EU Risk Management Plan
For
Stoboclo
(CT-P41 60 mg PFS, denosumab biosimilar)

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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.

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List of Abbreviations

Term	Explanation
ADR	Adverse Drug Reaction
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline phosphatase
AUC	Area Under the Curve
CAD	Coronary Artery Disease
CI	Confidence interval
CrCL	Creatinine clearance
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EMA	European medicines agency
EOS	End of study
EPAR	European public assessment report
EU	European union
GVP	Good pharmacovigilance practice
HR	Hazard Ratio
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
ONJ	Osteonecrosis of the jaw
OPG	Osteoprotegerin
PAD	Peripheral Artery Disease
PD	Pharmacodynamics
PL	Package leaflet
PK	Pharmacokinetics
PSUR	Periodic safety update report
PTH	Parathyroid Hormone
RANK	Receptor activator of nuclear factor kappa b
RANKL	RANK Ligand

Term	Explanation
RMP	Risk management plan
SmPC	Summary of product characteristics
TEAEs	Treatment Emergent Adverse Events
US	United States

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)	Stoboclo
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 neutralises 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 Deoxyribonucleic acid (DNA) technology.
Hyperlink to the Product Information	CTD Module 1.3.1
Indication(s) in the EEA	**Current:** Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women,

	denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
Dosage in the EEA	**Current:** The recommended dose is 60 mg denosumab administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm. Patients must be adequately supplemented with calcium and vitamin D.
Pharmaceutical form(s) and strengths	**Current:** • 60 mg/mL solution for injection in pre-filled syringe
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Stoboclo, 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 Stoboclo (CT-P41, biosimilar denosumab) is the innovator product Prolia, which contains denosumab. The Marketing Authorisation Holder (MAH) for the reference medicinal product also holds a separate marketing authorisation in the European Union (EU) for denosumab under the brand name Xgeva. 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 Cynomolgus monkeys were given weekly subcutaneous injections of 10 mg/kg CT-P41 (test article) or 10 mg/kg United States (US)-Prolia (reference article) to for 4 weeks. There were no apparent test article related effects on body weight, ophthalmoscopic findings, qualitative and quantitative ECG parameters, haematology, coagulation, urinalysis, macroscopic observations or organ weights. Test article-related changes occurred at the metaphysis of the bone of the proximal and distal femur and were most prominent at the distal femur. Both sexes administered 10 mg/kg/dose CT-P41 or 10 mg/kg/dose US-Prolia had mild to moderate decreases in calcium concentration that were often associated with minimal to mild decreases in phosphorus concentration. Both sexes administered 10 mg/kg/dose CT-P41 or 10 mg/kg/dose US-Prolia also had minimal to moderate decreases in alkaline phosphatase (ALP) activity. Overall, alterations in calcium, phosphorus, and ALP activity were of comparable magnitudes in animals administered CT-P41 and US-Prolia. Microscopic changes included increased numbers of primary trabeculae in males and females which were at similar incidence and/or severity in CT-P41 and US-Prolia-treated animals and correlated with decreased ALP, calcium and phosphorus on clinical pathology examination. Increased trabecular bone was not considered adverse due to the lack of corresponding clinical signs or indication of bone fragility (necrosis, degeneration, and/or fractures), localized nature limited to the metaphysis and low, minimal to mild, severity. Weekly subcutaneous administration of 10 mg/kg CT-P41 (test article) or 10 mg/kg US-Prolia (reference article) to Cynomolgus monkeys for 4 weeks was tolerated and resulted in changes that were comparable between the test and reference articles. Therefore, under the conditions of this study, the NOAELs were determined to be 10 mg/kg CT-P41 and 10 mg/kg US-Prolia (the only dose levels tested). **Repeat-dose toxicity of Prolia (European Public Assessment Report [EPAR])** In the 1 month repeat dose toxicity study (101447) in young adult Cynomolgus monkeys, as the only potentially drug-related change of statistically significant elevated thyroid weights were noted in females of the high dose group that were not confirmed by histopathological findings. Despite the high immunogenicity observed in all dose groups, a dose dependent change in some	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
Pharmacodynamic (PD) parameters was observed. In 6/12-Month Repeated-dose Study in Monkeys (102090) denosumab was administrated at doses of 0, 1, 10, and 50 mg/kg. Overall, no effects on organ weights or macroscopic or microscopic evidence of target organ toxicity were noted. Denosumab also had no untoward effects on sperm motility or morphology. The previously reported effects on thyroid weight (study 101447) were not confirmed. Consistent with the 1-month study, denosumab was highly immunogenic in monkeys.	
Reproductive/Developmental toxicity of CT-P41 Reproductive toxicology studies have not been performed because they are not required according to the European medicines agency (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 Prolia (RMP)** At area under the curve (AUC) exposures up to 100-fold higher than the human exposure (Q6M), denosumab showed no evidence of impaired fertility in cynomolgus monkeys. In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (Q6M), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined. In cynomolgus monkeys dosed with denosumab throughout pregnancy, effects including stillbirths and increased postnatal mortality; abnormal bone growth, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth were noted at AUC exposures up to 119-fold higher than the human exposure (60 mg Q6M). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal. In genetically engineered mice in which RANKL has been turned off by gene removal (a “knockout mouse”), studies suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum. In neonatal rats, administration of the RANKL inhibitor osteoprotegerin (OPG) bound to Fc (OPG-Fc) resulted in reduced weight gain, reduced bone growth, and inhibited tooth eruption. Despite reductions in bone growth, most bone strength parameters were increased with these treatments. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery	Monkeys exposed to denosumab in utero phenotypically resembled human infants with osteoclast-poor osteopetrosis due to inactivating mutations of RANK or RANKL. Therefore, Prolia is not recommended for use in pregnant women. Women should be advised not to become pregnant during and for at least 5 months after treatment with Prolia. It is not known if Prolia is excreted in human milk. Because denosumab has the potential to cause adverse reactions in nursing infants, a decision should be made on whether to discontinue nursing or discontinue the drug. Use in pregnant and lactating women is not considered a safety concern in this RMP. These populations are not included in the intended indications. In addition, risk minimization via product labelling to avoid pregnancy and breastfeeding is in place. Treatment with Prolia may inhibit eruption of dentition in paediatric patients and

Key Safety findings (from non-clinical studies) of CT-P41 (denosumab biosimilar)	Relevance to human usage
period from birth out to 6 months of age, the effects on bone generally returned to normal; there were no adverse effects on tooth eruption; and minimal to moderate mineralization in multiple tissues was seen in 1 recovery animal. Adolescent cynomolgus monkeys who received doses of denosumab 150 times the expected clinical exposure had enlargement of epiphyseal growth plates with decreased removal of cartilage matrix in this area, considered to be consistent with the pharmacological activity of denosumab.	may impair bone growth in paediatric patients with open growth plates. Prolia is not approved for use in paediatric patients and should not be used in paediatric patients. Risk minimization is in place via product labelling with respect to use in paediatric patients.
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 Prolia (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 Prolia (EPAR)** The safety pharmacology package included two studies; one of these was incorporated in a toxicology study in accordance with International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (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 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 Prolia (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 Prolia (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 Stoboclo and CT-P41 may be used interchangeably in this document.

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

- **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 Pharmacokinetics (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 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 recommended dose of Stoboclo is 60 mg administered as a single subcutaneous injection once every 6 months. Stoboclo is administered intermittently. Exposure to Stoboclo 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 doses. 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	5945
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: Hypersensitivity reactions is an important identified risk for denosumab and 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 Summary of product characteristics (SmPC) of Stoboclo (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)

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.

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

Rationale: Hypocalcaemia is an important identified risk for denosumab and the use of denosumab is contraindicated in patients with hypocalcaemia. This is adequately described in the SmPC of Stoboclo (Section 4.3 [Contraindication] and Section 4.8 [Undesirable effects]).

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 including denosumab 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: Infections are an important identified risk for denosumab and this risk has been adequately described in the SmPC Section 4.8 [Undesirable effects]. Routine risk minimisation activities recommending specific clinical measures to address the risk have been included in Stoboclo SmPC Section 4.4 [Special warnings and precautions for use].

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 is 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 alterations in bone mineral density, which may increase fracture risk.

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: 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]). Routine risk minimisation activities recommending specific clinical measures to address the risk before and during treatment have been adequately described in Stoboclo 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: 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 a higher risk of dropout.

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

Rationale: Patients with above mentioned exclusion criteria were excluded to prevent confounding the interpretation of efficacy and safety study endpoints.

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.

According to the reference product Prolia SmPC, in a double-blind, alendronate-controlled study, in postmenopausal women with low bone mineral density who had received bisphosphonates for at least 6 months preceding study entry, safety results were similar in the denosumab and alendronate treatment groups. In addition, studies were conducted to evaluate the effects of denosumab and a bisphosphonate (risedronate, ibandronate, or zoledronic acid, respectively) in postmenopausal women transitioning from previous bisphosphonate therapy. There were no new safety findings in these studies.

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

Rationale: May complicate the interpretation of efficacy and safety endpoints.

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 male and postmenopausal women with osteoporosis. Up to the data lock point of this RMP, 89 healthy volunteers in phase I studies (CT-P41 1.1 and 1.2) 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	

Type of special population	Exposure
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 55 patients 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 Stoboclo is a biosimilar, based on the safety profile of the reference product Prolia, 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.
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 Caucasian (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

Not applicable as the product has not received marketing authorisation yet in any jurisdiction.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

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

Potential for misuse for illegal purposes

Based on the given mechanism of action of Stoboclo 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 requirement, Stoboclo has been shown to have quality, safety and efficacy comparable to the reference product Prolia. The safety profile of Stoboclo is similar to that of the reference product and has been adequately described in the product information.

The following risks are labelled in the product information for the reference product and are not important safety concerns for either Stoboclo or Prolia:

Urinary tract infection, upper respiratory tract infection, diverticulitis, ear infection, sciatica, constipation, abdominal discomfort, rash, eczema, alopecia, lichenoid drug eruptions, pain in extremity, musculoskeletal pain, 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: Hypocalcaemia

Risk-benefit impact:

Calcium is crucial for life, and it must be kept at the right levels extracellularly. Hypocalcaemia can occur with various disorders and can be life-threatening. Acute hypocalcaemia causes muscle problems and seizures, but can be treated with intravenous calcium. Chronic hypocalcaemia is often less obvious. It can be caused by hypoparathyroidism. Another reason can be inadequate vitamin D (Bove-Fenderson and Mannstadt, 2018).

In the post-marketing setting with the reference product Prolia, severe symptomatic hypocalcaemia (including fatal cases) has been reported, with most cases occurring in the first weeks of initiating therapy, but it can occur later. Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia.

Also, according to the SmPC of the reference product Prolia and Stoboclo, rare cases of severe symptomatic hypocalcaemia have been reported predominantly in patients at increased risk of hypocalcaemia receiving denosumab. Examples of the clinical manifestations of severe symptomatic hypocalcaemia include QT interval prolongation, tetany, seizures and altered mental status. Symptoms of hypocalcaemia in denosumab clinical studies included paraesthesias or muscle stiffness, twitching, spasms and muscle cramps.

In clinical studies with reference product Prolia, patients with severe renal impairment (creatinine clearance < 30 mL/min) or those receiving dialysis were at greater risk of developing hypocalcaemia in the absence of calcium supplementation. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or those receiving dialysis.

The frequency of denosumab induced hypocalcaemia is ‘Rare’.

Additionally, hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.

The risk of hypocalcaemia 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 (Prolia RMP version 31.0).

Important identified risk: Skin infection leading to hospitalisation

Risk-benefit impact:

Skin infections occur when microorganisms infect the skin and sometimes the deep tissue beneath the skin. Cellulitis is a common type of skin infection that causes redness, swelling, and pain in the infected area of the skin. Another type of skin infection is skin abscess (Centers for Disease Control and Prevention, 2020).

Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

In placebo-controlled clinical trials with the reference product Prolia, the overall incidence of skin infections was similar in the placebo and the denosumab groups: in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus Prolia [1.5%, 59 out of 4,050]); in men with osteoporosis (placebo [0.8%, 1 out of 120] versus Prolia [0%, 0 out of 120]); in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus Prolia [1.4%, 12 out of 860]). Skin infections leading to hospitalisation were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving Prolia. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the Prolia (0.6%, 5 out of 860) groups in breast and prostate cancer studies.

According to the SmPC of the reference product Prolia and Stoboclo, the frequency of denosumab induced cellulitis is ‘uncommon’.

The risk of skin infection leading to hospitalisation 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 (Prolia RMP version 31.0).

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).

According to the SmPC of the reference product Prolia and Stoboclo, ONJ has been reported rarely in patients treated for osteoporosis. Long-term antiresorptive treatment (including both denosumab and bisphosphonates) may contribute to an increased risk for adverse outcomes such as ONJ and atypical femur fractures due to significant suppression of bone remodelling.

As per the clinical trials with the reference product Prolia, ONJ has been reported rarely in clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation including a total of 23,148 patients. The risk of ONJ increased with duration of exposure to denosumab. Incidence of ONJ was 0.04% at 3 years, 0.06% at 5 years and 0.44% at 10 years of denosumab treatment.

Patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.

According to the SmPC of the reference product Prolia and Stoboclo, the frequency of denosumab induced ONJ is ‘rare’.

The risk of ONJ has been considered in the product benefit-risk assessment. In light of the product labelling and additional risk minimisation activities addressing this risk, the overall risk-benefit balance is considered to be favourable (Prolia RMP version 31.0).

Important identified risk: Hypersensitivity reactions

Risk-benefit impact:

Hypersensitivity reactions are exaggerated or inappropriate immunologic responses occurring in response to an antigen or allergen. Type I, II and III hypersensitivity reactions are known as immediate hypersensitivity reactions because they occur within 24 hours of exposure to the antigen or allergen. Immediate hypersensitivity reactions are predominantly mediated by IgE, IgM, and IgG antibodies (Justiz Vaillant and Vashisht, 2023).

Rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in the postmarketing setting with the reference product Prolia.

According to the SmPC of the reference product Prolia and Stoboclo, the frequency of denosumab induced drug hypersensitivity, anaphylactic reaction, is ‘rare’.

Denosumab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

The risk of hypersensitivity reactions 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 (Prolia RMP version 31.0).

Important identified risk: Atypical femoral fracture

Risk-benefit impact:

Atypical femoral fractures have been reported in patients receiving denosumab. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterise these events. Atypical femoral fractures have also been reported in patients with certain co-morbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain medicinal products (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). 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.

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

According to the SmPC of the reference product Prolia and Stoboclo, the frequency of denosumab induced atypical Femoral Fracture is ‘rare’.

The risk of atypical femoral fracture 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 (Prolia RMP version 31.0).

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

Risk-benefit impact:

Calcium is the most abundant cation found in the human body and plays an integral role in neural transmission, enzyme activity, myocardial function, coagulation, and other cellular functions. Systemic acidosis decreases calcium binding to albumin increasing serum levels while alkalosis causes the opposite effect. Serum calcium concentrations are highest in neonates and infants, decrease during childhood and adolescence, and stabilise at adult values by 17 years of age (Sadiq et al., 2023).

According to the SmPC of the reference product Prolia and Stoboclo, denosumab should not be used in children aged <18 years because of safety concerns of serious hypercalcaemia, and potential inhibition of bone growth and lack of tooth eruption.

The risk-benefit profile of denosumab is not favourable in the paediatric patient population (Prolia RMP version 31.0).

Important potential risk: Fracture healing complications

Risk-benefit impact:

Fracture repair is a complex, coordinated biological process that relies on wound repair (stem cell recruitment, angiogenesis, mitogenesis), bone-specific anabolism (osteoblast differentiation/ proliferation, bone formation) and catabolism (bone remodelling) (Little et al., 2007). Although most fractures heal without complications, certain fractures are associated with abnormalities in healing. Expected fracture healing times vary significantly by site of fracture, demographic characteristics of the patient, and comorbidities (Bhandari et al., 2002). The most clinically significant adverse outcome associated with fracture healing is non-union.

In a double-blind, placebo-controlled study, 7,808 postmenopausal women were randomly assigned to receive either denosumab or a placebo control and 667 patients had a total of 851 non-vertebral fractures during study period. Neither delayed healing nor non-union was observed in any subject who had received denosumab within 6 weeks preceding or following the fracture. The complication rates associated with the fracture or intervention were not significantly different between the denosumab and placebo groups. The investigators concluded that denosumab did not delay fracture healing nor did it contribute to other complications, even when administered around the time of the fracture (Adami et al., 2012).

The potential risk of fracture healing complications has been considered in overall assessment supporting a favourable risk-benefit profile (Prolia RMP version 31.0).

Important potential risk: Infection

Risk-benefit impact:

It has been proposed that receptor activator of NF-κB (RANK) ligand (RANKL) inhibition may have immune modulating effects and this may increase the risk of infections. However, clinical

trials and observational studies have not conclusively shown that there is a significant risk of severe infections associated with the reference product Prolia (MEDSAFE, Risk of infections with Prolia).

A systematic review and meta-analysis revealed that, denosumab is associated with a higher incidence of serious infections compared with placebo, but the risk is similar to that of comparator drugs (Diker-Cohen et al., 2020).

The potential risk of infection has been considered in the overall assessment which supports a favourable risk-benefit profile in the indicated populations (Prolia RMP version 31.0).

Important potential risk: Cardiovascular events

Risk-benefit impact:

Cardiovascular events encompass four main conditions: Coronary Artery Disease (CAD), also referred to as coronary heart disease and ischaemic heart disease, cerebrovascular disease, Peripheral Artery Disease (PAD), and aortic atherosclerosis. CAD, in particular, arises from reduced blood flow to the heart, leading to angina due to ischemia and potentially resulting in Myocardial Infarction or heart failure (Olvera Lopez et al., 2023).

In a meta-analysis study (Lv F et al., 2019), treatment with denosumab was not associated with the specific or composite cardiovascular outcomes. The absolute risk for the composite cardiovascular outcome was 3.25% in denosumab-treated patients compared with 3.01% in control patients. In a similar fashion, there was no association between treatment with denosumab and risk for 3-point MACE (cardiovascular death, myocardial infarction, and stroke) or 4-point MACE (3-point MACE plus heart failure).

The potential risk of cardiovascular events has been considered in overall assessment supporting a favourable risk-benefit profile (Prolia RMP version 31.0).

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 (MedlinePlus).

As per the clinical trials with the reference product Prolia, in a large pivotal postmenopausal osteoporosis study, the subject incidence of new primary malignancy was 4.8% with denosumab and 4.3% with placebo (Hazard Ratio [HR] [95% CI] = 1.11 [0.90, 1.37]).In a hormone ablation therapy prostate cancer study of the reference product Prolia, the subject incidence of new primary malignancy was 5.1% with denosumab and 4.6% with placebo (HR [95% CI] = 1.08 [0.67, 1.72]), and overall survival was 94.1% in each treatment group (HR [95% CI] = 0.99 [0.65, 1.52]).

During the placebo-controlled phase of a male osteoporosis study of the reference product Prolia, 4 subjects in the denosumab group (3.3%) and no subject in the placebo group reported events of malignancy. The events were prostate cancer in 3 subjects and basal cell carcinoma in 1 subject. Two prostate cancer cases were likely present at baseline based on past medical history.

In a 24-month final analysis of a glucocorticoid-induced osteoporosis study of the reference product Prolia, subject incidence of malignancy was 3.0% with denosumab and 1.8% with risedronate (HR

[95% CI] = 1.75 [0.69, 4.44]). Subject incidence of serious adverse events of malignancy was 1.8% with denosumab and 1.6% with risedronate (Prolia RMP version 31.0).

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

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

Not applicable as this is an initial RMP.

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

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

Stoboclo (CT-P41, biosimilar denosumab) has been developed as a biosimilar of Prolia, which contains denosumab. The MAH for the reference medicinal product also holds a separate marketing authorisation in the EU for denosumab under the name Xgeva. The indications for Xgeva authorised in the EU are: 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 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.

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: Hypocalcaemia (Medical Dictionary for Regulatory Activities (MedDRA) PT Hypocalcaemia)

Potential mechanisms:

Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.

Evidence source(s) and strength of evidence:

Hypocalcaemia has been identified in the clinical trial programme of the reference product. This risk was identified in randomised, double-blind, placebo- or active-controlled studies (Prolia RMP version 31.0). A single 60-mg subcutaneous dose of denosumab presented an incidence of hypocalcaemia of 18.6 % in subjects with varying degrees of renal impairment (defined as a creatinine clearance (CrCl) <80 ml/min by Cockcroft-Gault estimation) (Block GA et al., 2012).

Characterisation of the risk:

Frequency with 95% Confidence Interval (CI) for Incidence per 100 Patient-year (PY)

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	11	0	11	8
Number of Patients with TEAEs [1]	8 (3.3%)	0	8 (2.4%)	7 (2.9%)
Incidence of TEAEs per 100 PYs	4.915	0.000	4.909	3.828
95% CI for Incidence of TEAEs per 100 PYs	(2.454, 8.795)	(NE, 1334.023)	(2.451, 8.784)	(1.653, 7.543)

[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 is 60 mg administered as a single subcutaneous injection once every 6 months.

Exposure-adjusted incidences of Treatment Emergent Adverse Events (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			Denosumab Reference Product** (N=238)
	CT-P41 only (N=239)	Switched from Denosumab Reference Product* (N=101)	Total (N=340)	
Total Number of TEAEs	11	0	11	8
Number of Patients with TEAEs [1]	8 (3.3%)	0	8 (2.4%)	7 (2.9%)
Incidence of TEAEs per 100 PYs	3.208	0.000	2.795	2.886
95% CI for Incidence of TEAEs per 100 PYs	(1.601, 5.740)	(NE, 7.290)	(1.395, 5.002)	(1.246, 5.686)

[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			Denosumab Reference Product** (N=238)
	CT-P41 only (N=239)	Switched from Denosumab Reference Product* (N=101)	Total (N=340)	
Total Number of TEAEs	11	0	11	8
Number of Patients with TEAEs [1]	8 (3.3%)	0	8 (2.4%)	7 (2.9%)
95% CI for Proportion of Patients with TEAEs	(1.46, 6.49)	(0.00, 3.59)	(1.02, 4.58)	(1.19, 5.97)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	7 (2.9%)	0	7 (2.1%)	7 (2.9%)
Grade 2	1 (0.4%)	0	1 (0.3%)	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0

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)	
Seriousness [3]				
Non-serious	8 (3.3%)	0	8 (2.4%)	7 (2.9%)
Serious	0	0	0	0
Outcomes [4]				
Missing/Unknown	0	0	0	0
Recovered/Resolved	6 (2.5%)	0	6 (1.8%)	7 (2.9%)
Recovered/Resolved with Sequelae	0	0	0	0
Recovering/Resolving	0	0	0	0
Not recovered/Not resolved	2 (0.8%)	0	2 (0.6%)	0
Fatal	0	0	0	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 19 TEAEs in 15 patients related to hypocalcaemia; 11 in the CT-P41 only group, none in the switched from reference product group, and eight (8) in the reference product group. The incidence of TEAEs per 100 patient-years in the CT-P41 only group was 4.915 (95% CI: 2.454, 8.795), in the switched from reference product group was 0.000 (95% CI: NE, 1334.023), and in the reference product group was 3.828 (95% CI: 1.653, 7.543).

Based on the duration of action of denosumab, the corrected incidence of TEAEs per 100 patient-years in the CT-P41 only group was 3.208 (95% CI: 1.601, 5.740), in the switched from reference product group was 0.000 (95% CI: NE, 7.290), and in the reference product group was 2.886 (95% CI: 1.246, 5.686).

All patients (eight [8] patients [3.3%] in the CT-P41 only group and seven [7] patients [2.9%] in the reference product group) were categorised as experiencing non-serious events.

Seven (7) patients each from the CT-P41 only group and reference product group reported Grade 1 events. One (1) patient reported Grade 2 event in the CT-P41 only group.

In 13 patients TEAEs related to hypocalcaemia were reported as "recovered" and in two (2) patients they were reported as "not recovered" at the end of the trial period.

The proportion of patients with TEAEs in the CT-P41 only group was 3.3% (95% CI: 1.46, 6.49) in the switched from reference product group was 0 (95% CI: 0.00, 3.59), and in the reference product group was 2.9% (95% CI: 1.19, 5.97).

Risk factors and risk groups:

Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, PTH resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (CrCL < 30 mL/min), dialysis, and some medications (Finkelstein, 2001).

Preventability:

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

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

Important identified risk: Skin infection leading to hospitalisation (MedDRA HLGT Skin and subcutaneous tissue infections and infestations NEC)

Potential mechanisms:

Keratinocytes can express RANL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response (Loser et al., 2006; Yamaguchi and Sakaguchi, 2006).

Evidence source(s) and strength of evidence:

This risk was identified in randomised, double-blind, placebo- or active-controlled studies with the reference product.

Characterisation of the risk:

In study CT-P41 3.1, there were no TEAEs reported for skin infection leading to hospitalisation in the CT-P41 only group (239 patients), switched from reference product group (101 patients), and the reference product group (238 patients).

Risk factors and risk groups:

Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs

(e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

Important identified risk: Osteonecrosis of the jaw (MedDRA PT Osteonecrosis of jaw)

Potential mechanisms:

Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodelling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact (Fassio et al., 2017; Aghaloo et al., 2015).

Evidence source(s) and strength of evidence:

This risk was identified in open-label long-term, randomised, double-blind, placebo-controlled studies with the reference product.

Characterisation of the risk:

In study CT-P41 3.1, there were no TEAEs reported for ONJ in the CT-P41 only group (239 patients), 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 include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis (Mehrotra and Ruggiero, 2006; Ruggiero et al., 2006).

Preventability:

A dental examination with appropriate preventive dentistry is recommended prior to treatment with Stoboclo, especially in patients with risk factors. While on treatment, patients should avoid invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while

on Stoboclo should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with Stoboclo, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

Important identified risk: Hypersensitivity reactions (MedDRA SMQ (narrow) Hypersensitivity)

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

This risk was identified in the post-marketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity reactions with the reference product (Prolia RMP version 31.0).

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	18	4	22	15
Number of Patients with TEAEs [1]	17 (7.1%)	4 (4.0%)	21 (6.2%)	12 (5.0%)
Incidence of TEAEs per 100 PYs	8.043	1446.535	9.818	7.178
95% CI for Incidence of TEAEs per 100 PYs	(4.767, 12.711)	(394.132, 3703.703)	(6.153, 14.865)	(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 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	18	4	22	15
Number of Patients with TEAEs [1]	17 (7.1%)	4 (4.0%)	21 (6.2%)	12 (5.0%)
Incidence of TEAEs per 100 PYs	5.250	7.905	5.591	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	(3.111, 8.297)	(2.154, 20.239)	(3.504, 8.465)	(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	18	4	22	15
Number of Patients with TEAEs [1]	17 (7.1%)	4 (4.0%)	21 (6.2%)	12 (5.0%)
95% CI for Proportion of Patients with TEAEs	(4.20, 11.14)	(1.09, 9.83)	(3.86, 9.29)	(2.63, 8.64)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	5 (2.1%)	2 (2.0%)	7 (2.1%)	8 (3.4%)
Grade 2	12 (5.0%)	2 (2.0%)	14 (4.1%)	4 (1.7%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Non-serious	17 (7.1%)	4 (4.0%)	21 (6.2%)	12 (5.0%)
Serious	0	0	0	0

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)	
Outcomes [4]				
Missing/Unknown	0	0	0	0
Recovered/Resolved	15 (6.3%)	4 (4.0%)	19 (5.6%)	10 (4.2%)
Recovered/Resolved with Sequelae	0	0	0	0
Recovering/Resolving	2 (0.8%)	0	2 (0.6%)	0
Not recovered/Not resolved	0	0	0	2 (0.8%)
Fatal	0	0	0	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 37 TEAEs in 33 patients related to hypersensitivity reactions; 18 in the CT-P41 only group, four (4) in the switched from reference product group, and 15 in the reference product group. The incidence of TEAEs per 100 patient-years in the CT-P41 only group was 8.043 (95% CI: 4.767, 12.711), in the switched from reference product group was 1446.535 (95% CI: 394.132, 3703.703), and in the reference product group was 7.178 (95% CI: 4.017, 11.839).

The apparent high incidence of hypersensitivity 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 the CT-P41 only group was 5.250 (95% CI: 3.111, 8.297), in the switched from reference product group was 7.905 (95% CI: 2.154, 20.239), and in the reference product group was 5.410 (95% CI: 3.028, 8.924).

All patients (17 patients [7.1%] in the CT-P41 only group, four [4] patients [4.0%] in the reference product group and 12 patients [5.0%] in the reference product group) were categorised as experiencing non-serious events.

Five (5) patients from the CT-P41 only group, two (2) patients switched from reference product group and eight (8) patients from reference product group reported Grade 1 events. Twelve (12) patients from CT-P41 only group, two (2) patients switched from reference product group and four (4) patients from reference product group reported Grade 2 events.

In 29 patients TEAEs related to hypersensitivity reactions were reported as "recovered", in two (2) patients they were reported as "recovering" and in two (2) patients they were reported as "not recovered" at the end of the trial period.

The proportion of patients with TEAEs in the CT-P41 only group was 7.1% (95% CI: 4.20, 11.14) in the switched from reference product group was 4.0% (95% CI: 1.09, 9.83), and in the reference product group was 5.0% (95% CI: 2.63, 8.64).

Risk factors and risk groups:

Known hypersensitivity to denosumab and any of the excipients in the product.

Preventability:

No data are available on potential measures to prevent hypersensitivity reactions to denosumab. The appropriate contraindication information on hypersensitivity to denosumab and any of its excipients is included in the SmPC.

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

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 atypical femoral fracture, but the pathogenesis remains unclear and the causes of atypical femoral fracture are likely multi-factorial. Based on nonclinical studies, collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralisation, remodelling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and atypical femoral fracture (Ismail et al., 2018; Shane et al., 2010).

Evidence source(s) and strength of evidence:

This risk was identified in an open-label long-term, randomised, double-blind, active-controlled study with the reference product (Prolia RMP version 31.0).

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 antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture (Meier et al., 2012; Giusti et al., 2011). Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, and proton pump inhibitors (Shane et al., 2010).

Preventability:

No data are currently available on potential measures to prevent atypical femoral fracture. 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 atypical femoral fracture has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be favourable.

Public health impact:

Based on the infrequency of atypical femoral fracture in patients treated with denosumab, no significant public health impact is expected.

Important identified risk: Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation (MedDRA PT Hypercalcaemia)

Potential mechanisms:

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

- Hypercalcaemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from resorbing bone matrix via an autocrine/paracrine mechanism.
- The magnitude of the resorptive response following treatment and withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons.
- The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in individuals with growing skeletons. The increased skeletal metabolism related to bone modelling and growth in children is therefore likely to impact the frequency of hypercalcaemia occurring both between the dosing interval and following discontinuation.

Evidence source(s) and strength of evidence:

Data to evaluate this safety concern were derived from the reference product clinical trials in paediatric subjects with osteogenesis imperfecta, denosumab clinical studies, and postmarketing adverse event reporting involving paediatric patients receiving denosumab at unapproved doses and/or unapproved indications for use (Prolia RMP version 31.0).

Characterisation of the risk:

There are no data for the important identified risk of hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation because paediatric patients were not included in the study CT-P41 3.1.

Risk factors and risk groups:

Paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta).

Preventability:

Stoboclo is not indicated in paediatric patients (age <18 years) and should not be used in paediatric patients. If used in a clinical trial setting, such as for paediatric glucocorticoid-induced osteoporosis, monitoring for signs and symptoms and periodic serum calcium would be advisable.

Impact on the risk-benefit balance of the product:

The benefit-risk profile of Stoboclo (denosumab) has not been shown to be favourable in the paediatric patient population.

Public health impact:

Stoboclo is not authorised for use in children. Significant public health impact is not expected as hypercalcaemia may be preventable with the appropriate risk mitigating measures communicated clearly in the SmPC.

Important potential risk: Fracture healing complications (MedDRA HLT Fracture complications)

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

This is a theoretical risk based on the mechanism of action of denosumab.

Characterisation of the risk:

There were no TEAEs reported for fracture Healing Complications 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:

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

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

No significant impact on public health is anticipated.

Important potential risk: Infection (MedDRA SOC Infections and infestations)

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

This is considered a potential risk based on theoretical concerns which has not been substantiated in the clinical study programme or in the postmarketing experience with the reference product (Prolia RMP version 31.0).

Characterisation of the risk:

Frequency with 95% CI for Incidence per 100 PY

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	180	34	214	125
Number of Patients with TEAEs [1]	111 (46.4%)	27 (26.7%)	138 (40.6%)	77 (32.4%)
Incidence of TEAEs per 100 PYs	80.430	12295.54	95.504	59.816
95% CI for Incidence of TEAEs per 100 PYs	(69.109, 93.076)	(8515.022, 17181.791)	(83.136, 109.193)	(49.790, 71.268)

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 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	180	34	214	125
Number of Patients with TEAEs [1]	111 (46.4%)	27 (26.7%)	138 (40.6%)	77 (32.4%)
Incidence of TEAEs per 100 PYs	52.495	67.189	54.385	45.087

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	(45.106, 60.749)	(46.530, 93.890)	(47.342, 62.180)	(37.530, 53.719)

[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	180	34	214	125
Number of Patients with TEAEs [1]	111 (46.4%)	27 (26.7%)	138 (40.6%)	77 (32.4%)
95% CI for Proportion of Patients with TEAEs	(39.99, 52.99)	(18.41, 36.46)	(35.32, 46.02)	(26.45, 38.70)
Severity/Nature of risk [2]				
Missing	0	1 (1.0%)	1 (0.3%)	0
Grade 1	18 (7.5%)	2 (2.0%)	20 (5.9%)	19 (8.0%)
Grade 2	93 (38.9%)	24 (23.8%)	117 (34.4%)	57 (23.9%)
Grade 3	0	0	0	1 (0.4%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Non-serious	111 (46.4%)	27 (26.7%)	138 (40.6%)	76 (31.9%)
Serious	0	0	0	1 (0.4%)

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)	
Outcomes [4]				
Missing/Unknown	0	1 (1.0%)	1 (0.3%)	0
Recovered/Resolved	102 (42.7%)	24 (23.8%)	126 (37.1%)	70 (29.4%)
Recovered/Resolved with Sequelae	1 (0.4%)	0	1 (0.3%)	1 (0.4%)
Recovering/Resolving	2 (0.8%)	1 (1.0%)	3 (0.9%)	1 (0.4%)
Not recovered/Not resolved	6 (2.5%)	1 (1.0%)	7 (2.1%)	5 (2.1%)
Fatal	0	0	0	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 339 TEAEs in 215 patients related to infection; 180 in the CT-P41 only group, 34 in the switched from reference product group, and 125 in the reference product group. The incidence of TEAEs per 100 patient-years in CT-P41 only group was 80.430 (95% CI: 69.109, 93.076), in the switched from reference product group was 12295.54 (95% CI: 8515.022, 17181.791), and in the reference product group was 59.816 (95% CI: 49.790, 71.268).

The apparent high incidence of infection 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 the CT-P41 only group was 52.495 (95% CI: 45.106, 60.749), in the switched from reference product group was 67.189 (95% CI: 46.530, 93.890), and in the reference product group was 45.087 (95% CI: 37.530, 53.719).

Of the 215 patients, 111 patients (46.4%) in the CT-P41 only group, 27 patients (26.7%) in the switched from reference product group and 76 patients (31.9%) in the reference product group were categorised as experiencing non-serious events. One (1) patient (0.4%) in the reference product group was categorised as experiencing serious event.

Eighteen (18) patients from CT-P41 only group, two (2) patients switched from reference product group and 19 patients from reference product group reported Grade 1 events. Ninety-three (93) patients from CT-P41 only group, 24 patients switched from reference product group and 57 patients from reference product group reported Grade 2 events. One (1) patient from reference product group reported Grade 3 event. One (1) patient reported severity as missing in the switched from reference product group.

In 196 patients TEAEs related to infection were reported as "recovered", in four (4) patients they were reported as "recovering", in two (2) patients they were reported as "recovered with sequelae", in 12 patients they were reported as "not recovered" and in one (1) patient it was reported as "unknown" at the end of the trial period.

The proportion of patients with TEAEs in the CT-P41 only group was 46.4% (95% CI: 39.99, 52.99) in the switched from reference product group was 26.7% (95% CI: 18.41, 36.46), and in the reference product group was 32.4% (95% CI: 26.45, 38.70).

Risk factors and risk groups:

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

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

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

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

Potential mechanisms:

Elevated levels of osteoprotegerin 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 osteoprotegerin 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:

This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease.

Characterisation of the risk:

Frequency with 95% CI for Incidence per 100 PY

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	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)

[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 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			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	7.583	5.928	7.370	5.410
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			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%)
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

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)	
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]				
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.

Protocol Number: CT-P41 3.1

[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, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-2 inhibitors (Murphy and Dargie, 2007; Smith et al., 2004).

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of cardiovascular events has been considered in overall assessment supporting a favourable benefit-risk profile.

Public health impact:

Significant public health impact of Stoboclo on cardiovascular disease severity or incidence is not anticipated.

Important potential risk: Malignancy (MedDRA SMQ (narrow) Malignant or unspecified tumours)

Potential mechanisms:

RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumour types provide no evidence for carcinogenic risk associated with RANKL inhibition (Armstrong et al., 2008; Jones et al., 2006; Mori et al., 2007). In in vivo rodent cancer models, RANKL inhibition has been shown to have a beneficial effect (Branstetter et al., 2008; Canon et al., 2008a, 2008b; Vanderkerken et al., 2003; Yonou et al., 2003; Zhang et al., 2001).

If denosumab should affect immune function, a hypothetical association with malignancies linked to immune modulation could exist and would be expected to show the pattern of malignancy associated with immune deficiency.

Evidence source(s) and strength of evidence:

This is considered a potential risk based on theoretical concerns and has not been substantiated in the clinical study programme or in the postmarketing experience with the reference product.

Characterisation of the risk:

Frequency with 95% CI for Incidence per 100 PY

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	7	0	7	4
Number of Patients with TEAEs [1]	6 (2.5%)	0	6 (1.8%)	4 (1.7%)
Incidence of TEAEs per 100 PYs	3.128	0.000	3.124	1.914
95% CI for Incidence of TEAEs per 100 PYs	(1.258, 6.445)	(NE, 1334.023)	(1.256, 6.437)	(0.522, 4.901)

[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 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			**Denosumab Reference Product** (N=238)**
	CT-P41 only (N=239)	**Switched from Denosumab Reference Product* (N=101)**	**Total (N=340)**	
Total Number of TEAEs	7	0	7	4
Number of Patients with TEAEs [1]	6 (2.5%)	0	6 (1.8%)	4 (1.7%)
Incidence of TEAEs per 100 PYs	2.041	0.000	1.779	1.443
95% CI for Incidence of TEAEs per 100 PYs	(0.821, 4.206)	(NE, 7.290)	(0.715, 3.665)	(0.393, 3.694)

[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	7	0	7	4
Number of Patients with TEAEs [1]	6 (2.5%)	0	6 (1.8%)	4 (1.7%)
95% CI for Proportion of Patients with TEAEs	(0.93, 5.38)	(0.00, 3.59)	(0.65, 3.80)	(0.46, 4.25)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	1 (0.4%)	0	1 (0.3%)	1 (0.4%)
Grade 2	2 (0.8%)	0	2 (0.6%)	1 (0.4%)
Grade 3	2 (0.8%)	0	2 (0.6%)	2 (0.8%)
Grade 4	0	0	0	0
Grade 5	1 (0.4%)	0	1 (0.3%)	0
Seriousness [3]				
Non-serious	1 (0.4%)	0	1 (0.3%)	2 (0.8%)
Serious	5 (2.1%)	0	5 (1.5%)	2 (0.8%)
Outcomes [4]				
Missing/Unknown	0	0	0	0
Recovered/Resolved	1 (0.4%)	0	1 (0.3%)	3 (1.3%)
Recovered/Resolved with Sequelae	1 (0.4%)	0	1 (0.3%)	0
Recovering/Resolving	1 (0.4%)	0	1 (0.3%)	1 (0.4%)
Not recovered/Not resolved	2 (0.8%)	0	2 (0.6%)	0
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 11 TEAEs in 10 patients related to malignancy; seven (7) in the CT-P41 only group, none in the switched from reference product group, and four (4) in the reference product group. The incidence of TEAEs per 100 patient-years in CT-P41 only group was 3.128 (95% CI:

1.258, 6.445), in the switched from reference product group was 0.000 (95% CI: NE, 1334.023), and in the reference product group was 1.914 (95% CI: 0.522, 4.901).

Based on the duration of action of denosumab, the corrected incidence of TEAEs per 100 patient-years in CT-P41 only group was 2.041 (95% CI: 0.821, 4.206), in the switched from reference product group was 0.000 (95% CI: NE, 7.290), and in the reference product group was 1.443 (95% CI: 0.393, 3.694).

Of the 10 patients, one (1) patient (0.4%) in the CT-P41 only group, two (2) patients (0.8%) in the reference product group were categorised as experiencing non-serious events. Five (5) patients (2.1%) in the CT-P41 only group and two (2) patients (0.8%) in the reference product group were categorised as experiencing serious events.

One (1) patient from CT-P41 only group and one (1) patient from reference product group reported Grade 1 event. Two (2) patients from CT-P41 only group and one (1) patient from reference product group reported Grade 2 events. Two (2) patients each from CT-P41 only group and from reference product group reported Grade 3 events. One (1) patient from CT-P41 group reported Grade 5 event.

In four (4) patients TEAEs related to malignancy were reported as “recovered”, in two (2) patients they were reported as “recovering”, in one (1) patient it was reported as “recovered with sequelae”, in two (2) 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 2.5% (95% CI: 0.93, 5.38), in the switched from reference product group was 0 (95% CI: 0.00, 3.59), and in the reference product group was 1.7% (95% CI: 0.46, 4.25).

Risk factors and risk groups:

General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment (Anand et al., 2008; World Health Organization [WHO], 2010).

Preventability:

No specific preventive measures are known.

Impact on the risk-benefit balance of the product:

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

Public health impact:

Significant public health impact is not anticipated.

SVII.3.2. Presentation of the missing information

There is no missing information for inclusion in the list of safety concerns in the RMP.

Part II: Module SVIII - Summary of the safety concerns

Table 8: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

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):

- Hypocalcaemia
- Skin infection leading to hospitalisation and Infection
- Osteonecrosis of the jaw
- Atypical femoral fracture
- Fracture healing complications
- Malignancy
- Hypersensitivity reactions

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

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

III.3 Summary Table of additional Pharmacovigilance activities

Table 9: 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				

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
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 Stoboclo.

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

V.1. Routine Risk Minimisation Measures

Table 10: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified risk - Hypocalcaemia	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package leaflet (PL) sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for correcting of hypocalcaemia prior to initiating treatment and monitoring of calcium during the treatment 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 - Skin infection leading to hospitalisation	Routine risk communication: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine).
Important Identified risk - Osteonecrosis of the jaw	Routine risk communication: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: 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 - Hypersensitivity reactions	Routine risk communication: SmPC sections 4.3 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: *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 Identified risk - Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	Routine risk communication: SmPC sections 4.2, 4.4 and 4.8 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).
Important Potential risk - Fracture healing complications	Routine risk communication: SmPC section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine).
Important Potential risk - Infection	Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: *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 - Malignancy	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 Stoboclo injections for osteoporosis and bone loss. 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 Stoboclo 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 Periodic safety update report (PSUR) for denosumab.

V.3 Summary of risk minimisation measures

Table 11: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified risk - Hypocalcaemia	Routine risk minimisation measures: SmPC sections 4.2, 4,3, and 4.8 SmPC section 4.4, where recommendations for correcting and monitoring of calcium levels are included. PL sections 2 and 4 Legal status: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Important Identified risk - Skin infection leading to hospitalisation	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Important Identified risk - Osteonecrosis of the jaw	Routine risk minimisation measures: SmPC section 4.8 SmPC section 4.4, where maintenance of oral hygiene	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
	and regular dental management are included. PL sections 2 and 4 Legal status: Restricted medical prescription Additional risk minimisation measures: Patient reminder card	
Important Identified risk - Hypersensitivity reactions	Routine risk minimisation measures: SmPC sections 4.3 and 4.8 PL sections 2 and 4 Legal status: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Important Identified risk - Atypical femoral fracture	Routine risk minimisation measures: SmPC section 4.8 SmPC section 4.4, where recommendations for reporting potential signs and symptoms is included. PL sections 2 and 4 Legal status: Restricted medical prescription 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
Important Identified risk - Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimisation measures: SmPC section 4.2, 4.4, and 4.8 PL section 2 Legal status: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important Potential risk - Fracture healing complications	Routine risk minimisation measures: SmPC section 5.3 Legal status: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Important Potential risk - Infection	Routine risk minimisation measures: SmPC section 4.8 PL section 4 Legal status: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Important Potential risk - Cardiovascular events	Routine risk minimisation measures: Legal status: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential risk - Malignancy	Routine risk minimisation measures: Legal status: Restricted medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Stoboclo (denosumab)

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

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

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

I. The medicine and what it is used for

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

Further information about the evaluation of Stoboclo's benefits can be found in Stoboclo'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/stoboclo*.

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

Important risks of Stoboclo, together with measures to minimise such risks and the proposed studies for learning more about Stoboclo'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 minimization* measures.

In the case of Stoboclo, these measures are supplemented with *additional risk minimization 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 Stoboclo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Stoboclo 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 Stoboclo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

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

II.B Summary of important risks

Important identified risk: Hypocalcaemia	
Evidence for linking the risk to medicine	Hypocalcaemia has been identified in the clinical trial programme of the reference product. This risk was identified in randomised, double-blind, placebo- or active-controlled studies.
Risk factors and risk groups	Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, PTH resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (CrCL < 30 mL/min), dialysis, and some medications.
Risk minimisation measures	Routine risk minimisation measures:

	• *SmPC section 4.4, where recommendations for correcting of hypocalcaemia prior to initiating treatment and monitoring of calcium during the treatment is provided* • *SmPC sections 4.2, 4.3, and 4.8* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important identified risk: Skin infection leading to hospitalisation	
Evidence for linking the risk to medicine	This risk was identified in randomised, double-blind, placebo- or active-controlled studies with the reference product.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC sections 4.4, and 4.8* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important identified risk: Osteonecrosis of the jaw	
Evidence for linking the risk to medicine	This risk was identified in open-label long-term, randomised, double-blind, placebo-controlled studies with the reference product.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.4, where recommendations for dental examination prior to/during treatment, maintenance of good oral hygiene during treatment, immediate report of any oral symptoms, and management plan is provided* • *SmPC section 4.8*

	• *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: Patient reminder card
Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to medicine	This risk was identified in the postmarketing setting based on a clinically plausible association between administration of denosumab and hypersensitivity reactions with the reference product.
Risk factors and risk groups	Known hypersensitivity to denosumab and any of the excipients in the product.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC sections 4.3 and 4.8* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important identified risk: Atypical femoral fracture	
Evidence for linking the risk to medicine	This risk was identified in an open-label long-term, randomised, double-blind, active-controlled study with the reference product.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia) and with use of bisphosphonates, and proton pump inhibitors.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.4, where recommendation for repoting potential symptoms is provided* • *SmPC section 4.8* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important identified risk: Hypercalcaemia in paediatric patients receiving denosumab and after treatment	
Evidence for linking the risk to medicine	Data to evaluate this safety concern were derived from the reference product clinical trials in paediatric subjects with osteogenesis imperfecta, denosumab clinical studies, and postmarketing adverse event reporting involving paediatric

	patients receiving denosumab at unapproved doses and/or unapproved indications for use.
Risk factors and risk groups	Paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta).
Risk minimisation measures	Routine risk minimisation measures: • *SmPC sections 4.2, 4.4, and 4.8* • *PL section 2* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important potential risk: Fracture healing complications	
Evidence for linking the risk to medicine	This is a theoretical risk based on the mechanism of action of denosumab.
Risk factors and risk groups	General risk factors for fracture healing complications include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC secion 5.3* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important potential risk: Infection	
Evidence for linking the risk to medicine	This is considered a potential risk based on theoretical concerns which has not been substantiated in the clinical study programme or in the postmarketing experience with the reference product.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.8* • *PL section 4* 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	This is a theoretical risk based on epidemiological data demonstrating elevated osteoprotegerin in patients with cardiovascular disease.
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, sex, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and COX-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: Malignancy	
Evidence for linking the risk to medicine	This is considered a potential risk based on theoretical concerns and has not been substantiated in the clinical study programme or in the postmarketing experience with the reference product.
Risk factors and risk groups	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
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 Stoboclo.

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

There are no studies required for Stoboclo.

Part VII: Annexes

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Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

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Questionnaire for Infection	1.0
Questionnaire for Osteonecrosis of the jaw	1.0
Questionnaire for potential atypical fracture	1.0
Questionnaire for Fracture healing complications	1.0
Questionnaire for Malignancy	1.0
Questionnaire for Hypersensitivity	1.0

CELLTRION

DENOSUMAB Questionnaire
Hypocalcaemia

AER #

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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 _____

SIGNS AND SYMPTOMS (Check all that apply)

☐ Numbness
(Specify if involving digits and/or peri-oral region) _____

☐ Convulsions ☐ Muscle twitching

☐ Muscle cramping ☐ Paresthesia

☐ Syncope ☐ Tetany

☐ None ☐ Other _____

DIAGNOSIS (Check all that apply)

Serum calcium at time of event: _____mg/dL ☐ Unknown

Please provide serum albumin result _____
Serum albumin at the time of event < 4.0 g/dL?
☐ Yes ☐ No ☐ Unknown

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

Serum creatinine at time of event was > 2.0 X times upper limit of normal?
(Please provide result) _____ ☐ Yes ☐ No ☐ Unknown

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

TREATMENT

Treated only as an outpatient? ☐ Yes ☐ No
If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Treated in the ER? ☐ Yes ☐ No
If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Treatment inluded general hospital admission for calcium replacement?
☐ Yes ☐ No ☐ Unknown

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Treatment included ICU admission? ☐ Yes ☐ No ☐ Unknown

If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown

Overall length of hospital stay:
☐ ≤ 1 day ☐ > 1 day ☐ ≤ 7 days ☐ > 7 days

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

Anti-arrhythmic medications _____

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

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CELLTRION

DENOSUMAB Questionnaire Hypocalcaemia (continued)

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

Patient Identifier	Patient Initials	Date of This Report

RISK FACTORS (Check all that apply)

Medical History Risk Factors

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

If yes, please provide dates and details:

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

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

_____

☐ Prior hypocalcemia event (before denosumab treatment)
Please provide dates and details of prior hypocalcemia event.

_____

_____

Medication Risk Factors

Antineoplastic agents? (Check which apply): ☐ cisplatin ☐ cytosine arabinoside ☐ Other _____ ☐ None

Antimicrobials? (Check which apply): ☐ pentamidine ☐ ketoconazole ☐ Other _____ ☐ None

Concomitant Medications

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

_____

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

_____

Other concomitant medications _____

Hypocalcemic Event Resolved ☐ Yes ☐ No ☐ Unknown

If yes, what date? (DD/MM/YYYY) _____

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone: (include country code)

Signature _____

Title **Date**

Celltrion
Office Fax:

CELLTRION

DENOSUMAB Questionnaire Infection

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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 _____

SIGNS AND SYMPTOMS (Check all that apply)

☐ Fever _____ ☐ Pain _____ ☐ Discharge _____

☐ Cough _____ Location _____ Location _____

☐ Swelling _____ ☐ Rash _____ Description _____

Location _____ Location _____ ☐ Chills _____

☐ Shortness of breath ☐ Prolonged fatigue ___ ☐ Night sweats _____

_____ ☐ Diarrhea _____ ☐ Other _____

☐ Organ system affected: ☐ Musculoskeletal (including joints)
☐ Cardiac ☐ Nervous (cerebrospinal fluid)
☐ Ear/nose ☐ Skin Location_____
☐ Throat ☐ Kidney/genito-urinary
☐ Gastrointestinal ☐ Systemic (bacteremia and/or sepsis)
☐ Respiratory ☐ Other

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please attach copy of report)

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

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

CONTINUED ON NEXT PAGE (PAGE 1 OF 3)

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CELLTRION

DENOSUMAB Questionnaire Infection (continued)

AER #

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

Patient Identifier	Patient Initials	Date of This Report

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

CHECK WHICH INFECTION APPLICES

- ☐ Cardiac infections
  - ☐ Endocarditis _____
  - ☐ Pericarditis (purulent; tuberculous) _____
  - ☐ Other, please specify: _____
- ☐ Ear and labyrinth infections
  - ☐ Otitis media _____
  - ☐ Ostitis externa _____
  - ☐ Other, please specify: _____
- ☐ Gastrointestinal/abdominal infections
  - ☐ Colitis _____
  - ☐ Diverticulitis _____
  - ☐ Appendicitis _____
  - ☐ Abdominal sepsis (including peritonitis) _____
  - ☐ Hepatic abscess _____
  - ☐ Hepatitis B _____
  - ☐ Hepatitis C _____
  - ☐ Other, please specify: _____
- ☐ Musculoskeletal and connective tissue infections
  - ☐ Osteomyelitis _____
  - ☐ Septic arthritis _____
  - ☐ Other, please specify: _____
- ☐ Nervous system infections
  - ☐ Meningitis _____
  - ☐ Encephalitis _____
  - ☐ Other, please specify: _____
- ☐ Respiratory tract infections
  - ☐ Pneumonia _____
  - ☐ Pulmonary TB _____
  - ☐ Lung abscess _____
  - ☐ Legionnella pneumonia _____
  - ☐ Mycoplasma pneumonia _____
  - ☐ Other, please specify: _____
- ☐ Kidney and genito-urinary tract infections
  - ☐ Cystitis _____
  - ☐ Pyelonephritis _____
  - ☐ Urinary tract infection _____
  - ☐ Other, please specify: _____
- ☐ Systemic infections
  - ☐ Bacteremia _____
  - ☐ Sepsis _____
  - ☐ Toxic shock syndrome _____
  - ☐ Other, please specify: _____
- ☐ Wound and skin infections
  - ☐ Cellulitis _____
  - ☐ Erysipelas _____
  - ☐ Necrotizing fasciitis _____
  - ☐ Abscess _____
  - ☐ Other skin infections, please specify: _____
- ☐ Opportunistic infections
  - ☐ Aspergillus (invasive forms only) _____
  - ☐ Blastomycosis pulmonary or extra-pulmonary infections _____
  - ☐ Candidiasis systemic _____
  - ☐ Coccidioidemycosis secondary/systemic _____
  - ☐ Cryptococcal infection – pulmonary and non-pulmonary:
  - ☐ Cytomegalovirus – include systemic site _____
  - ☐ Herpes simplex (meningitis or encephalitis) _____
  - ☐ Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes) _____
  - ☐ Histoplasma infections – chronic disseminated or severe acute ___
  - ☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin _____
  - ☐ Mycobacterium tuberculosis _____
  - ☐ Non-tuberculosis mycobacterium _____
  - ☐ Noncardia infection – of brain, lungs, kidney, skin _____
  - ☐ Paracoccidioides infections of lungs, skin other _____
  - ☐ Pneumocystis carinii pneumonia _____
  - ☐ Sporotrichosis – disseminated infections _____
  - ☐ Toxoplasmosis encephalitis or disseminated _____
  - ☐ Other opportunistic infections, please specify: _____
- ☐ Other infections, please specify: _____
- ☐ Parasitic evaluation (ova, etc.): _____

CONTINUED ON NEXT PAGE (PAGE 2 OF 3)

CELLTRION

DENOSUMAB Core Questionnaire Infection (continued)

AER #

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

Patient Identifier | Patient Initials | Date of This Report

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

DIAGNOSTICS

Cultures done ☐No ☐Yes ☐Unknown

If yes, check which apply:

☐Blood culture _____
Culture positive ☐No ☐Yes ☐Unknown
If yes, which ☐Bacterial ☐Fungal ☐Viral
☐Pathogen identified: _____

☐Urine culture _____
Culture positive ☐No ☐Yes ☐Unknown
If yes, which ☐Bacterial ☐Fungal ☐Viral
☐Pathogen identified: _____

☐Sputum culture _____
Culture positive ☐No ☐Yes ☐Unknown
If yes, which ☐Bacterial ☐Fungal ☐Viral
☐Pathogen identified: _____

☐Synovial culture _____
Culture positive ☐No ☐Yes ☐Unknown
If yes, which ☐Bacterial ☐Fungal ☐Viral
☐Pathogen identified: _____

☐Cerebrospinal fluid culture
Culture positive ☐No ☐Yes ☐Unknown
If yes, which ☐Bacterial ☐Fungal ☐Viral
☐Pathogen identified: _____

☐Tissue culture _____
If yes, specify: ☐Brain ☐Lung ☐Liver ☐Kidney ☐Skin ☐Bone ☐Other
Culture positive ☐No ☐Yes ☐Unknown
If yes, which ☐Bacterial ☐Fungal ☐Viral
☐Pathogen identified: _____

☐Catheter Tip/Line _____
Culture positive ☐No ☐Yes ☐Unknown
If yes, which ☐Bacterial ☐Fungal ☐Viral
☐Pathogen identified: _____

☐PPD placement ☐No ☐Yes ☐Unknown
If yes, PPD positive ☐No ☐Yes ☐Unknown
_____
_____

☐Parasitic evaluation (ova, etc.) _____
☐X-ray ☐No ☐Yes ☐Unknown ___
☐MRI ☐No ☐Yes ☐Unknown ___
☐CT scan ☐No ☐Yes ☐Unknown
_____
☐Bone scan ☐No ☐Yes ☐Unknown
_____
☐Other _____
☐Rapid test _____
☐Serum titres _____
☐Hospital discharge report _____
_____
☐Other consult report _____
_____
☐Provide final diagnosis and treatment, if available (please specify) _____
_____
☐Outcome and resolution date _____

TREATMENT

☐ER antibiotics ☐No ☐Yes ☐Unknown
If yes, route
☐IV ☐Oral ☐SC ☐Both oral and IV

☐Required hospital admission
☐No ☐Yes ☐Unknown

☐ICU admission ☐No ☐Yes ☐Unknown
If yes, reason for ICU admission _____

Overall length of hospital stay
☐< 1 day ☐> 1 day or < 7 days ☐> 7 days
_____

☐In-hospital antibiotics
☐No ☐Yes ☐Unknown
If yes, route of administration
☐IV ☐Oral ☐Both oral and IV

☐Other in-hospital treatment
☐Antivirals ☐No ☐Yes ☐Unknown
If yes, route of administration ☐IV ☐Oral
☐Antifungals ☐No ☐Yes ☐Unknown
If yes, route of administration ☐IV ☐Oral
☐Surgery ☐No ☐Yes ☐Unknown
☐Hyperbaric oxygen ☐No ☐Yes ☐Unknown

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

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

☐Chronic lung disease _____
☐Hepatitis _____
☐Chronic kidney disease _____
☐Liver disease _____
☐Congenital infections/malformations _____
☐Osteomyelitis _____
☐HIV _____
☐Diabetes mellitus _____
☐Cancer (specify) _____
☐Recent wounds/infections _____
☐Immunosuppression _____
☐Known exposure to TNF inhibitors _____
☐Chemotherapy _____
☐Malnutrition/failure to thrive _____
☐Exposure to infectious agents _____
☐Persnoal contact _____ ☐Body fluids _____
☐Share personal items (razor, needles, etc) _____
☐Potentially contaminated food/liquied _____

Exposure to infectious agents (continued)
☐Hospital acquired
☐Other _____
☐Steroid exposure _____
☐Insect/tick bite _____
☐Drug or IV drug abuse: Type _____
Amount _____
Frequency _____
☐Alcohol/tobacco use: Type _____
Amount _____
Frequency _____
☐Indwelling catheters _____
_____
_____
☐Recent skin injury
_____
_____
☐Recent travel (specify)
_____
_____

☐Exposure to animals/zoonotic diseases (exposure to infected animal)
☐Unprotected sex _____
☐Immobility _____
☐Indwelling catheters _____
☐Nursing home resident _____
☐Occupational exposure _____
☐Ostomy _____
☐Post influenza _____
☐Surgery < 30 days _____
☐TB exposure _____
☐Other history/risk factors _____

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

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Office Fax:

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DENOSUMAB Questionnaire
Osteonecrosis of the Jaw

AER #

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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:

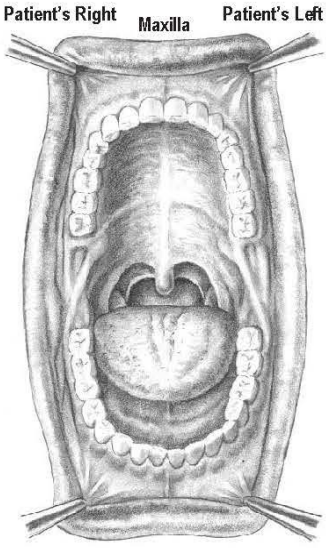
☐ No ☐ Yes ☐ Unknown

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

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CELLTRION

DENOSUMAB Questionnaire
Osteonecrosis of the jaw (continued)

AER #

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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 #

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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)

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CELLTRION

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

AER #

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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

REPORTER

Name:

Address:

City:

State/ Province:

Postal Code:

Country:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

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CELLTRION

DENOSUMAB Questionnaire
Fracture healing

AER #

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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 Event reported term

Age at time of event: _____

Study Number (If applicable)

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 diagnosis _____

☐ 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) _____ (study #) _____

Last denosumab dose before event (date) _____

Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown

If yes, please specify _____

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

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

DIAGNOSIS (Check all that apply, please indicate dates as DD/MM/YYYY)

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

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

Specify location (check all that apply):

☐ Cervical spine ☐ Radius

☐ Clavicle ☐ Rib

☐ Hand/metacarpal/phalange ☐ Scapula

☐ Head/face/skull ☐ Shoulder

☐ Humerus ☐ Sternum

☐ Olecranon ☐ Ulna

☐ Wrist/carpal

☐ Other _____

_____

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

Specify location (check all that apply):

☐ Ankle ☐ Hip

☐ Femur (please specify location: ☐ Patella

neck, subtrochanteric, mid shaft, etc) ☐ Pelvis

_____ ☐ Tibia

_____ ☐ Fibula

☐ Foot/tarsal/metatarsal/phalange

☐ Other _____

_____

_____

Type of trauma reported at time of fracture (check one):

☐ Severe trauma (e.g., falling from roof, motor vehicle accident)

☐ Minimal trauma (e.g., falling from standing position or less)

☐ Non-traumatic

Characteristics of fracture (check all that apply):

☐ Comminuted ☐ Poor immobilization of segments

☐ Compound ☐ Soft tissue injury

☐ Pathologic ☐ Unknown

☐ Poor alignment

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CELLTRION

DENOSUMAB Questionnaire
Fracture healing (continued)

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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 (check all that apply):

☐ Casting _____ ☐ Surgery _____

☐ Non-surgical reduction _____ ☐ Traction _____

☐ Revision surgery (2nd surgery) _____ ☐ Other _____

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

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

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

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

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

MEDICAL HISTORY/RISK FACTORS (Check all that apply, provide dates and attach relevant reports)

☐ Current smoker/tobacco use _____

☐ History or current corticosteroid use _____

☐ Prior fracture history _____

☐ Diabetes _____

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Office Fax:

REPORTER

Name:

Address: State/ Province:

City: Postal Code:

Country:

Email:

Phone: (include country code)

Signature _____

Title _____ **Date** _____

DENOSUMAB Questionnaire for Malignancy

Office Patient Identifier _____Patient Initials _____Celltrion AER No. _____

Questionnaire for Malignancy Adverse Events

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

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

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

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

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

Tumor stage, if known: _____

Primary site of malignancy: _____

Tumor Stage:

Tumor Size (Check which one applies):

TX ☐ T0 ☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐

Tumor Grade (Check which one applies):

GX ☐ G1 ☐ G2 ☐ G3 ☐

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

(If yes, skip next 2 questions)

Lymph Node Involvement (Check which one applies):

NX ☐ N1 ☐ N2 ☐ N3 ☐

Metastases (Check which one applies):

MX ☐ M0 ☐ M1 ☐

CONTINUED ON NEXT PAGE (PAGE 1 OF 2)

CELLTRION DENOSUMAB Questionnaire for Malignancy

TREATMENT:

Hospitalized? Yes ☐ No ☐ Unknown ☐

ICU admission? Yes ☐ No ☐ Unknown ☐

Overall length of hospital stay: ≤ 1 day ☐ > 1 day or ≤ 7 days ☐ > 7 days ☐

Surgical treatment? Yes ☐ No ☐ Unknown ☐

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

Hormonal treatment? Yes ☐ No ☐ Unknown ☐

Radiation treatment? Yes ☐ No ☐ Unknown ☐

Bone marrow transplant? Yes ☐ No ☐ Unknown ☐

If yes, autologous ☐ heterologous ☐

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

RISK FACTORS (Check all that apply):

Smoking ☐

Prior Malignancy ☐

Positive Family History (Check all that apply):

Same cancer ☐

Different cancer ☐

Prior therapeutic radiation exposure ☐

Environmental exposure ☐

Specify: _____

CELLTRION

DENOSUMAB Questionnaire Hypersensitivity

AER #

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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 Event reported term

Age at time of event: _____

Study Number (If applicable)

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)_____(study #)_____
Last denosumab dose before event (date) _____
☐ Doses of denosumab were skipped ☐ Yes ☐ No ☐ Unknown
If yes, please specify _____
☐ Doses of denosumab given after event began ☐ Yes ☐ No ☐ Unknown
If yes, date of first dose following start of event

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

SIGNS AND SYMPTOMS (Check all that apply)

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

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please indicate and attach copy of report if available)

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N
Results at BASELINE (prior to Celltrion drug)					
CBC with Differential					
WBC					
RBC					
Eosinophils					
Hgb					
Hct					
Platelets					
Other					
Albumin					
Total Protein					
BUN					
Serum Creatinine					
ALT					
AST					
ALP					
Billirubin					
Calcium					
K+					
Na+					
Phosphorus					
Mg++					
Cl-					
CrCl					

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached Y	Report Attached N
Results at BASELINE (prior to Celltrion drug)					
CBC with Differential					
WBC					
RBC					
Eosinophils					
Hgb					
Hct					
Platelets					
Other					
Albumin					
Total Protein					
BUN					
Serum Creatinine					
ALT					
AST					
ALP					
Billirubin					
Calcium					
K+					
Na+					
Phosphorus					
Mg++					
Cl-					
CrCl					

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CELLTRION

DENOSUMAB Questionnaire Hypersensitivity (continued)

AER #

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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)

☐ ER corticosteroids

Route: ☐ IV ☐ Oral

☐ ER anti-histaminics

Route: ☐ IV only ☐ Oral only ☐ Both oral and IV

☐ Required hospital admission ☐ Yes ☐ No

Overall length of hospital stay

☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐ ICU admission ☐ Yes ☐ No ☐ Unknown

Overall length of hospital stay

☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days

☐ In-hospital corticosteroids

Route: ☐ IV only ☐ Oral only ☐ Both oral and IV

☐ In-hospital anti-histaminics

Route: ☐ IV only ☐ Oral only ☐ Both oral and IV

☐ Other in-hospital treatment

☐ IV vasopressors ☐ Yes ☐ No ☐ Unknown

☐ Intubation/mechanical ventilation ☐ Yes ☐ No ☐ Unknown

CONCOMITANT MEDICATIONS

☐ ACE inhibitors
☐ Allopurinol
☐ Cancer chemotherapy
☐ Dapsone
☐ IV contrast
☐ NSAIDs/aspirin
☐ Penicillamine
☐ Rifampin

☐ Anticonvulsants (check which apply):

- ☐ Phenytoin
- ☐ Carbamazepine
- ☐ Phenobarbital

☐ Antibiotics (check which apply):

- ☐ Beta-lactams including penicillin and cephalosporin
- ☐ Macrolides
- ☐ Sulfonamides
- ☐ Quinolones

☐ Hypersensitivity event resolved ☐ Yes ☐ No ☐ Unknown

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

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

☐ Hospital admissions/discharge report (please attach if available)

_____

_____

_____

_____

_____

_____

_____

_____

☐ Other consult report (please indicate any attachments) _____

_____

_____

_____

REPORTER Name:

Address:

City: State/ Province:

Country: Postal Code:

Email:

Phone: (include country code)

Signature_____

Title_____ **Date** _____

Celltrion
Office Fax:

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

Draft key messages of the additional risk minimisation measures for Stoboclo

Patient reminder card:

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) will be distributed to healthcare professionals of Stoboclo 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 (Stoboclo) injections for osteonecrosis and bone loss, including:

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