab)

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

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

This summary of the RMP for Osenvelt 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 Osenvelt's RMP.

I. The medicine and what it is used for

Osenvelt is authorised 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 tumour 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 injection.

Further information about the evaluation of Osenvelt's benefits can be found in Osenvelt's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: *https://www.ema.europa.eu/en/medicines/human/EPAR/osenvelt*.

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

Important risks of Osenvelt, together with measures to minimise such risks and the proposed studies for learning more about Osenvelt'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 package leaflet 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 Osenvelt, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, 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 Osenvelt is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Osenvelt 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 Osenvelt. 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	Osteonecrosis of the jaw Atypical femoral fracture
Important potential risks	Cardiovascular events Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	Patients with prior intravenous bisphosphonate treatment Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

II.B Summary of important risks

Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to medicine	Osteonecrosis of the jaw (ONJ) is a condition where the jawbone is not covered by the gums and is exposed. It can be caused by two types of medicines: Antiresorptive medicines (including bisphosphonates (BPs) and receptor activator of nuclear factor kappa-B ligand [RANK-L] inhibitors) and antiangiogenic medicines. In the clinical development programme of the reference product, the subject incidence of ONJ was 1.8% in the denosumab group. In a multiple myeloma study, the subject incidence of ONJ was 4.1% in the denosumab group. The incidence of ONJ increased with longer duration of treatment with denosumab. In a post-marketing study with the reference product, the incidence of ONJ per 100 person-years was 3.0 (2.3, 3.7) in patients that started treatment with denosumab, and 4.3 (2.8, 6.3) in patients who switched to denosumab from alternative treatment.

Risk factors and risk groups	Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous 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 minimisation measures	Routine risk minimisation measures: • *SmPC sections 4.3, 4.8 and 5.1* • *SmPC sections 4.4 where maintenance of oral hygiene, regular dental management and potential oral symptoms of ONJ are included* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: Patient reminder card
Important identified risk: Atypical femoral fracture	
Evidence for linking the risk to medicine	In the clinical development programme of the reference product, 0.2% (15 of 8342) of all subjects who received at least one dose of denosumab experienced atypical femoral fracture (AFF). AFF has been reported uncommonly in patients treated with denosumab and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued.
Risk factors and risk groups	Long-term anti-resorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF. AFFs 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 minimisation measures	Routine risk minimisation measures: • *SmPC section 4.8* • *SmPC section 4.4 where recommendations for monitoring patients for signs and symptoms of hypercalcaemia after discontinuation of treatment are included* • *PL section 2 where recommendations for reporting new or unusual pain in hip, groin, or thigh are included* • *PL section 4 where possible signs of thigh bone fracture are included* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None

Important potential risk: Cardiovascular events	
Evidence for linking the risk to medicine	The risk of cardiovascular events is a regulatory concern based on the epidemiological association between osteoprotegerin (OPG) levels and cardiovascular disease in humans. Clinical data have not substantiated a cause-and-effect between OPG and atherosclerotic processes nor between denosumab or inhibition of RANKL and undesirable cardiovascular outcomes. In pooled pivotal solid tumour studies with the reference product, subject incidence of cardiovascular adverse events was 29.7% in both treatment groups; the hazard ratio was 0.98 (95% CI: 0.89, 1.08). In a study with denosumab 120 mg Q4W in subjects with castration-resistant prostate cancer (Study 20050147), the subject incidence of cardiovascular adverse events was 33.1% in the denosumab group. In a multiple myeloma study, the subject incidence of adverse events of cardiac disorders was 11.6% and vascular disorder was 20.9% in the denosumab group.
Risk factors and risk groups	The denosumab development programme comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population. 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 inhibitors.
Risk minimisation measures	Routine risk minimisation measures: None Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important potential risk: Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	
Evidence for linking the risk to medicine	Hypercalcaemia after several months of 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 paediatric populations. Cases of hypercalcaemia in the off-treatment period have been reported in clinical studies of the reference product, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcaemia in patients other than those with GCTB or with growing skeletons could not be attributed to discontinuation of denosumab based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.

Risk minimisation measures	Routine risk minimisation measures: None Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Missing information: Patients with prior intravenous bisphosphonate treatment	
Risk minimisation measures	Routine risk minimisation measures: • *SmPC sections 4.5 and 5.1* • *PL section 2* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Missing information: Off label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	
Risk minimisation measures	Routine risk minimisation measures: None Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None

PL: Package Leaflet; SmPC: Summary of Product Characteristics

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 Osenvelt.

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

There are no studies required for Osenvelt.

Part VII: Annexes

Table of contents

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Table of Contents

CELLTRION

DENOSUMAB Questionnaire
Osteonecrosis of the Jaw

AER #

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐ Male ☐ Female Weight: _____ lb _____ kg

Age at time of event: _____

Study Number (If applicable)

Event

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/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

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

☐ Other Please specify _____

☐ Don't know

Denosumab Exposure

Denosumab first administered (date) _____

Last denosumab dose before event (date)

☐ Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown

If yes, please specify _____

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

If yes, date of first dose following start of event _____

EVIDENCE OF EXPOSED BONE (Please indicate dates as DD/MM/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:

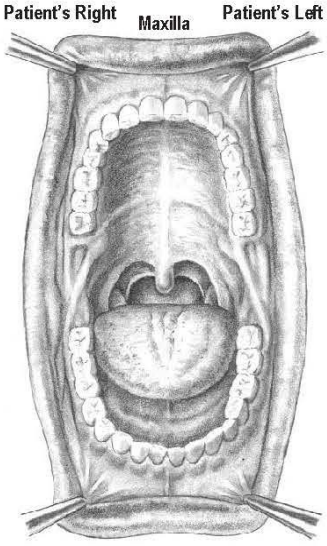
☐ No ☐ Yes ☐ Unknown

Describe: _____

Please indicate the location of involved area(s) on the diagram at right (mark site(s) clearly with 'X').

Please describe location(s):

- ☐ Right maxilla, teeth and lateral jaw
- ☐ Left maxilla, teeth and lateral jaw
- ☐ Right maxilla, medial jaw
- ☐ Left maxilla, medial jaw
- ☐ Right mandible teeth and lateral jaw
- ☐ Left mandible teeth and lateral jaw
- ☐ Right mandible, medial jaw
- ☐ Left mandible, medial jaw
- ☐ Maxilla hard palate
- ☐ Other (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 _____

CLINICAL SYMPTOMS (Please indicate date as DD/MM/YYYY)

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

Please describe the clinical signs/symptoms/location:

Patient Reminder Card Status (For EU Patients)

Received a patient reminder card prior to the ONJ event:

☐ Yes ☐ No ☐ Unknown

CONTINUED ON NEXT PAGE (PAGE 1 OF 2)

v.1.0

CELLTRION

DENOSUMAB Questionnaire
Osteonecrosis of the jaw (continued)

AER #

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Date of This Report

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

Antibiotics ☐No ☐Yes ☐Unknown If yes, agent(s)/route/dose _____ Start date_____Stop date_____

Please describe outcomes of treatment _____

Oral rines ☐No ☐Yes ☐Unknown If yes, agent(s) /dose _____

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 _____

DENTAL HISTORY (Please indicate dates as DD/MM/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 dates as DD/MM/YYYY)

PO bisphosphonate ☐No ☐Yes ☐Unknown If yes, agent(s)/dose _____

If yes, agent(s)/dose _____

Start date _____ Stop date _____

IV bisphosphonate ☐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 If yes, agent(s)/dose _____

Start date _____ Stop date _____

OTHER HISTORY (Please indicate all dates as DD/MM/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

Celltrion
Office Fax:

REPORTER Name:

Address:

City: State/

Country: Province:

Email: Postal Code:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

CELLTRION

DENOSUMAB Questionnaire
Potential atypical fracture

(low energy, subtrochanteric/femoral shaft fractures)

AER #

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Date of Event Onset | Date of This Report

Gender: ☐ Male ☐ Female Weight: _____ lb _____ kg

Age at time of event: _____

Study Number (If applicable)

Event

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/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 ☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks

☐ Other (Please specify) _____ ☐ Don't know

Denosumab Exposure: Denosumab first administered (date)_____

Last denosumab dose before event (date) _____

☐ Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown

If yes, please specify _____

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

If yes, date of first dose following start of event _____

DIAGNOSIS (Check all that apply)

Location of fracture:

☐ Femur neck

☐ Femur distal

☐ Femur midshaft

☐ Femur intertrochanter

☐ Femur subtrochanter

☐ Other location (specify): _____

Diagnostic imaging used to confirm fracture:

☐ X-ray ☐ CT scan ☐ MRI

Date of imaging at time of femur fracture (DD/MM/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 beaking of the cortex:

☐ Yes ☐ No ☐ Not reported

Diffuse cortical thickening of the proximal femoral shaft:

☐ Yes ☐ No ☐ Not reported

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

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 (DD/MM/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

CONTINUED ON NEXT PAGE (PAGE 1 OF 2)

CELLTRION

DENOSUMAB Questionnaire
Potential atypical fracture (Continued)
(low energy, subtrochanteric/femoral shaft fractures)

AER #

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Date of This Report

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:

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

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: _____

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

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

Celltrion
Office Fax:

REPORTER

Name:

Address:

City:

State/ Province:

Postal Code:

Country:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

Annex 6 – Details of proposed additional risk minimisation activities (if applicable) Draft key messages of the additional risk minimisation measures for Osenvelt

Patient reminder card:

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) will be distributed to healthcare professionals of Osenvelt with 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 (Osenvelt) injections for cancer-related conditions, including:

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

Annex 7 – Other supporting data (including referenced material)

List of publications and other bibliographic material referenced in this RMP

Aghaloo T, Hazboun R, Tetradis S. Pathophysiology of Osteonecrosis of the Jaws. Oral Maxillofac Surg Clin North Am. 2015 Nov;27(4):489-96. doi: 10.1016/j.coms.2015.06.001

Almazrooa SA, Woo SB. Bisphosphonate and nonbisphosphonate-associated osteonecrosis of the jaw. J Amer Dental Assoc. 2009;140:864-875.

EMEA/CHMP/BMWP/42832/2005 Rev 1. CHMP (Committee for medicinal products for human use). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. London: EMA (European Medicines Agency); 2014. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf

EMEA/CHMP/BMWP/403543/2010. CHMP (Committee for medicinal products for human use). Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. London: EMA (European Medicines Agency); 2012. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf

Estilo CL, Fornier M, Farooki A, et al. Osteonecrosis of the jaw related to bevacizumab. J Clin Oncol. 2008;26:4037-4038.

Fassio A, Bertoldo F, Idolazzi L, Viapiana O, Rossini M, Gatti D. Drug-induced osteonecrosis of the jaw: the state of the art. Reumatismo. 2017;69(1):9-15.

Giusti A, Hamdy NA, Dekkers OM, et al. Atypical fractures and bisphosphonate therapy: a cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features. Bone. 2011;48(5):966-971.

Hak AE, Pols HAP, van Hemert AM, et al. Progression of aortic calcification is associated with metacarpal bone loss during menopause. Arterioscler Thromb Vasc Biol. 2000;20:1926-1931.

Ismail A, Bekhet AH, Abushouk AI, Mirbaha S, Baratloo A. Denosumab and atypical femoral fractures: A scoping literature review. Trauma Monthly. 2018;23(1):e42869.

Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaw. Hematol. 2006:356-360.

Meier RP, Perneger TV, Stern R, et al. Increasing occurrence of atypical femoral fractures associated with bisphosphonate use. Arch Intern Med. 2012;172:930-936.

Murphy CA, Dargie HJ. Drug-induced cardiovascular disorders. Drug Safety. 2007;30(9):783-804.

Olvera Lopez E, Ballard BD, Jan A. Cardiovascular Disease. [Updated 2023 Aug 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535419/

Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G. Medication-related osteonecrosis of the jaw: Clinical and practical guidelines. J Int Soc Prev Community Dent. 2016 Mar-Apr;6(2):97-104.

Ruggiero S, Gralow J, Marx RE, et al. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Pract.2006;2:7-14.

Schulz E, Kiumars A, Xiaodong L, et al. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab. 2004;89:4246-4253.

Smith SC, Milani RV, Arnett DK, et al. Atherosclerotic Vascular Disease Conference, Writing Group II: Risk Factors. Circulation. 2004;109(21):2613-2616.

Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society of Bone and Mineral Research. J Bone Miner Res. 2010;25:2267-2294.

Xgeva® Risk Management Plan (RMP) version 37.1