EU Risk Management Plan
For

Eladynos 80 micrograms/dose solution for injection in pre-filled pen

(abaloparatide)

RMP version to be assessed as part of this application:

RMP Version number: 0.5

Data lock point for this RMP: 27 April 2022 (As of last Periodic Benefit-Risk Evaluation Report (PBRER) with DLP of 27 April 2022).

Date of final sign-off: 15 December 2022

Rationale for submitting an updated RMP: Not applicable due to this is an initial marketing authorisation application submission.

Summary of significant changes in this RMP: Not applicable.

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP: Not applicable.

QPPV name: Dilyana Karaivanova, MD

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

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List of Abbreviations

Abaloparatide-SC	Abaloparatide subcutaneous
ABL	Abaloparatide
ADR	Adverse Drug Reaction
AE	Adverse Event
ALN	Alendronate
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
AVA	Anabolic Versus Antiresorptive
BMD	Bone Mineral Density
BPM	Beats Per Minute
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CrCl	Creatine Clearance
CT	Computed Tomography
CTX	C-terminal telopeptide
CV	Cardiovascular
CVA	Cerebrovascular Accident
DILI	Drug-Induced Liver Injury
DLP	Data Lock Point
EEA	European Economic Area
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERK	Extracellular Signal-Related Kinase
EU	European Union
FAERS	FDA Adverse Event Reporting System
GePaRD	German Pharmacoepidemiological Research Database
HCP	Health Care Professional
hERG	Human Ether-a-go-go-Related Gene
HF	Heart Failure
HR	Hazard Ratio

IOF	International Osteoporosis Foundation
IR	Incidence Rate
IV	Intravenous
lyo	Lyophilisate
MAA	Marketing Authorisation Application
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MTD	Maximum Tolerated Dose
NHANES	National Health and Nutrition Examination Survey
OP	Osteoporosis
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PINP	Procollagen Type 1 N Terminal Propeptide
PK	Pharmacokinetics
PKA	Protein Kinase A
PKC	Protein Kinase C
PL	Package Leaflet
PMWO	Postmenopausal Women With Osteoporosis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTH(1-34)	Parathyroid Hormone
PTH(1-84)	Parathyroid Hormone (intact)
PTHR1	Parathyroid Hormone Receptor 1
PTHrP	Parathyroid Hormone Related Peptide
QALY	Quality of Life Years
QD	Daily
QTcI	Individual-Specific QT Interval Correction
RMP	Risk Management Plan
SAD	Single Ascending Dose
SC	Subcutaneous
SCCS	Self-Controlled Case Series

SCOPE	Scorecard For Osteoporosis In Europe
SD	Standard Deviation
SIR	Standardized Incidence Ratio
SmPC	Summary of Product Characteristics
SNDS	Système National Des Données de Santé
SOC	System Organ Class
TD	Transdermal
TIA	Transient ischaemic attack
UK	United Kingdom
US	United States
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Abaloparatide
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group:** Calcium homeostasis, Parathyroid hormones and analogues Anatomical Therapeutic Chemical (ATC) code: HO5AA04
Marketing Authorisation Applicant	Radius Health (Ireland) Ltd.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Eladynos 80 micrograms/dose solution for injection in pre-filled pen.
Marketing authorisation procedure	Centralised procedure (H0005928)
Brief description of the product	**Chemical class** Abaloparatide is a 34 amino acid peptide.
	Summary of mode of action Abaloparatide shares 41% homology to parathyroid hormone [PTH(1-34)] and 76% homology to parathyroid hormone related peptide [PTHrP](1-34)], and is an activator of the PTH1 receptor signalling pathway. Abaloparatide stimulates new bone formation on trabecular and cortical bone surfaces by stimulation of osteoblastic activity. Abaloparatide causes transient and limited increases in bone resorption and increases bone density
	Important information about its composition None.
Hyperlink to the Product Information	
Indication(s) in the EEA	**Current:** Treatment of osteoporosis in postmenopausal women at increased risk of fracture.
	Proposed: Not applicable.

Dosage in the EEA	**Current:** The recommended dose is 80 micrograms once daily. The route of administration is subcutaneous injection in the lower abdomen.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	**Current (if applicable):** Solution for injection in pre-filled pen Each dose (40 microliters) contains 80 micrograms of abaloparatide. Each pre-filled pen contains 3 mg of abaloparatide in 1.5 mL of solution (corresponding to 2 milligrams per mL).
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

Part II: Safety specification

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

Indication

Eladynos 80 micrograms/dose solution for injection in pre-filled pen is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. (Hereinafter Eladynos will be referred to as abaloparatide)

The indication targets a subpopulation of patients with osteoporosis i.e., postmenopausal women with osteoporosis at increased risk of fracture.

Guidelines are being developed by the National Osteoporosis Foundation to address the diagnosis and management of osteoporosis. A detailed history and physical examination together with bone mineral density (BMD) assessment, vertebral imaging to diagnose vertebral fractures, and, when appropriate, the World Health Organization (WHO) 10-year estimated fracture probability (FRAX®) are utilized to establish the individual patient's fracture risk (LeBoff, 2022).

The information on epidemiology summarised in this section has been limited to data for the subjects with osteoporosis over 50 years of age for the following reasons:

- The epidemiological data on osteoporosis in the literature are generally presented by age and gender. The target population corresponds to women with osteoporosis approximately 50 years of age and over; the median menopausal age in Europe is 54 years (Dratva, 2009).
- Osteoporosis is a disease most common in the elderly population (Hernlund, 2013). Very few fragility fractures occur before the age of 50 years, and the incidence of these fractures increases progressively with age after 50 years.

Incidence:

Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (Rizzoli, 2001; WHO, 2007; LeBoff, 2022). This disease is characterised by low BMD and fractures. The fractures associated with the greatest morbidity and mortality, as well as economic burden to society, together make up the clinically significant and medically relevant group of fractures termed major osteoporotic fractures.

Worldwide, the incidence of osteoporosis is difficult to accurately determine because of variations of definition and diagnosis. The most useful way of comparing osteoporosis prevalence between populations is to use fracture rates in older people.

In Europe, 22 million women and 5.5 million men were estimated to have osteoporosis in 2010; and 3.5 million new osteoporotic fractures were sustained, comprising 520,000 vertebral, 620,000 hip, 560,000 forearm and 1,800,000 fractures at other sites. This equates to 400 fractures per hour, which places a large burden on the health care system. The economic burden of incident and prior fragility fractures was estimated at € 37 billion, with the greatest burden associated with major osteoporotic fractures, and an overall average cost of about € 11,000 per fracture. In 2010, European women experienced 2,300,000 fractures (263 fractures per hour), 14% of which were vertebral and 86% of which were nonvertebral, with a burden of over € 24 billion (Hernlund, 2013; Svedbom, 2013).

Due in part to an aging population, total fragility fractures in the 5 largest EU countries plus Sweden are estimated to increase from 2.7 million in 2017 to 3.3 million in 2030, representing a 23% increase. The resulting annual fracture-related costs (€37.5 billion in 2017) are expected to increase by 27% (Borgstrom, 2020).

Prevalence:

Data from the scorecard for osteoporosis in Europe (SCOPE), a project of the International Osteoporosis Foundation (IOF) that seeks to raise awareness of osteoporosis care in Europe, represented the prevalence of osteoporosis resulting fractures for each of the 27 countries of EU plus the United Kingdom (UK) and Switzerland (termed EU27+2) which was calculated from the age and gender-specific BMD in the National Health and Nutrition Examination Survey (NHANES) III study, presented in Hernlund et al 2013 and applied to the current population estimates for people ages >50 (Kanis, 2021).

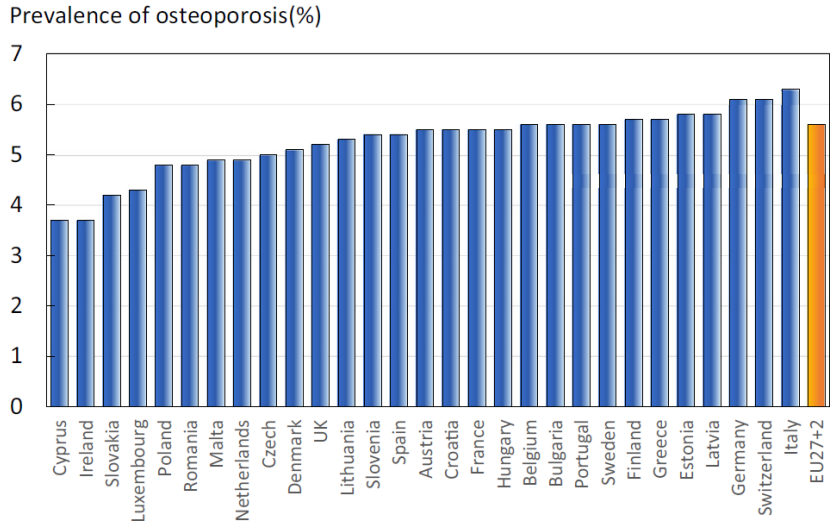
In 2019, there were approximately 32.0 million individuals with osteoporosis in the EU27+2, of which 6.5 million were men and 25.5 million were women, i.e. there were about four times as many women with osteoporosis as there were men. Of all member states, Germany was estimated to have the highest number of individuals with osteoporosis with approximately 1.2 million men, and 4.5 million women with osteoporosis. According to estimates from Hernlund et al 2013, the prevalence of osteoporosis in the EU27 was 6.6% and 22.1%, respectively in men and women aged 50 years or more (Table 1). In men over the age of 50 years, the prevalence of osteoporosis varied from 5.7% (Slovakia) to 6.9% (Sweden). In women, the prevalence ranged from 19.3% (Cyprus) to 23.4% (Italy) (Kanis, 2021).

The prevalence of osteoporosis in the entire EU27+2 population (i.e. all ages) was 5.6% and ranged from 3.7% in Cyprus and Ireland, to 6.3% in Italy (Figure 1) (Kanis, 2021).

Table 1. Estimated number and prevalence of men and women with osteoporosis in 2019

Country	Men with osteoporosis	Women with osteoporosis	Men and women with osteoporosis	Prevalence in male population aged 50+ (%)	Prevalence in female population aged 50+ (%)	Prevalence in total population (%)
Austria	113,230	438,894	552,124	6.5	22.2	5.5
Belgium	142,428	538,944	681,372	6.6	22.4	5.6
Bulgaria	82,432	337,744	420,176	6.4	20.9	5.6
Croatia	48,050	204,248	252,298	6.2	21.1	5.5
Cyprus	11,346	38,986	50,332	6.2	19.3	3.7
Czech Republic	114,600	457,776	572,376	6.0	20.4	5.0
Denmark	72,670	254,888	327,558	6.5	21.1	5.1
Estonia	13,082	68,820	81,902	6.2	22.2	5.8
Finland	69,376	266,815	336,191	6.4	21.5	5.7
France	802,660	3,188,700	3,991,360	6.7	22.5	5.5
Germany	1,159,884	4,499,208	5,659,092	6.6	22.6	6.1
Greece	143,796	539,883	683,679	6.9	22.3	5.7
Hungary	99,758	459,347	559,105	6.2	21.1	5.5
Ireland	47,120	162,200	209,320	6.2	20.0	3.7
Italy	878,922	3,479,814	4,358,736	6.9	23.4	6.3
Latvia	18,849	105,925	124,774	6.1	22.3	5.8
Lithuania	28,487	152,117	180,604	6.1	21.7	5.3
Luxembourg	6,466	23,100	29,566	6.1	21.0	4.3
Malta	5,015	18,216	23,232	5.9	19.8	4.9
Netherlands	215,901	760,240	976,141	6.3	20.8	4.9
Poland	367,430	1,617,246	1,984,676	5.8	20.1	4.8
Portugal	133,263	547,360	680,623	6.7	22.0	5.6
Romania	207,390	863,870	1,071,260	6.2	20.5	4.8
Slovakia	50,160	213,788	263,948	5.7	19.4	4.2
Slovenia	24,720	100,190	124,910	6.0	21.5	5.4
Spain	612,272	2,332,998	2,945,270	6.8	22.6	5.4
Sweden	130,755	452,480	583,235	6.9	22.4	5.6
Switzerland	111,210	412,450	523,660	6.6	22.6	6.1
UK	821,152	2,953,653	3,774,805	6.7	21.9	5.2
EU27+2	6,532,426	25,511,028	32,043,453	6.6	22.1	5.6

Figure 1. The prevalence of osteoporosis (%) by country, and the average prevalence in the EU27+2.



Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin- and risk factors for the disease:

The vast majority of osteoporotic fractures occur in postmenopausal women and the incidence increases markedly with age. Most fractures occur at the spine, wrist and hip. Fractures are associated with substantial pain and suffering, disability and even death (Reginster, 2006).Fifty percent of women and 20% of men will experience an osteoporotic fracture during their lifetime, highlighting the need for therapies to build bone and rapidly prevent fractures during treatment (Office of the Surgeon General (US), 2004).

Fracture incidence varies widely by geography, ethnicity and socioeconomic status (Hernlund, 2013; Svedbom, 2013; Kanis, 2019). A 3-fold difference in the incidence of vertebral fracture between European countries was demonstrated, with Scandinavian countries having the highest rates (O'Neill, 1996), and an approximately 11-fold variation was demonstrated within Europe for hip fractures, which could not be accounted for by differences in activity levels, smoking, obesity, alcohol consumption or migration status (Elffors, 1994). The explanation for global variation in fracture incidence is likely multifaceted, with ethnic differences in BMD, bone geometry and bone microarchitecture thought to contribute to these differences (Curtis, 2016). If this fracture burden is translated into Quality of Life Years (QALY), the total QALYs lost due to fracture was 1,180,000 during 2010 in the EU (Hernlund, 2013; Svedbom, 2013; Kanis, 2019). An estimated 1.0 million QALYs were lost in 2017 due to fragility fractures in 6 European countries (Borgstrom, 2020). The total value of QALYs lost is 60.4 billion Euros. This is twice the domestic product/capita. In addition, with the aging population, it is estimated that by 2025 in Europe, there will be a 23% increase in the diagnosis of osteoporosis in men and women and that the economic burden will increase by 25% (Hernlund, 2013; Svedbom, 2013; Kanis, 2019).

Risk factors for the disease

Advancing age, female sex, White or Asian race, low body weight/body mass index, family history of osteoporotic fractures, early menopause, sedentary lifestyle, excessive alcohol, caffeine, and tobacco use, low calcium and/or vitamin D intake and, inadequate sun exposure, stress, air pollution, secondary causes (e.g. chronic use of certain medication, such as prolonged corticosteroids; hypogonadism; hyperparathyroidism, chronic liver disease; renal disease; cardiovascular disease; diabetes; dementia; inflammatory diseases such as rheumatoid arthritis) are risk factors for osteoporosis (Barrett-Connor, 2008; Pouresmaeili, 2018).

Osteoporosis represents a major public health problem because of its association with low-energy trauma or fragility fractures. Osteoporotic fractures affect up to one-half of women and one-third of men over age fifty, and are often associated with low bone density (Jones, 1994; Ross, 1996; Cummings, 2002).

Major osteoporotic fractures (those of the wrist, shoulder, hip and clinical spine) account for 94% of the fracture risk for women with low or minimal trauma (Ensrud, 2008). The lifetime risk for osteoporosis-related hip, spine or wrist fracture in European women is 23%, 29% and 21%, respectively. In European men, the risk is 11%, 14%, and 5%, respectively (Clynes, 2020).

Women with 1, 2, or 3 prior fractures have 2-, 3-, and 5-fold more risk to have any subsequent incident fracture (Barrett- Connor, 2008; Gehlbach, 2012; Giangregorio, 2010; Hodsman, 2008).

Major osteoporotic fractures contribute to accumulated frailty such that the Frailty Index is significantly larger in those elderly women who have experienced a major osteoporotic fracture. As a result, these women have worsening frailty and greater morbidity after a major osteoporotic fracture (Li, 2016). The Frailty Index was associated with a predicted increase in the risk of falls, fractures, death and overnight hospitalisations (Li, 2014). Consequently, prevention of clinically significant and medically relevant major osteoporotic fractures will reduce health care costs and benefit postmenopausal women due to reduced frailty, reduced risk of falls, fractures, hospitalisations, and death.

Suffering from a major osteoporotic fracture substantially increases the risk of subsequent fractures (Centre for Metabolic Bone Diseases; Burshell, 2010; Clynes, 2020), and this risk is highest in the first few years after a fracture. There is strong evidence showing that after hospital discharge, osteoporotic fracture patients are faced with higher morbidity, subsequent fractures, and increased mortality (Nazrun, 2014).

The main existing treatment options:

Available therapies in the European Union for osteoporosis can be considered in two broad classes, the antiresorptives (dominated by bisphosphonates and denosumab) and those with anabolic activity (currently limited to teriparatide and romosozumab in the EU). Most antiresorptive products provide only a moderate rate of increase in BMD and take a number of years to reach their fracture reduction benefit.

Given that abaloparatide is an anabolic, the approved anabolics teriparatide and romosozumab, are discussed below as treatment options.

Teriparatide - rhPTH(1-34) – is more closely related to abaloparatide, and among its European Medicines Agency (EMA)-approved indications is the treatment of osteoporosis in postmenopausal women (and men) at increased risk of fracture. This approval was based on a significant reduction in the incidence of vertebral and nonvertebral fractures. As outlined in the Summary of Product Characteristics (SmPC), the clinical evidence in post-menopausal women is comprised of one large scale (n=1637) Phase 3 study in which up to 24 months (median: 19 months) of treatment with teriparatide was shown to demonstrate statistically significant fracture reduction (Forsteo SmPC, 2022).

Published clinical data supporting teriparatide's anabolic effects include elevated serum levels of the bone formation marker procollagen type 1 N terminal propeptide (PINP) in the Anabolic Versus Antiresorptive (AVA) study in subjects receiving teriparatide 20 µg daily (Dempster, 2016). Teriparatide treatment was also associated with increased serum levels of the bone resorption marker C-terminal telopeptide (CTX). CTX levels progressively increased starting at month 3 of treatment, whereas PINP levels increased starting at 1 month and showed greater percent increases relative to CTX. These results are consistent with the interpretation of a "net anabolic effect" of teriparatide.

In the AVA study, using quadruple fluorochrome labelling to identify newly-formed bone by histomorphometry, teriparatide increased from baseline all modes of bone formation (modelling, remodelling, and overflow modelling bone formation) on cancellous and endocortical bone surfaces of iliac crest bone biopsies, and increased modelling-based bone formation was seen on the periosteum (Dempster, 2018).

Being the closest comparator to abaloparatide, teriparatide 20 µg was used as the active comparator in the pivotal study supporting this application (Study BA058-05-003 - ACTIVE). The ACTIVE study included more subjects on teriparatide 20 µg than any trial conducted before or since.

Romosozumab is a monoclonal antibody that acts by inhibiting sclerostin and was approved in 2019 for treatment of osteoporosis in postmenopausal women at high risk of fracture. Non-clinical and clinical studies have demonstrated a mixed anabolic/antiresorptive effect on bone. Romosozumab was approved on the basis of two pivotal randomised controlled studies in two overlapping but distinct populations based on different levels of fracture risk. In the active comparator-controlled ARCH study (Saag, 2017), romosozumab demonstrated statistically significant improvements in fracture rate at 12 months compared to alendronate, including improvement in the rate of nonvertebral fracture. However, in the placebo-controlled FRAME study Cosman, 2016), while romosozumab significantly reduced the overall fracture rate, the rate of improvement of nonvertebral fractures was not statistically significant.

Clinical data supporting anabolic effects of romosozumab include a rapid increase in bone formation demonstrated by serum PINP levels that peak at month 1. However, serum PINP then declined to baseline levels by month 6 and further declined to below baseline by month 12 in both the FRAME and ARCH studies. Romosozumab also suppressed bone resorption, as evidenced by ~50% reductions from baseline in serum CTX levels by month 1 and continued CTX suppression through month 12.

In one of the pivotal randomised controlled trials, an increase in serious cardiovascular events (myocardial infarction and stroke) was observed in romosozumab treated subjects compared to controls and, as a result, romosozumab is contraindicated in subjects with previous myocardial infarction or stroke (Evenity SmPC, 2021).

Despite availability of several approved therapies that reduce the risk of fractures, only a minority of individuals with osteoporosis receive treatment, and therefore the personal and societal burden of fragility fractures remains high. There is a clear need for additional osteoporosis therapies, driven by the limited effectiveness of current treatments on hip and nonvertebral fractures, and by the perceived impact of rare side effects that limit the willingness of many patients to use or physicians to prescribe some therapies (Clynes, 2020). There is a particular need for new osteoporosis medications with improved safety profiles, greater efficacy, and/or better convenience to increase patient and clinician choice and acceptability, thereby maximizing benefits for subjects, reducing morbidity, improving quality of life, and minimizing costs and risks.

Regarding concomitant medication, intakes of at least 1,000 mg/day of calcium, 800 IU of vitamin D and of 1 g/kg body weight of protein can be recommended in the general management of patients with osteoporosis according to the European guidance for the diagnosis and management of osteoporosis in postmenopausal women (Kanis, 2013).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In 2010 in the EU 27, the number of deaths causally related to fractures was estimated at 43,000 (Hernlund, 2013). In women: approximately 50% of fracture related deaths were due to hip fractures, 28% to clinical vertebral and 22% to other fractures.

A systematic review of the literature showed that hip fracture is associated with excess mortality (over and above mortality rates in non-hip fracture/community control populations) during the first year after fracture, ranging from 8.4% to 36% (Abrahamsen, 2009).

Osteoporosis represents a major public health problem because of its association with low-energy trauma or fragility fractures. Fragility fractures affect up to one-half of women and one-third of men over age fifty, and are often associated with low bone density (Cummings, 2002; Jones, 1994; Kanis, 2000; Nguyen, 1996; Riggs, 1995; Ross, 1996). Such fractures occur most commonly in the hip, spine, and wrist (Kanis, 1994; Svedbom, 2013).Clinical trials have demonstrated that treatment of patients with fragility fractures can reduce the risk of future fractures by up to 50% (Delmas, 2002; Hochberg, 2000). Thus, it is important that these patients not only receive treatment for the presenting fracture, but also for prevention of future fractures (Rosier, 2001; Tosi, 1998). Spine related fractures of this type have also been associated with poor outcomes and high mortality rates (Suzuki, 2008). Once a patient has sustained a vertebral fracture, the subsequent risk of any fracture increases 200% and the risk of a subsequent hip fracture increases 300% (Black, 1999). Almost half of the patients with a prior vertebral fracture will experience additional vertebral fractures within three years, many within the first year (Lindsay, 2001; Robinson, 2002). Those patients who sustain a vertebral body fragility fracture show a prolonged course that can lead to significant disability even one year later (Suzuki, 2008). Patients who have had any one fracture have an 86% increase in their risk for another fracture (Kanis, 2004). With the severity of these implications, prevention of a secondary fracture has become a primary focus from a patient care and societal standpoint.

Important co-morbidities:

Osteoporosis in postmenopausal women is associated with numerous co-morbidities. This is due to the fact that osteoporosis occurs in an older population. A high percentage of women with an osteoporosis diagnosis presents at least one other chronic disease (Nuno-Solinis, 2014). The most common health issues confronting women aged >50 years can be considered to be cardiovascular disease (coronary heart disease; cerebrovascular disease), cancer (breast; cervical; lung; colorectal), diabetes mellitus, neuropsychiatric conditions (dementia; Alzheimer's disease; depression), respiratory disorders, and musculoskeletal disorders (rheumatoid arthritis; osteoporosis and osteoporotic fracture). Precise EU data on the incidence, prevalence and mortality of co-morbid disease in postmenopausal women with osteoporosis are not available. However, these co-morbidities are mainly associated with the age and gender of the target population (postmenopausal women with osteoporosis) rather that the disease itself. Although certain co-morbidities (diabetes, renal failure, chronic inflammatory disease, and breast cancer treated with chemotherapy or hormone therapy) may adversely impact the severity of osteoporosis (David, 2010), there is little evidence for the converse (i.e., osteoporosis impacting other co-morbidities). Apart from the increased risk of fractures in postmenopausal women with osteoporosis, no other co-morbid conditions were identified for which the incidence is increased compared with the incidence in the general population of the same age and sex as a result of the disease.

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

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

Toxicity

- Key issues identified from acute or repeat-dose toxicity studies

The main toxicological findings observed during the non-clinical toxicology studies in rats and monkeys with supraphysiological doses of abaloparatide included haematological changes, transient increased serum calcium levels, and mineralisation of organs, including the kidney, heart and lungs.

Related to the pharmacology of abaloparatide, almost all rats and monkeys demonstrated clear signs of increased bone formation, increased trabecular number and thickness, and decreased bone marrow spaces. The subsequent reduction in bone marrow haematopoiesis resulted in effects on haematology in both species that were generally mild and included both anaemia and thrombocytopenia and signs of extramedullary haematopoiesis.

Another pharmacological effect of abaloparatide consisted of transient increased serum calcium levels in rats and monkeys 3 hours after treatment, returning to baseline levels by 24 hours. This effect was accompanied by increased urinary calcium excretion, a normal compensatory response to transiently increased blood calcium, and with an increased urinary phosphorus excretion.

Mineralisation of organs was observed in rats after 26 weeks treatment at ≥10 µg/kg/day in kidneys, and at longer treatment times (2-year carcinogenicity study) in the major arteries at doses ≥10 µg/kg/day. Tissue mineralisation occurred in monkeys at ≥10 µg/kg/day after 39 weeks, and at 200 µg/kg/day after 13 weeks in kidneys, heart, lungs, and urinary bladder muscle. In a longer, 16-month, study in aged ovariectomized monkeys at 5 µg/kg/day no increase in kidney mineralisation compared to vehicle controls was observed.

Immunogenicity was determined in rats and monkey and was generally low with ≤10% treated rats confirmed positive to anti-abaloparatide antibodies after ≥26 weeks at 1 to 50 µg/kg and for up to 2 years, and 11% monkeys treated with a dose of 70/50 µg/kg/day elicited antibodies after 39 weeks of treatment.

Relevance to human usage:

- Haematology

The haematological results suggest the effects on haematology parameters were secondary to primary effects of abaloparatide on bone formation, with obliteration of the marrow space. To date no abnormalities in haematology laboratory results have been observed for abaloparatide.

- Nephrotoxicity

In view of the potential risk of mineralisation to the kidney, renal computed tomography (CT) scan measurements were performed during the Phase 3 study BA058-05-003 conducted in a subset of subjects receiving abaloparatide for 18 months. Results from the renal CT scans to assess kidney calcification indicated there was no firm evidence of a trend of increased nephrolithiasis or nephrocalcinosis mineralisation or soft tissue calcification in the abaloparatide treated subjects as compared to placebo.

The analysis of data from the pivotal abaloparatide-SC study (BA058-05-003) and recently completed clinical study in men (BA058-05-019[1]) and transdermal-abaloparatide formulation (BA058-05-021[1]), concluded that although treatment with abaloparatide can cause hypercalcemia and hypercalciuria which can contribute to the development of nephrolithiasis, there were no safety signals regarding other organ calcification-related events. During study BA058-05-019, which investigated the use of abaloparatide in men, nephrolithiasis was observed in 2.0% (n = 3) abaloparatide-treated and 1.3% (n = 1) placebo-treated subjects; however, all four events were considered unrelated to study drug. Severity was assessed as mild (n = 3) or moderate (n = 1) and no action was taken with study drug for any of these events. The outcome was reported as resolved for only two events. During study BA058-05-021, nephrolithiasis was observed in 1.2% (n = 3) abaloparatide-SC-treated and 0.8% (n = 2) abaloparatide-transdermal-treated subjects. Severity was assessed as mild (n= 4) or moderate (n = 1) and no action was taken with study drug for any of these events. One event was deemed probably related; two were possibly related and one each was unlikely or not related to study drug. One event resolved, while the remaining 4 events were not resolved.

In addition, a cumulative review of post-marketing data from the United States (US), which included literature and disproportionality analyses, concurred with the findings observed during the abaloparatide clinical development program. 64 cases of nephrolithiasis (33 serious, 31 non-serious) have been observed in the US post-marketing experience since its launch in 2017, but only 4 cases (1 serious, 3 non-serious) were Health Care Professional (HCP) confirmed. Eleven patients reported a history of kidney stones. In general, many factors play a role in the development of organ calcification that includes hypercalcaemia, trauma, infections, aging, inflammation, autoimmune/connective tissue disorders and malignancies. Most cases from either the clinical or US post-marketing experience reported confounders other than hypercalcaemia. In conclusion, the review of nonclinical, clinical and post-marketing surveillance data from the US does not show an association of organ calcification-related events with the use of abaloparatide except for nephrolithiasis.

Since abaloparatide can cause hypercalcemia and hypercalciuria which can contribute to the development of nephrolithiasis, all three events (hypercalcaemia, hypercalciuria and nephrolithiasis) are considered Adverse Drug Reactions (ADRs) with abaloparatide therapy and have been adequately represented in the SmPC.

- Immunogenicity

In study BA058-05-003, 42.9% of patients completing 18 months of therapy developed anti-abaloparatide antibodies and 28.5% developed in vitro neutralizing antibodies. Although there appeared to be differences in exposure (increased clearance) for antibody positive patients, this is thought to be due to interference with the bioanalytical pharmacokinetics (PK) method. Compared to antibody negative patients, no clinically relevant differences in safety or efficacy (in terms of increase of BMD and reduction of fractures) were observed for patients who were antibody positive or who were positive for in-vitro neutralizing antibodies.

- Hepatotoxicity

Repeat-dose toxicity studies in rats and monkeys up to 26 weeks and 39 weeks, respectively, have not demonstrated any evidence of liver toxicity. The observed extramedullary haematopoiesis in rats is secondary to the exaggerated pharmacological effect and is of no clinical significance.

Relevance to human usage:

[1] Data from Study BA058-05-019 and Study BA058-05-021 added for a completeness of information. These two studies are not included in this submission.

In study BA058-05-003, the incidences of liver function test abnormalities were generally comparable among treatment groups and no findings were indicative of drug-induced liver injury (DILI). A cumulative review of the US post-marketing experience did not identify a signal for DILI following treatment with abaloparatide in women with osteoporosis.

- Genotoxicity

Abaloparatide was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) nor was it clastogenic in the in vitro chromosome aberration test using human peripheral lymphocytes.

In vivo, abaloparatide showed no induction of chromosome damage in mammalian cells up to 130 mg/kg/day in mice.

Relevance to human usage:

These data suggest no evidence of mutagenic and genotoxic-induced potential for carcinogenic effect of abaloparatide

- Carcinogenicity

In the 2-year carcinogenicity study in rats, abaloparatide at doses of 0, 10, 25 and 50 µg/kg/day, has demonstrated a dose-dependent increase in bone-related osteosarcomas and multicentric osteosarcomas in both males and in females at ≥10 µg/kg/day. These observations were similar to the findings in rats given hPTH (1-34) (30 µg/kg/day) as a positive control. These represent similar drug exposure multiples to the respective therapeutic doses of abaloparatide and rhPTH (1-34). The metastatic osteosarcomas appeared after 11 months treatment with ≥25 µg/kg/day.

Relevance to human usage:

Based on the 2-year carcinogenicity study, osteosarcoma is considered as an Important Potential risk. However, in view of the differences in bone metabolism between rodent and non-rodent species including humans, as well as of the absence of evidence of treatment-related occurrence of osteosarcomas in patients treated with either abaloparatide or teriparatide, the occurrence of osteosarcomas observed during the 2-year carcinogenicity is considered of low clinical significance. At 10, 25, and 50 µg/kg/day treatment, the exposure (Area Under Curve (AUC)) of abaloparatide is 4-, 16-, and 28-fold higher than the human exposure at the proposed 80 µg clinical dose, respectively.

Due to the fact that both teriparatide and abaloparatide mediate anabolic effects on bone and cause development of osteosarcoma in rats through signalling via the PTH1 receptor, the clinical data with teriparatide may also be used to assess the relevance of the rat carcinogenicity study results to risk of osteosarcoma in humans following treatment with abaloparatide.

Although, no adverse event cases of osteosarcoma have been reported in abaloparatide clinical trials or during the cumulative post-marketing experience since its launch in 2017 within the US, osteosarcoma is considered an Important Potential Risk.

Safety pharmacology

- Cardiovascular system, including potential effect on the QT interval

Cardiovascular effects of abaloparatide included in vitro testing of hERG inhibition and changes in action potential duration in rabbit Purkinje fibres which showed a non-specific ~3.4-7.7% inhibition of the hERG channel across a range of 1 to 30 µM, and a weak increase of ~ 20 ms in action potential duration at 2.16 µM, with no clear dose related effects. In vivo telemetry studies in dogs at 3 µg/kg revealed a reduction of QTc interval, however, the effects were transient and did not appear dose-related.

Haemodynamic effects of abaloparatide were evaluated in anaesthetised dogs. Abaloparatide administered intravenously at increasing doses from 0.03 to 3 µg/kg resulted in dose-dependent peripheral arteriolar vasodilatation from 0.1 µg/kg leading to hypotension, with a maximal decrease in mean arterial blood pressure of 45% at 3 µg/kg dose. In addition, abaloparatide dose-dependently increased heart rate at doses of 0.1 µg/kg and higher in the anesthetized dog, with a maximal heart rate increase of 48% at the 3 µg µg/kg dose.

Following subcutaneous administration in conscious dogs abaloparatide administration (1,3 and 10 µg/kg) had marginal effect on arterial blood pressure, although a tendency towards a decrease was observed at 3 and 10 µg/kg. Abaloparatide transiently and dose-dependently increased heart rate 68%, 82% and 120% at 1, 3 and 10 µg/kg from pre-administration heart rate, respectively. Maximum increase occurred at 15, 15 and 30, and 30 minutes post-administration at 1,3 and 10 µg/kg, respectively. Recovery to initial (pre-administration) values was achieved in about 3 hours post-administration.

Abaloparatide exerted a direct marked positive chronotropic effect as exhibited by dose dependent heart rate increase in both anesthetized and conscious dogs. It is likely that the chronotropic effect was due to reflex tachycardia in response to hypotension as seen by decreases in aortic blood pressure in anesthetized dogs.

Relevance to human usage:

Based on the C_{max} of abaloparatide of 812 pg/mL (0.205 nM) measured in the clinical Study BA058-001B after administration of a therapeutic dose of 80 µg SC abaloparatide, the safety margins are ~ 1,500-fold and 400-fold for the hERG and the rabbit Purkinje fibre studies, suggesting the risk of arrhythmogenic effects at clinically relevant doses is low.

To assess the possible impact of abaloparatide on QT interval, a thorough QTc study was conducted in which 55 healthy volunteers received single doses of placebo, abaloparatide SC, 80 µg (to be marketed dose) and 240 µg (supratherapeutic dose) and moxifloxacin, 400 µg orally in a 4-way cross over Phase 1 study (BA058-05-012). This study showed no clinically relevant effect on Individual-Specific QT Interval Correction (QTcI). Based on electrocardiogram (ECG) evaluation in study BA058-05-003 aside from a transient change in heart rate, the ECG evaluation did not reveal any safety concerns.

The thorough QT study showed dose dependent and transient increase on heart rate and no clinically relevant effect on QTcI. Based on ECG evaluation in study BA058-05-003, aside from a transient change in heart rate, the ECG evaluation did not reveal any safety concerns. The maximal placebo-corrected mean heart rate increases after treatment with abaloparatide 80 or 240 µg were 14.5 and 20.3 beats per minute (BPM), respectively, observed 15 minutes after administration. After 2.5 hours post-dose, the placebo-corrected heart rates were 5 and 9.7 BPM for abaloparatide 80 and 240 µg, respectively. The heart rates decreased towards baseline values by 6 hours post-dose. The transient increases in heart rate following abaloparatide administration appeared to follow a similar time course as the systemic plasma exposure of abaloparatide.

In postmenopausal women with osteoporosis in study BA058-05-003, abaloparatide and teriparatide each increased heart rate after dosing versus placebo. The mean increase from baseline in the abaloparatide group ranged (from Day 1 to Month 12) between 6.9 and 7.8 BPM at 1 hour post dose. For teriparatide, the corresponding range was 5.5 to 6.7 BPM, and for placebo 1.0 to 1.9 BPM. There was, however, substantial overlap in the range of heart rates between these treatment groups.

The abaloparatide-mediated transient increase in heart rate could theoretically increase the risk of serious cardiovascular events in women, particularly older, with osteoporosis.

Thus, serious cardiovascular events (i.e., Major Adverse Cardiovascular Events (MACE), arrhythmia) are considered an Important Potential Risk.

- Hypercalciuria

After abaloparatide SC administration in the rat, abaloparatide produced an increase in urinary calcium without a modification in urinary volume (Study BA058-138).

Relevance to human usage:

Hypercalciuria was expected based on the abaloparatide mechanism of action and underlying medical condition of osteoporosis. In study BA058-05-003, the incidence of at least one adverse event related to hypercalciuria (including the reported terms of hypercalciuria, urine calcium increased and urine calcium/creatinine ratio increased) were reported in 86 (12.5%), 108 (15.6%), and 124 (18.1%) subjects receiving placebo, abaloparatide and teriparatide, respectively.

Hypercalciuria is considered an Identified Risk. However, this risk was already characterized in the clinical programme, labelled, and does not require any further characterisation and is followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting. Since risk minimisation messages in the product information are available and expected to be adhered to by prescribers, hypercalciuria will not be included in the list of safety concerns in Module SVII and SVIII of the Risk Management Plan (RMP).

- Drug interactions

Abaloparatide is a selective Parathyroid Hormone Receptor 1 (PTHR1) agonist with a low potential for cytochrome P450 enzymes inhibition and induction, as well as for transporter inhibition

Relevance to human usage:

Abaloparatide is not expected to interact with the pharmacokinetics of other drugs administered concomitantly and no drug-drug studies were conducted.

Other toxicity-related information or data

None.

Part II: Module SIII – Clinical trial exposure

This is the initial EU Marketing Authorisation Application (MAA) submission of abaloparatide.

This section includes all completed studies up to the data lock point of 31 January 2021.

The clinical development programme of abaloparatide administered subcutaneously to postmenopausal women with osteoporosis consists of a total of 12 studies conducted in Europe, North America, South America and Asia including (Table 2):

- seven Phase 1 studies in healthy postmenopausal women, healthy volunteers, subjects with renal impairment and postmenopausal women with osteoporosis (Studies 2-52-52127-001, BA058-05-001, BA058-05-001B, BA058-05-010, BA058-05-011, BA058-05-012; BA058-05-020);

- two Phase 2 studies (Study BA058-05-002 and Study BA058-05-007) in postmenopausal women with osteoporosis;

- two confirmatory Phase 3 studies:
    - Study BA058-05-003 in postmenopausal women with osteoporosis. This pivotal Phase 3 study was followed by an open-label extension study (BA058-05-005). Completed Study BA058-05-005 was an extension study to evaluate 24 months of treatment with alendronate following completion of 18 months of abaloparatide or placebo treatment in protocol BA058-05-003.
    - Study ITM-058-301 in postmenopausal women and men with osteoporosis in Japan;

- and one prospectively planned retrospective observational cohort study (BA058-05-028) in postmenopausal women.

The number of subjects exposed across these studies is presented in (Table 2).

Overall, the prospective clinical trials included a total of 2,624 subjects with osteoporosis (including 20 men with osteoporosis in study ITM-058-301), and 310 subjects in Phase 1 studies without osteoporosis.

Among subjects with osteoporosis in prospective clinical studies, there were 1,039 exposed to abaloparatide, 731 to teriparatide and 854 to placebo. The vast majority of subjects with osteoporosis were postmenopausal women. Only study ITM-058-301 also included men with osteoporosis: 14 men in the abaloparatide group and 6 men in the placebo group. In the Phase 1 studies in subjects without osteoporosis, there were 266 subjects exposed to abaloparatide (of those 266 subjects exposed to abaloparatide, 242 healthy volunteers and 24 subjects with renal impairment) and 92 subjects were exposed to placebo.

Additionally, 33,255 patients were eligible for the non-interventional retrospective cohort Study BA058-05-028 prior to matching, of which 11,028 patients were exposed to abaloparatide and 22,227 patients to teriparatide. Following the propensity score matching, the number of patients was 11,027 subjects in each treatment cohort. These patients were not treated with Investigational Product, but with the approved marketed product in the USA in alignment with the approved label.

Of the postmenopausal women with osteoporosis exposed to abaloparatide in the context of prospective clinical studies (n= 1,039), 953 received the intended abaloparatide 80 µg daily dose (694 in the Phase 3 study BA058-05-003, 140 in the Phase 3 study ITM-058-301, 23 in Phase 1 study BA058-05-020, and in the Phase 2 studies: 45 in study BA058-05-002 and 51 in study BA058-05-007); furthermore, in the Phase 2 study BA058-05-002, 43 subjects received 20 µg abaloparatide daily and 43 subjects received 40 µg abaloparatide daily.

Of note, 80 µg was also the dose in the retrospective non-interventional observational study BA058-05-028, since the approved and recommended dose as per US label is 80 µg. A total of 11,027 postmenopausal women with osteoporosis received 80 µg abaloparatide in study BA058-05-028.

Table 2.Studies in abaloparatide clinical development programme

Study	Study Type/subject population	Treatment regimen
Studies in postmenopausal women and men with osteoporosis		
BA058-05-020	Open-label Phase 1, Single-arm Histomorphometry study 3 months of treatment, Substudy: 6 months of treatment in Postmenopausal women with osteoporosis	Abaloparatide: 80 µg QD SC (23/23)*
BA058-05-002 Extension Study: BA058-05-002 (amendment 5)	Randomised, double blind (for ABL-SC/Placebo), placebo controlled, parallel group, Phase 2 dose finding study in postmenopausal subjects with osteoporosis Extension of Study BA058-05-BA058-05-002 to provide longer term safety & efficacy data.	Initial 24 weeks treatment Abaloparatide 20 µg QD SC (n=43/43)* Abaloparatide 40 µg QD SC (n=43/43)* Abaloparatide 80 µg QD SC (n=45/45)* Teriparatide 20 µg QD SC (n=45/45)*, Placebo QD SC (n=45/45)* 48-Week Treatment Period Abaloparatide 20 µg QD SC (n=13), Abaloparatide 40 µg QD SC (n=10) Abaloparatide 80 µg QD SC (n=7), Teriparatide 20 µg SC (n=14) Placebo QD SC (n=11)
BA058-05-007	Randomised, double blind for Abaloparatide-TD/Placebo) Placebo-controlled, Parallel Group Phase 2 dose finding study in postmenopausal subjects with osteoporosis	Abaloparatide 80 µg QD SC over 24 weeks (n=51) Placebo TD over 24 weeks (n=50) Abaloparatide-TD 1 50 µg over 24 weeks (50) Abaloparatide-TD 1 100 µg over 24 weeks (51) Abaloparatide-TD 1 150 µg over 24 weeks (47)
BA058-05-003	Randomised, Double-blind, Placebo-controlled, comparative Phase 3 safety and efficacy study in postmenopausal subjects with osteoporosis	Abaloparatide 80 µg QD SC over 18 months (n=696/694)* Teriparatide 20 µg QD SC over 18 months (n=686/686)* Placebo QD SC over 18 months (n=688/687)*
BA058-05-005	Open-label extension of Study BA058-05-003 to provide longer term safety & efficacy data after alendronate treatment Safety and efficacy – Extension Phase 3 study in postmenopausal subjects with osteoporosis	Alendronate 70 mg orally once per week 469 entered/ 465 dosed (previously treated with abaloparatide in Study BA058-05-003) 494 entered/ 493 dosed (previously treated with placebo in Study BA058-05-003) All subjects randomised to ABL-SC/Placebo in Study BA058-05-003 and who are candidates for alendronate treatment
ITM-058-301	Randomised, Double blind, Placebo-controlled, Parallel-group confirmatory Safety and Efficacy Phase 3 study in Postmenopausal women with osteoporosis and men with osteoporosis (This study included 20 men with osteoporosis)	Abaloparatide: 80 µg QD SC (141/140)* Placebo QD SC (72/72)*
BA058-05-028	Retrospective non-interventional observational cohort Phase 3b study in Postmenopausal women with osteoporosis, who are new to anabolic therapy	Abaloparatide (11,027) Teriparatide (11,027) Prescribed doses: not specified in the protocol as doses were as prescribed in a real-world setting. However, both treatments are in alignment with the respective approved (US) labels: Abaloparatide: recommended dose 80 µg QD SC; Teriparatide: recommended dose 20 µg QD SC
Phase 1 studies in healthy postmenopausal women, healthy volunteers and subjects with renal impairment		
2-52-52127-001	Phase 1 study in healthy subjects Part A: Randomised open-label, single-dose, standard 2-treatment, 2-period crossover Part B: Double-blind, randomised, placebo-controlled, single ascending dose (SAD) study-arm	Part A: abaloparatide (lyophilisate [lyo])-SC): 2, 5, 7.5, 10, 15, 20, 40, 60, 80 and 100 µg -SC (n=6/dose group; total=60) Placebo (20) Part B (IV & SC administration sequence randomised): Abaloparatide (lyophilisate)- IV 2.5 µg (n=16/16)* Abaloparatide (lyophilisate)- SC 15 µg (n=16/15)*
BA058-05-001	Randomised, Double blind, Placebo-controlled, Parallel group, Dose escalating Phase 1 study in healthy postmenopausal women	Abaloparatide (lyo) 5, 20, 40 and 80 µg QD over 7 days (n=8/group) Placebo (7)
BA058-05-001B	Randomised, Double blind, Placebo-controlled, Parallel group, Dose escalating Phase 1 study in healthy postmenopausal women	Abaloparatide (lyo) 80, 100 and 120µg QD over 7 days (n=8/group) Placebo (6)
BA058-05-010	Phase 1 study in healthy subjects Bioavailability: Cohort 1: randomised, open-label, single-dose, 2-treatment (SC and IV abaloparatide), 2-sequence crossover study. Single dose Maximum Tolerated Dose (MTD): Cohorts 2-5: randomised, double-blind, placebo-controlled, single ascending dose of abaloparatide in healthy subjects (MTD determined for the QTc study). Single dose	Bioavailability: Cohort 1: Abaloparatide SC 80 µg and ABL IV 40 µg over a 2-hour continuous infusion, (n=19) MTD: Cohort 2: Abaloparatide 120 µg (n=8); Placebo (n=2) Cohort 3: Abaloparatide 240 µg (n=8); Placebo (n=2) Cohort 4: Abaloparatide 320 µg (n=8); Placebo (n=2) Cohort 5: Abaloparatide 280 µg (n=8); Placebo (n=2)
BA058-05-011	Open-label, parallel group, single-dose Phase 1 study to evaluate the PK, PD and safety of a single dose of abaloparatide in subjects with varying degrees of renal function	Abaloparatide 80 µg single dose (n=32) Normal renal function: 8 Renal impairment: Mild (8); Moderate (8); Severe (8)
BA058-05-012	Phase 1 thorough QT/QTc study: Randomised, partially double-blind, single dose, positive controlled and placebo-controlled, 3-way cross-over study to evaluate the effects of abaloparatide on the QT/QTc interval in healthy subjects, Single dose in healthy subjects	Abaloparatide 80 µg (n=52) Abaloparatide 240 µg (n=52) Placebo (n=51) Moxifloxacin (n=50) Note: total number of subjects in the safety population of this study was n= 55 as this was a 4-way-cross-over study

*Number of subjects (Randomised/dosed). QD: Daily. SC: Subcutaneous. TD: Transdermal. ABL: Abaloparatide.

For the purposes of this risk management plan, the safety evaluation focuses on the data from the Phase 3 study BA058-05-003 where the subjects were exposed to abaloparatide for 18 months. Safety results from the Phase 2 study BA058-05-002 are used to evaluate the influence of the dose on the safety. The treatment duration in study BA058-05-002 was 24 weeks followed by an optional extension of 24 weeks. Note that patients in the open-label extension study BA058-05-005, do not receive abaloparatide; this study is an extension study to evaluate 24 months of standard-of-care osteoporosis management following completion of 18 months of abaloparatide or placebo treatment in protocol study BA058-05-003.

The following tables (Table 3 to Table 7) present the available data exposure to abaloparatide (by duration, by dose, by ethnic or racial origin, by age group and by special population) in postmenopausal women and men with osteoporosis. These tables involved pooled data from the studies BA058-05-002, BA058-05-003, BA058-05-007 and BA058-05-020. Note, the data from study ITM-058-301 are presented in separate tables (Tables 3b and 5b) since this is a Japanese study conducted by a Partner and not sponsored by the applicant, included men with osteoporosis in addition to women, and the full study data set is not available to the applicant to be integrated with the other pooled studies. In addition, the data from study BA058-05-028 are presented in separate tables (Tables 3c and 5c) since this is a non-interventional observational study which is part of the clinical development program of abaloparatide.

Table 3a. Duration of exposure

Indication: Treatment of osteoporosis in postmenopausal women		
Duration of exposure (at least)	**Persons**	**Person time (months)**
1 Day	899	10,939.6
1 Month	795	10,911.1
3 Months	751	10,833.1
5 Months	708	10679.3
7 Months	578	9,929.5
9 Months	568	9,847.2
11 Months	557	9,740.6
13 Months	522	9,327.0
15 Months	516	9,242.7
17 Months	510	9,150.0
Total	**860**	**10,939.6**

Includes BA058-05-002, BA058-05-007, BA058-05-003 and BA058-05-020 studies.
1 Month = 30 Days.
In study BA058-05-003, 39 subjects with unknown stop dates were excluded from calculation of total person time (in months) but were included in the number of subjects with a duration of one day at least. Therefore, for duration "1 day", there are 899 subjects and for "Total" there are 860 subjects while the person time is equal for both durations.
In studies BA058-05-002 and BA058-05-007, one month was defined as four weeks.

Table 3b. Duration of exposure

Indication: Treatment of osteoporosis in postmenopausal women and men		
Duration of exposure (at least)	**Persons**	**Person time (months)*****
Duration of completed study drug exposure (days)	140*; 424.2**	90.06***

Data from study ITM-058-301. (This study included men with osteoporosis: 14 men in the abaloparatide group and 6 men in the placebo group).
Data from Clinical Safety report of study ITM-058-301 (subsection 12.1-Extent of Exposure).
*Study ITM-058-301: The investigational drug (80µg) was administered to 140 subjects in the ITM-058 group.
**The mean ± Standard Deviation (SD) of the total number of days of administration of the investigational drug as specified in the protocol was 424.2 ± 153.2 days in the ITM-058 group.
***The value provided in this column does not refer to the person time (months), but rather to the mean value of the subject's rate of the exposure. The mean ± SD of the rate of administration of the investigational drug ([treatment period –number of days on which the investigational drug was not administered as specified in the protocol]/[treatment period] × 100) was 90.06 ± 11.47% in the ITM-058 group.

Table 3c. Duration of exposure

Indication: Treatment of osteoporosis in postmenopausal women		
Duration of exposure (at least)	**Persons**	**Person time (months)**
Overall Treatment Duration n (%)		
≤1 Month	1,990 (18.0)	---
>1 to ≤3 Months	1,291 (11.7)	---
>3 to ≤6 Months	1,129 (10.2)	---
>6 to ≤9 Months	831 (7.5)	---
>9 to ≤12 Months	782 (7.1)	---
>12 Months	5,004 (45.4)	---
Total	**11,027 (100)**	**---**

Data from Clinical Safety report of study BA058-05-028 (subsection 12.1-Extent of Exposure). (Abaloparatide: Overall propensity matched subject (PS-matched)= 11,027)
Duration of Exposure (days) = Date of last anabolic drug prescription fill plus supply days – index date. The overall mean duration of abaloparatide exposure was 301.0 days, with >45% of patients exposed to treatment >12 months.
Duration of Exposure (months) = Duration of Exposure (days)/30. The maximum treatment duration is set as 570 days (or 19 months, 18 months plus 30 days follow-up) if a patient was treated longer than 570 days.
The mean cumulative duration of abaloparatide exposure was 257.6 days, with >33% of patients exposed to treatment >12 months.

Table 4. By dose

Indication: Treatment of osteoporosis in postmenopausal women		
Dose of exposure	**Persons**	**Person time (months)**
20 µg/day	43	271.5
40 µg/day	43	269.1
80 µg/day	774	10,399.0
Total	**860**	**10,939.6**

Includes BA058-05-002, BA058-05-007, BA058-05-003 and BA058-05-020 studies.
1 Month = 30 Days.
In study BA058-05-003, 39 subjects with unknown stop dates were excluded from calculation of total person time.
In studies BA058-05-002 and BA058-05-007, one month was defined as four weeks.

Table 5a. By age group

Indication: Treatment of osteoporosis in postmenopausal women		
Age group	**Persons**	**Person time (months)**
<65	189	1,975.6
65 to <75	518	6,909.5
≥75	153	2,054.5
Total	**860**	**10,939.6**

Includes BA058-05-002, BA058-05-007, BA058-05-003 and BA058-05-020 studies.
1 Month = 30 Days.
In study BA058-05-003, 39 subjects with unknown stop dates were excluded from calculation of total person time.
In studies BA058-05-002 and BA058-05-007, one month was defined as four weeks.

Table 5b. By age group

Indication: Treatment of osteoporosis in postmenopausal women	
Age group	**Persons**
<65	31
65 to <75	84
≥75	21
Total	**136**

Data from study ITM-058-301. (This study included men with osteoporosis: 14 men in the abaloparatide group and 6 men in the placebo group).

Table 5c. By age group

Indication: Treatment of osteoporosis in postmenopausal women	
Age group	**Persons n (%)**
50 – 64	4,543 (41.2)
65 – 74	3,769 (34.2)
≥75	2,715 (24.6)
Total	**11,027 (100)**

Data from Clinical Safety report of study BA058-05-028 (subsection 11.2-Demographic and Other Baseline Characteristics).

Table 6a. By ethnic or racial origin

Indication: Treatment of osteoporosis in postmenopausal women		
Ethnic/racial origin	**Persons**	**Person time (Months)**
American Indian or Alaska Native	1	5.6
Asian	157	2,143.5
Black or African American	23	384.1
Other	28	245.5
White	651	8,160.9
Total	**860**	**10,939.6**

Includes BA058-05-002, BA058-05-007, BA058-05-003 and BA058-05-020 studies.
1 Month = 30 Days.
In study BA058-05-003, 39 subjects with unknown stop dates were excluded from calculation of total person time.
In studies BA058-05-002 and BA058-05-007, one month was defined as four weeks.

Table 6b. By ethnic or racial origin

Indication: Treatment of osteoporosis in postmenopausal women		
Ethnic/racial origin	**Persons n(%)**	**Person time (Months)**
African American	144 (1.3)	---
Asian	100 (0.9)	---
White	4,137 (37.5)	---
Hispanic	646 (5.9)	---
Other	127 (1.2)	---
Unknown	5,873 (53.3)	---
Total	**11,027 (100)**	---

Data from Clinical Safety report of study BA058-05-028 (subsection 11.2-Demographic and Other Baseline Characteristics).

Table 7. Special populations

Indication: Treatment of osteoporosis in postmenopausal women		
	Persons	**Person time (Months)**
*Renal function at baseline[2]		
Creatinine clearance < 60 mL/min	180	2329.1
Creatinine clearance 60< 90 mL/min	447	5843.0
Creatinine clearance ≥ 90 mL/min	210	2694.9

*Includes studies BA058-05-002, BA058-05-007 and BA058-05-003.
1 Month = 30 Days.
In study BA058-05-003, 40 subjects with unknown stop dates were excluded from calculation of total person time.
In studies BA058-05-002 and BA058-05-007, one month was defined as four weeks.

[2] Based on creatinine clearance estimated using the Cockcroft-Gault formula.

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

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

Bone disorders (e.g., Paget's disease) other than postmenopausal osteoporosis

Reason for exclusion: Increased risk of osteosarcoma.

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

Rationale: Abaloparatide is indicated for the treatment of osteoporosis in postmenopausal women, thus abaloparatide should not be used for the treatment of other bone diseases such as Paget's disease.

Unexplained elevation of serum alkaline phosphatase

Reason for exclusion: Increased risk of osteosarcoma.

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

Rationale: criteria remains as contraindication.

History of radiotherapy (radiation therapy) in which bone is within the radiation field, other than radioiodine

Reason for exclusion: Increased risk of osteosarcoma.

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

Rationale: criteria remains as contraindication.

Patients with skeletal malignancies or bone metastases

Reason for exclusion: Increased risk of osteosarcoma.

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

Rationale: criteria remains as contraindication.

Albumin-adjusted serum calcium levels above normal range

Reason for exclusion: Increased risk of hypercalcaemia.

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

Rationale: criteria remains as contraindication.

Hypersensitivity

Reason for exclusion: Increased risk of allergic reaction.

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

Rationale: criteria remains as contraindication.

Severe renal impairment

Reason for exclusion: Increased risk of undesirable effects due to increased abaloparatide exposure.

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

Rationale: Patients with severe renal impairment are contraindicated for receiving abaloparatide. Results from the renal impairment study (BA058-05-011) showed abaloparatide exposure increased with decreasing creatinine clearance (CrCl). In addition, a statement regarding renal impairment is included in the section 4.2 'Posology-special populations' of the SmPC as well as a contraindication of use in severe renal impairment in section 4.3 'Contraindications'. Moreover, information about the study results about abaloparatide exposure in patients with renal impairment is indicated in section 5.2 'Pharmacokinetic properties'.

Heart rate is >100 bpm

Reason for exclusion: Increased risk of undesirable effects such as palpitations and tachycardia.

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

Rationale: Abaloparatide use should be preceded by more careful monitoring in patients with tachycardia. Statements regarding transient increase in heart rate and tachycardia post dosing are included in section 4.4 'Warnings and Precautions' and section 4.8 'Undesirable effects' of the SmPC.

Uncontrolled hypertension

Reason for exclusion: Increased risk of undesirable effects.

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

Rationale: Blood pressure measurements during study BA058-05-003 showed that abaloparatide treatment is not associated with an increase in systolic blood pressure. No contraindication regarding uncontrolled hypertension is required. It is not expected that the efficacy and safety of abaloparatide will differ in patients with uncontrolled hypertension.

Age > 85 years old

Reason for exclusion: The reason to exclude patients aged > 85 years old was to ensure an appropriate safety evaluation of abaloparatide as very elderly patients have significant morbidity that may confound the assessment of the safety of abaloparatide.

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

Rationale: It is not expected that the efficacy and safety of abaloparatide will differ in very elderly patients.

In Study BA058-05-003, due to very low number of subjects > 85 years old (n = 4), no meaningful conclusions were made in subjects older than 85 years of age.

As of 27 April 2022 (Data Lock Point (DLP) of last PBRER) Radius received a total of 17,655 post-marketing Adverse Event (AE) reports in the US. Of these cases, patient's age was provided in 14,051 cases, of which 13,510 reports were reported in patients aged ≤ 84 years, and 541 reports were reported in patents aged ≥ 85 years. In the remaining 3,604 reports, patient's age was not documented. In the ≤ 84-year-old age group, there were a total of 37,853 events reported of which 869 [2.3%] were serious AE's and 36,984 were non-serious AE's. Only 1,658 (4.4%) events were HCP confirmed. Patient ages ranged from 11 to 84-years-old. Onset latency of the events was from immediately after the first injection to 34+ months after initiation of abaloparatide treatment. In the ≥ 85-years and older age group, there

were a total of 1,430 events reported of which 113 [7.9%] were serious AE's and 1,317 were non-serious AE's. Only 46 (3.2%) events were HCP confirmed. Patient ages ranged from 85 to 99-years-old. Onset latency of the events was from day 1 to 17 months after initiation of abaloparatide treatment. Based on the review of the adverse events reported in both the age groups, there were no difference in regards to the frequency and characteristics of the AE's and the safety profile between both age groups were similar.

A review of MACE or Heart Failure (HF) reported within each age group was also conducted. In the ≤ 84-year-old age group, a total of 35 (0.09%) MACE or HF PTs including Myocardial Infarction (MI) (16), Cerebrovascular Accident (CVA) (17), and cardiac congestive (2) were reported. In almost half of these cases, confounding factors such as prior medical history (e.g. hypertension, coronary artery disease, myocardial infarction, stroke, diabetes mellitus, Transient ischaemic attack (TIA), smoking, blood clots and heart disease) may have contributed to the MACE. In the remaining cases, very limited information was provided to make any temporal association between the event of MACE or HF and abaloparatide administration. Two events of cardiac failure congestive and one event of myocardial infarction were fatal; however, none of these events were HCP confirmed. In the ≥ 85-years and older age group, a total of 12 (0.7%) MACE or HF PT's including cardiac failure congestive (6), MI (3), and CVA (3) were reported. Confounding factors such as prior medical history (e.g. peripheral vascular disease, diabetes mellitus, hypertension, hypercholesterolemia, "heart problems" and smoking) may have contributed to the MACE or HF in these cases. One event of myocardial infarction and two events of cardiac failure congestive were fatal; however, none of these events were HCP confirmed. The review did not identify any cardiovascular signal in the ≥ 85-years and older age group.

Statement regarding abaloparatide use in elderly population is included in section 4.2 'Posology-special populations' and in section 5.2 'Pharmacokinetic properties' of the SmPC.

PTH(1-84) (Parathyroid Hormone intact) and serum phosphorus levels out of normal range

Reason for exclusion: Patients who had PTH(1-84) or serum phosphorus levels above the normal range were excluded to ensure an appropriate safety evaluation of abaloparatide.

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

Rationale: It is not expected that the efficacy and safety of abaloparatide will differ in patients with PTH(1-84) or serum phosphorus above the normal range.

History of nephrolithiasis or urolithiasis within the past 5 years.

Reason for exclusion: Patients with a history of nephrolithiasis or urolithiasis were excluded to avoid an exacerbation of these symptoms. The period of 5 years without nephrolithiasis or urolithiasis before study inclusion, was to ensure that patients had not relapsed.

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

Rationale: Abaloparatide use should be preceded by more careful monitoring in those with renal stones and is contraindicated in case of pre-existing hypercalcaemia. Since abaloparatide can cause hypercalcemia and hypercalciuria which can contribute to the development of nephrolithiasis, all three events (hypercalcaemia, hypercalciuria and nephrolithiasis) are considered ADRs with abaloparatide therapy and have been adequately represented in the SmPC. A statement regarding hypercalcaemia, hypercalciuria and urolithiasis has been included in section 4.4 'Warnings and precautions' of the SmPC. In addition, hypercalcaemia, hypercalciuria and nephrolithiasis are included in the tabulated list of adverse reactions in section 4.8 'Undesirable effects' of the SmPC.

Orthostatic hypotension or symptomatic hypotension at screening

Reason for exclusion: Patients with orthostatic hypotension and/or symptomatic hypotension were excluded as this was a warning for teriparatide use, and to avoid confounding the safety assessment of abaloparatide. For example, if these patients were not excluded, it would not have been possible to distinguish whether orthostatic hypotension and/or hypotension were caused by abaloparatide or not.

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

Rationale: Abaloparatide can cause orthostatic hypotension. A statement regarding orthostatic hypotension is included in section 4.4 'Warnings and precautions' of the SmPC. It is also included in the tabulated list of adverse reactions in section 4.8 'Undesirable effects' of the SmPC.

Orthostatic hypotension is considered as an Identified Risk. However, this risk was already characterized in the clinical programme, labelled, and does not require any further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting. Since risk minimisation messages in the product information are available and expected to be adhered to by prescribers, orthostatic hypotension will not be included in the list of safety concerns in Module SVII and SVIII of the RMP.

Abnormal 12-lead electrocardiogram and a QTc >470 msec during screening

Reason for exclusion: Patients with abnormal 12-lead electrocardiogram and a QTc >470 msec were excluded to avoid confounding the safety assessment of abaloparatide- SC. The non-clinical findings had shown that the cardiovascular effects on the ECG are of low intensity, not coherent through studies and not dose dependent (see Part II SII).

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

Rationale: To assess the possible impact of abaloparatide on QT interval, a thorough QTc study was conducted in which 55 healthy volunteers received single doses of placebo, abaloparatide, 80 µg (to be marketed dose) and 240 µg SC (supratherapeutic dose) and moxifloxacin, 400 µg orally in a 4-way cross over Phase 1 (study BA058-05-012). This study showed an abaloparatide dose dependent and transient increase on heart rate and no clinically meaningful effect on QTcI. In this study the upper limit for the QTcI interval did not exceed 10ms in either abaloparatide treatment groups, and thus fulfilled the criterion for a negative QT study for both doses (abaloparatide 80 µg and 240 µg µg, respectively). Based on the results of the thorough QT study the abaloparatide treatment is not associated with the prolongation of the QT interval.

Abnormalities of the lumbar spine that would prohibit assessment of spinal bone mineral density, defined as having at least 2 radiologically evaluable vertebrae within L1-L4

Reason for exclusion: These patients were excluded to ensure an appropriate efficacy evaluation.

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

Rationale: It is not expected that the efficacy and safety of abaloparatide will differ in patients which abnormalities of the lumbar spine would prohibit assessment of lumbar spine BMD.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are uncommon	953 postmenopausal women with osteoporosis (PMWO) subjects who received a therapeutic dose of abaloparatide 80 micrograms.	ADRs with a frequency greater than 1 in 290 could be detected if there were no background incidence
Due to prolonged exposure	In study BA058-05-003, 694 postmenopausal women were exposed to abaloparatide-SC of who 507 received abaloparatide-SC for 18 months. Of these, 469 postmenopausal women were enrolled into the extension study BA058-05-005 during which they were treated with alendronate (ALN) for up to 24 months.	During both study periods no major safety concerns were identified which were considered to be related to prolonged exposure to abaloparatide treatment. Based on the carcinogenicity study in rats there is a potential for development of osteosarcoma following long term administration of abaloparatide. Potential for development of osteosarcoma is identified as Important Potential Risk. Medical conditions known to have an increased risk for development of osteosarcoma are included in section 4.3 'Contraindications' of the SmPC. In addition, section 4.2 'Posology and method of administration' indicates that the maximum total duration of treatment with abaloparatide should be 18 months
Due to cumulative effects	Potential for kidney mineralization	The analysis of data from the pivotal abaloparatide-SC study (BA058-05-003) and recently completed clinical study in men (BA058-05-019[3]) and transdermal-abaloparatide formulation (Study BA058-05-021[3]) concluded that although treatment with abaloparatide can cause hypercalcemia and hypercalciuria which can contribute to the development of nephrolithiasis, there were no safety signals regarding other organ calcification-related events except for nephrolithiasis. Hypercalcaemia, hypercalciuria and nephrolithiasis are considered ADRs with abaloparatide therapy and have been adequately represented in the SmPC.

[3] Data from Study BA058-05-019 and Study BA058-05-021 added for a completeness of information. These studies are not included in this submission.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which have a long latency	In study BA058-05-003, 469 subjects exposed to abaloparatide-SC for 18 months, and 494 placebo subjects, transitioned to ALN in study BA058-05-005 for 24 months	In study BA058-05-005 through Month 18, no adverse events suggestive of long- term latency effects have been identified.

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

Table 8. 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 program
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Small number of subjects (n = 23) with abnormal liver values at baseline were enrolled in the clinical development programme who were randomized to an abaloparatide treatment group (Study BA058-05-003: n=22; Study BA058-05-019[4]: n=1).
• Patients with renal impairment	In the Study BA058-05-011 carried out to evaluate the PK profile of abaloparatide in subjects with impaired renal function, the following subjects with mild, moderate or severe renal function were exposed: - mild (N=8, CLCR⩾60-<90 mL/min); - moderate (N=8, CLCR≥30-<60 mL/min); - severe (N=8, CLCR≥15-<30 mL/min).
• Patients with cardiovascular impairment	Subjects with severe cardiovascular diseases were excluded from clinical studies. However, in the pivotal phase 3 study (study BA058-05-003), approximately 66% of subjects in all three treatment groups had at least one cardiovascular risk factor present at baseline. Included cardiovascular risk factors were hypertension, dyslipidaemia, diabetes mellitus, coronary disease, cerebrovascular accident, atrial fibrillation/flutter, and revascularization.
• Immunocompromised patients	Not included in the clinical development program

[4] Data from Study BA058-05-019 added for a completeness of information. This study is not included in this submission.

Type of special population	Exposure
• Patients with a disease severity different from inclusion criteria in clinical trials	The study population in study BA058-05-003 is in agreement with the population recommended in the Committee for Medicinal Products for Human Use (CHMP) Guideline on new medicinal products in the treatment of primary osteoporosis (CPMP/EWP/552/95 Rev. 2). The enrolled patients had an increased risk of fracture, as shown by the mean FRAX probability of major osteoporotic fracture at baseline (with BMD) was 13.15 for the 3 arms, and a FRAX probability of hip fracture at baseline (with BMD) of 4.84 for all 3 groups).
Population with relevant different ethnic origin	Exposure to abaloparatide for treatment of osteoporosis in postmenopausal women: Data from studies BA058-05-002, BA058-05-007, BA058-05-003 and BA058-05-020: - American Indian or Alaska Native: 1 person; Person time (months): 5.6. - Asian: 157 persons; Person time (months): 2,143.5. - Black or African American: 23 persons (Person time (months): 384.1 - Other: 28 persons (Person time (months): 245.5. - White :651 persons (Person time (months): 8,160.9.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	None

Part II: Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Post-marketing exposure has been estimated based on the pens sales, and also including pens distributed for free goods (investigator initiated/sponsored studies or patients access programs).

Considering that 1 pen provides treatment for 30 days (1 month), the patient-exposure (patient-years) has been calculated according to this formula:

$$PPPPPPPPPPPP - yyPPPPyyyy = \frac{PPnnnnnnPPyy\ oooo\ ppPPPPyy\ ddPPyyPPyyPPnnnnPPPPdd}{12\ (PPnnnnnnPPyy\ oooo\ nnooPPPPhyy\ PPPP\ ooPPPP\ yyPPPPyy)}$$

SV.1.2 Exposure

As stated in the latest PBRER (DLP 27 April 2022), since abaloparatide launch in the US (under the trade name of Tymlos) in May 2017 through to March 2022, it was estimated that a total of 571,415 abaloparatide pens were dispensed resulting in an estimated 47,618 patient-years of exposure to abaloparatide.

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

Potential for misuse for illegal purposes

Abaloparatide has no specific effects likely to induce a potential for misuse for illegal purposes.

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

The following adverse reactions are not included as safety concerns (important identified or important potential risks) in the RMP since these events have minimal benefit-risk impact to patients in relation to the severity of the indication treated:

> Headache, dizziness, palpitation, hypertension, nausea, fatigue, tachycardia, injection site reaction, abdominal pain, constipation, diarrhoea, vomiting, abdominal distension, asthenia, malaise, pain, hyperuricaemia, arthralgia, back pain, bone pain, muscle spasms (back and legs), pain in extremity, insomnia, nephrolithiasis, pruritus, rash

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:

> Hypersensitivity and anaphylactic reaction

Known risks that are already characterized in the clinical programme and labelled and 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 available and expected to be adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

> Hypercalcemia, hypercalciuria and orthostatic hypotension

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

Important Identified Risk:

None.

Important Potential Risk 1: Osteosarcoma

Risk-benefit impact:

In the general population, osteosarcoma is the most common nonhematological primary bone malignancy, however its incidence is rare (Cipriani, 2012). The differences observed in bone metabolism between rodents and primates likely explain why the high incidence of osteosarcomas observed in rats has not been observed in monkeys and in humans. No clinical cases have been identified with abaloparatide treatment, and post-marketing studies with teriparatide did not show an increased risk of osteosarcoma with teriparatide treatment than expected in the population. Currently, the impact on the risk-benefit from drug-related osteosarcoma is expected to be minimal.

Important Potential Risk 2: Serious Cardiovascular events (i.e., MACE, arrhythmia)

Risk-benefit impact:

Cardiovascular disease can cause significant disability and may negatively impact the patient's quality of life. Other than transient increase in heart rate, the cardiovascular risk evaluated as serious cardiovascular events (MACE) in subjects receiving abaloparatide has been demonstrated to be lower than that in the placebo population. In addition, the cumulative US post-marketing experience, since its launch in 2017, has not identified a safety signal for serious cardiovascular events. However, a potential

exists for the risk of serious cardiovascular events (i.e., MACE, arrhythmia) due to transient increase in heart rate in the general osteoporosis population.

Missing information:

None.

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

Not applicable due to this is the first submission of the RMP.

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

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

Important Identified Risk:

None

Important Potential Risk: Osteosarcoma

Potential mechanisms:

The mechanism by which osteosarcoma is induced by PTH and PTHrP analogues is not fully understood, although several studies suggest that the PTH1 receptor contributes to the pathogenesis of osteosarcoma (Nikitovic, 2016). Osteosarcoma cells express PTH1 receptor and upon activation by PTH or PTHrP, this receptor induces cAMP signalling resulting in the release of cAMP-dependent protein kinases. Activated protein kinases such as Protein Kinase A (PKA), Protein Kinase C (PKC) or Extracellular Signal-Related Kinase (ERK) translocate to the nucleus and phosphorylate transcription factors such as cAMP-response element-binding protein and runt-related transcription factor 2 (Runx-2). These phosphorylated transcription factors then regulate expression of target genes including transforming growth factor, connective tissue growth factor, fibroblast growth factor and HA synthase-2 that can promote development of osteosarcoma. Another downstream target for PTH1 receptor signalling includes the Wnt pathway genes which may regulate cell proliferation, migration, and invasion of osteosarcoma cells (Li, 2017).The relevance of the rat species to evaluate the risk of osteosarcoma in humans is low, primarily due to the differences in continued bone growth and metabolism that occurs in rodents, as opposed to remodelling that occurs in primates (including humans).

Evidence source(s) and strength of evidence:

In the general population, osteosarcoma is the most common nonhematological primary bone malignancy, however its incidence is rare (Cipriani, 2012). The incidence of osteosarcoma has a biphasic trend by age, with a first peak around puberty and a smaller peak in subjects over 60 years of age (Cipriani, 2012). The number of cases per million per year ranges worldwide between 3 and 4.5 in childhood and adolescence, 2 in individuals 25 to 59 years old, and 1.5 to 4.5 in subjects over the age of 60 years.

The exaggerated anabolic response in rats indicates a significant anabolic stimulus driving osteoblast activity, likely stimulating a proliferative response (or preventing osteoblast apoptosis) (Jilka, 1999; Schnoke, 2009), and leading to an abnormal accumulation of osteoblasts, and osteosarcomas, in rodents.

The differences in bone metabolism between rodents and primates likely explain why the high incidence of osteosarcomas observed in rats has not been observed in monkeys and in humans. A limited number of monkeys have been exposed to abaloparatide during the development programme at doses up to 70 µg/kg (with a protocol defined reduction to 50 µg/kg) for 39 weeks and 5 µg/kg for 16 months. In these studies, no neoplasms were noted.

Studies in rats indicate an increased incidence of osteosarcoma with long-term administration of abaloparatide. The relevance of these rat findings to humans is uncertain, thus the use of abaloparatide should be avoided for patients at increased risk of osteosarcoma.

Characterisation of the risk:

- Clinical data:

Frequency with 95 % CI:

There were no cases of osteosarcoma reported during the entire clinical programme.

- Post-marketing data:

As of the last PBRER (DLP 27 April 2022), no cases of osteosarcoma have been reported with abaloparatide treatment in the post-marketing surveillance.

Due to the fact that both teriparatide and abaloparatide mediate anabolic effects on bone and cause development of osteosarcoma in rats through signalling via the PTH1 receptor, the clinical data with teriparatide may also be used to assess the relevance of the rat carcinogenicity study results to risk of osteosarcoma in humans following treatment with abaloparatide.

Data from several surveillance studies on the incidence rate of osteosarcoma among patients treated with teriparatide have been published (see below table). In the 15-year Osteosarcoma Surveillance Study (Gilsenan, 2021b), 3 teriparatide-treated patients had osteosarcoma; no teriparatide-treated patients had osteosarcoma in the 10-year Forteo Osteosarcoma Post-Approval Surveillance Study (Midkiff, 2014); and no teriparatide-treated patients had osteosarcoma in the 10-year Forteo Patient Registry (Gilsenan, 2021a). In addition, in an assessment of Medicare Part D and the US State Cancer Registry Data, no osteosarcoma cases were identified among 153,316 teriparatide-treated patients (Gilsenan, 2020). The results from these public domain long-term studies provide evidence that the findings in the carcinogenicity studies do not result in an increased risk of osteosarcoma during clinical use of teriparatide.

Study	Design	Key Findings
15-year Surveillance Study (Gilsenan, 2021b)	Identified incident cases of osteosarcoma diagnosed between 01 January 2003 and 31 December 2016 through participating cancer registries in the US. Interviews were completed for 24% of patients diagnosed with osteosarcoma between 2003 and 2016 (n=1,173 interviewed patients).	Three reports of teriparatide use before diagnosis were identified. The expected number of cases would have been 4.17 based on the background incidence rate of osteosarcoma in the US. Thus, the incidence of osteosarcoma associated with teriparatide use was no different from the expected number based on the background incidence rate of osteosarcoma.
10-year Forteo Osteosarcoma Post-Authorisation Safety Study (PASS) (Midkiff, 2014)	Potential subjects were identified through the Scandinavian Sarcoma Group registry and the Finnish and Swedish National Cancer Registries. Patients were eligible if they were ≥ 40 years of age at the time of diagnosis and had histological confirmation of osteosarcoma or 1 of 5 other tumour types with a primary bone site. A total of 112 patients who had osteosarcoma and available medical records were abstracted.	None of the 112 patients identified with osteosarcoma had previously used teriparatide.

Study	Design	Key Findings
10-year Forteo Patient Registry Study (Gilsenan, 2021a)	This registry estimated the incidence of osteosarcoma in US patients treated with teriparatide and enrolled in the study between 2009 and 2019. Data for 75,247 enrolled patients (representing 361,763 cumulative person-years) were linked to each of 42 participating state cancer registries (covering 93% of the US population), which included information on 6180 cases of osteosarcoma. A Standardized Incidence Ratio (SIR) of observed cases to the expected number of cases adjusted to the age and sex of teriparatide users (3 per million person-years) and corresponding exact 95% Confidence Interval (CI) was also calculated.	No incident cases of osteosarcoma were identified. Based on the 361,763 cumulative person-years without an observed case compared with the expected number of 3 cases per million person-years, the SIR 95% CI was 0 to 3.0. Thus, the study was adequate in size to exclude up to a 3-fold risk of osteosarcoma. A 3-fold risk increase would equate to an absolute risk increase of approximately one additional case per 185,000 patient-years observed.
A Population-Based Comparative-Cohort Study using Medicare Part D Prescription Claims (Gilsenan, 2020)	Overall, 153,316 patients who were teriparatide users and 613,247 patients in a comparator cohort were linked to 811 osteosarcoma cases from 26 participating cancer registries (covering 68% of US osteosarcoma cases in patients ≥ 65 years of age diagnosed from 2007-2014). Teriparatide users and comparator users were balanced for known osteosarcoma risk factors and Charlson comorbidity index.	The mean duration of teriparatide treatment was 10 months. No osteosarcoma cases were observed among the teriparatide users.

Risk factors and risk groups:

In elderly patients, osteosarcoma is often considered a secondary neoplasm attributed to the sarcomatous transformation of Paget's disease of bone (Mirabello, 2009).

Exposures to radiation therapy, alkylating agents, could increase the chance of secondary osteosarcoma (Mirabello, 2009 Wu, 2012).

Preventability:

The SmPC includes in section 4.3 'Contraindications' circumstances in which abaloparatide should not be used due to an increased risk of osteosarcoma including: patients with unexplained elevations of serum alkaline phosphatase, patients with known risks for osteosarcoma such as those who have received prior external beam or implant radiation therapy involving the skeleton, and patients with skeletal malignancies or bone metastases. Moreover, the SmPC indicates in section 4.2 'Posology and method of administration' that abaloparatide should not be used in children and adolescents less than 18 years because of safety concerns. In addition, section 4.2 'Posology and method of administration' of the SmPC states that the maximum total duration of treatment with abaloparatide should be 18 months. Section 4.4 'Special warnings and precautions for use' of the SmPC also states that the maximum duration of treatment with abaloparatide should be 18 months and includes an additional statement that an increased risk of osteosarcoma was observed in rats following long-term administration of abaloparatide. Furthermore, section 5.3 'Preclinical safety data' includes preclinical safety data from a 2-year rat carcinogenicity study related to osteosarcoma. Risk minimisation measures for this risk are detailed in Part V.

Impact on the risk-benefit balance of the product:

Osteosarcoma is a debilitating and life-threatening disease that may require patients to undergo limb amputations and is associated with poor long-term survival. Most patients who present with osteosarcoma of the extremities complain of pain prior to soft tissue swelling. Symptoms also depend on where the cancer has spread to. The most common site of spread for this cancer is the lungs.

Currently, the impact on the risk-benefit from drug-related osteosarcoma is expected to be minimal. No clinical cases have been identified with abaloparatide treatment, and the incidence with over 15 years' experience with teriparatide is not increased over that expected in the population.

Public health impact:

Osteosarcoma per se does not have public health impact.

Important Potential Risk: Serious cardiovascular events (i.e. MACE, arrhythmia)

Potential mechanisms:

PTH and PTHrP can cause vascular smooth muscle relaxation, resulting in nonsignificant effects on blood pressure and an increase in the incidence of symptoms such as palpitations, nausea, and dizziness. Although, there were no safety signal in regard to serious cardiovascular events in the pivotal study, there is a potential for serious cardiovascular events (i.e. MACE, arrhythmia) due to transient increase in heart rate.

Evidence source(s) and strength of evidence:

In clinical pharmacology studies, abaloparatide has been associated with dose-dependent increase in heart rate which developed within 15 minutes after injection and resolved in about 6 hours. In clinical studies, pre-dose heart rates were similar to baseline values and post-dose heart rate increases were similar across visits indicating no cumulative effect on heart rate. In the Pivotal clinical study (ACTIVE-study BA058-05-003), treatment with abaloparatide and teriparatide resulted in a transient increase in heart rate and a small decrease in 1-hour post-dose blood pressure. Potential clinical consequences of the observed increase in heart rate included an increase in the incidence of reports of tachycardia and reports of palpitations compared with placebo, but there was no difference in the incidence of other cardiovascular events across the treatment groups.

In study BA058-05-003 there were no reports of adverse events of increased heart rate as a single Preferred Term (PT) in any of the treatment groups. The events of tachycardia, including sinus tachycardia, were reported in 1.6% of patients receiving abaloparatide and 0.4% of patients in the placebo group in study BA058-05-003.

Characterisation of the risk:

- Clinical data:

Frequency with 95 % CI:

Proportion of patients experiencing treatment-emergent MACE, HF and Cardiovascular (CV) death.

The following Medical Dictionary for Regulatory Activities (MedDRA) terms were used for MACE: acute myocardial infarction, cerebrovascular accident, haemorrhage intracranial, ischemic stroke, lacunar infarction, myocardial infarction; for HF: cardiac failure, cardiac failure chronic, cardiac failure congestive; and for CV death: cardio-respiratory arrest, myocardial ischemia, sudden death.

Study BA058-05-003 (19 months):

MACE (including CV death):

Abaloparatide (3/694): 0.4% [0.5 (95% CI: 0.18, 1.69)]*

Teriparatide (5/686): 0.7% [0.8 (95% CI: 0.34, 1.96)]*

Placebo (8/687): 1.2% [1.4 (95% CI: 0.69,2.75)]*

*K-M Estimated event rate (95% CI).

Hazard Ratio (HR) (95% CI) vs placebo: Abaloparatide: 0.4 (0.10, 1.47); Teriparatide: 0.6 (0.20, 1.89).

HR (95% CI) vs teriparatide: Abaloparatide: 0.63 (0.15, 2.63).

p-value vs placebo: Abaloparatide: 0.15; Teriparatide: 0.40.

p-value vs teriparatide: Abaloparatide: 0.52.

MACE and Heart Failure (including CV death):

Abaloparatide (3/694): 0.4% [0.5 (95% CI: 0.18, 1.69)]*

Teriparatide 5/686: 0.7% [0.8 (95% CI: 0.34, 1.96)]*

Placebo (12/687): 1.7% [2.1 (95% CI: 1.18, 3.63)]*

*K-M Estimated event rate (95% CI).

HR (95% CI) vs placebo: Abaloparatide: 0.26 (0.07, 0.92); Teriparatide: 0.41 (0.14, 1.17).

HR (95% CI) vs teriparatide: Abaloparatide: 0.63 (0.15, 2.63).

p-value vs placebo: Abaloparatide: 0.02; Teriparatide: 0.08.

p-value vs teriparatide: Abaloparatide: 0.52.

Study BA058-05-005: 24 months (BA058-05-005 baseline)

MACE:

Placebo/Alendronate (5/493): 1.0% [1.1 (0.46, 2.63)] *

Abaloparatide/Alendronate (5/465): 1.1% [1.1 (0.47, 2.68)]*

*K-M Estimated event rate (95% CI).

HR (95% CI): Abaloparatide/Alendronate: 1.04 (0.30, 3.61).

p-value: Abaloparatide/Alendronate: 0.95.

MACE and HF:

Placebo/Alendronate (7/493): 1.4% [1.5 (0.74, 3.20)]*

Abaloparatide/Alendronate (7/465): 1.5% [1.6 (0.75, 3.27)]*

*K-M Estimated event rate (95% CI).

HR (95% CI): Abaloparatide/Alendronate: 1.04 (0.37, 2.98).

p-value: Abaloparatide/Alendronate: 0.94.

Study BA058-05-005: 43 months (Study BA058-05-003 baseline)

MACE:

Placebo/Alendronate (13/687): 1.9% [2.5 (1.44, 4.25)]

Abaloparatide/Alendronate (8/694): 1.2% [1.7 (0.83, 3.32)]

*K-M Estimated event rate (95% CI).

HR (95% CI): Abaloparatide/Alendronate: 0.64 (0.27, 1.54).

p-value: Abaloparatide/Alendronate: 0.32.

MACE and HF:

Placebo/Alendronate (19/687): 2.8% [3.6 (2.3, 5.60)]*

Abaloparatide/Alendronate (10/694): 1.4% [2.1 (1.14, 3.90)]*

*K-M Estimated event rate (95% CI).

HR (95% CI): Abaloparatide/Alendronate: 0.55 (0.25, 1.17).

p-value: Abaloparatide/Alendronate: 0.12.

Seriousness/outcomes

In study BA058-05-003 after 19 months, including 18 months of treatment with abaloparatide 80 micrograms daily and 1 months of follow-up period, the incidence of at least one serious cardiovascular adverse event (i.e., MACE) was reported in 8/687 (1.2%), 3/694 (0.4%) and 5/686 (0.7%) of subjects in placebo, abaloparatide and teriparatide treatment arms, respectively. In each treatment group one subject died due to a cardiovascular event. In the placebo treatment arm of a total 8 subjects, in 6 subjects MACE adverse events (AEs) were reported as serious (1 AE of cerebrovascular accident, 3 AEs of ischemic stroke, 1 AE of myocardial infarction, and 1 AE of sudden death), and 2 AEs of cerebrovascular accident were reported as non-serious. In the abaloparatide group of a total 3 subjects in 2 subjects MACE AEs were reported as serious (1 AE of intracranial haemorrhage, and 1 AE of myocardial ischemia which resulted in a fatal outcome, and 1 AE of lacunar infarction reported as non-serious). In the teriparatide group, in all 5 subjects MACE AEs were considered as serious (1 AE of each: acute myocardial infarction, myocardial infarction, cerebrovascular accident, lacunar infarction, and cardio-respiratory arrest which resulted in a fatal outcome).

Following review of heart failure AEs in addition to MACE AEs the number of subjects in abaloparatide and teriparatide groups remained the same, i.e. 3 and 5 subjects, respectively. However, in teriparatide group 1 of 5 subjects reported an additional non-serious AE of cardiac failure. In placebo treatment arm, a total of 12 subjects reported a total of 13 AEs (8 MACE and 5 heart failure AEs). Of the 5 heart failure AEs, 1 one was reported as serious (congestive heart failure), and the remaining 4 AEs were reported as non-serious (3 AEs heart failure and 1 AE of chronic heart failure).

Study BA058-05-005 is an extension study to study BA058-05-003. In this study subjects who were previously receiving either placebo (N= 493) or abaloparatide (N= 465), transferred to subsequent alendronate treatment once weekly for additional 24 months. At the end of 24 months of alendronate treatment 5 subjects in each treatment group reported at least one MACE AE. In the placebo/alendronate group the reported AEs were: 2 AEs of cerebrovascular accident, and one AE of acute myocardial infarction, myocardial infarction and ischemic stroke. In the abaloparatide/alendronate group the reported AEs were: 2 AEs of ischemic stroke, and 1 AE of myocardial infarction, basal ganglia stroke, and cerebral thrombosis. None of the cardiovascular AEs in both treatment groups resulted in a fatal outcome.

Following review of AEs of HF in addition to MACE AEs, at the end of the 24 months of alendronate treatment, there were 7 subjects in each treatment group who reported at least one AE of MACE+HF. Two subjects in the placebo/alendronate treatment group reported 2 AEs of congestive heart failure, and in the abaloparatide/alendronate treatment group 2 subjects reported 2 AEs of cardiac failure. None of these AEs resulted in a fatal outcome.

- Post-marketing data:

As per the latest PBRER (DLP 27 April 2022) describing cumulative post-marketing experience since the abaloparatide launch in 2017 in the US, a total of 1,258 adverse events of 'heart rate increased' were received of which 1,252 were non-serious and 6 were serious. Symptoms potentially associated with

increased heart rate include palpitations, tachycardia, and dizziness; during the post-marketing period a total of 1,206 adverse events of palpitations were received, 1,201 non-serious and 5 serious, 167 adverse events of tachycardia, 160 non-serious and 7 serious, and 1,836 adverse events of dizziness, 1,829 non-serious and 7 serious.

In addition, reports of serious MACE are closely monitored on an ongoing basis and reports are prepared quarterly. The following search criteria is used to identify events of MACE, HF, and arrhythmia-related events.

- MACE + HF: Acute myocardial infarction, basal ganglia stroke, cerebral thrombosis, cerebrovascular accident, haemorrhage intracranial, ischaemic stroke, lacunar infarction, left ventricular failure, myocardial infarction, cardiac failure, cardiac failure chronic, and cardiac failure congestive
- Fatal adverse events in the Cardiac disorders and Vascular disorders System Organ Classes (SOCs),
- PT of Sudden death
- Arrhythmia-related Events:

- SMQ Supraventricular tachyarrhythmias (narrow scope)
- SMQ Tachyarrhythmia terms, non-specific (narrow scope)

In addition, the search was conducted to identify any PT sudden death or fatal cases that could be potentially due to MACE or HF.

As of 31 March 2022, a total of 57 case reports of MACE+HF events were reported, consisting of 60 MACE+HF events (myocardial infarct 23, cardiac failure congestive 8, cerebrovascular accident 29). Approximately 34 of 57 (60.0%) cases reported medical histories with significant CV comorbidities such as hypertension, coronary artery disease, myocardial infarction, stroke, diabetes mellitus, and obstructive sleep apnoea. Seven of the 57 (12.3%) cases reported fatal outcomes after experiencing MACE or HF event. Five fatal cases were confounded by patients' concurrent illnesses or prior medical history of cardiac or pulmonary disorders and 2 cases provided a very limited information, which precluded a full medical assessment. In addition, no disproportionality signal was identified in the FDA Adverse Event Reporting System (FAERS) database for serious CV events with abaloparatide. Moreover, the review of recently completed clinical trial and post-marketing data reporting arrythmia-related events did not identify any safety signals and concluded that there was insufficient evidence of an association of arrythmia-related events with abaloparatide treatment at this time.

- Study BA058-05-019 and Study BA058-05-021[5]:

Overall, in recently completed studies (BA058-05-019 and Study BA058-05-021) there were 14 cases reporting a total of 15 CV or arrythmia-related events (myocardial infarction (2); CVA (1); Cardiac failure (3); supraventricular tachycardia (3), supraventricular extrasystoles (1), atrial fibrillation (4), and cardiac flutter (1)). Of these, 5 were serious, and none (0) of the events were fatal. One subject experienced 2 events. Subject ages ranged between 63 and 83-years. Onset latency of all but 1 event was between 5.5 and 12.5 months. Most events (13/15) were assessed as not related or unlikely related to study drug. Contributing factors in almost of the cases included underlying cardiac conditions and/or other comorbidities (such as diabetes) and the subjects were treated for these conditions with multiple concomitant medications. One serious event was assessed as probably related to study drug and after unblinding the subject it was determined that the subject was randomized to the placebo arm. Seven

[5] Data from Study BA058-05-019 and Study BA058-05-021 added for a completeness of information. These two studies are not included in this submission.

subjects continued study drug at the same prescribed dose post event. The review of MACE + HF and arrythmia-related events reported in these large, completed studies did not identify any new safety signals in regard to serious cardiovascular events with abaloparatide treatment.

- Study BA058-05-028:

A retrospective, observational cohort study was conducted of which the secondary objective was to evaluate the cardiovascular safety of abaloparatide for the treatment of osteoporosis in postmenopausal women in the real-world healthcare setting in the USA compared with teriparatide using the same cohort of PS-matched patients. A total of 78,086 patients were identified during the index period for this study with 17,071 and 61,015 in the abaloparatide and teriparatide cohorts, respectively. PS-matching yielded 11,027 patients in each treatment cohort. For the secondary endpoint, the risk of the composite endpoint of MI/stroke/hospital CV death from the beginning of the index period through 19 months was similar between the abaloparatide and teriparatide cohorts [HR (95% CI): 1.08 (0.89, 1.30)]. Similarly, the risk of new events of the composite endpoints of MI/stroke/heart failure/hospital CV death from the beginning of the index period was similar between the abaloparatide and teriparatide cohorts [HR (95% CI): 1.08 (0.95, 1.22)]. Subgroup analyses were performed on 4 prespecified risk groups (i.e., age, race/ethnicity, prior CV risk factors, and prior history of MI or stroke) and, in general, outcomes were consistent among all subgroups when compared to the overall CV event data. Sensitivity analyses to evaluate possible overestimation of the first post-index incidence of MI, stroke, or heart failure was defined as having no previous diagnosis of MI, stroke, or heart failure in the 183 days preceding the first post-index event. In general, outcomes were consistent among sensitivity analyses including various treatment durations and different composite endpoint definitions. Overall, cardiovascular safety based on the composite endpoints (MI/stroke/CV death with or without heart failure) and individual cardiovascular events was similar in patients treated with abaloparatide and teriparatide.

Risk factors and risk groups:

Patients with significant cardiovascular disease may be at increased risk of serious MACE.

Preventability:

The SmPC includes in section 4.2 'Posology and method of administration' a statement about the appropriate administration. In section 4.4 'Special warnings and precautions for use', a warning for 'orthostatic hypotension and increased heart rate' is mentioned and indicating the measures to be assessed prior to beginning abaloparatide treatment as well as instruction for monitoring potential adverse events and action to be taken in case they occur. A statement about the concomitant use of vasoactive medicinal products that may predispose to orthostatic hypotension since the blood pressure lowering effect of abaloparatide may be increased is pointed out in section 4.5 'Interaction with other medicinal products and other forms of interaction'. The SmPC includes as cardiac disorders: palpitations and tachycardia, in the tabulated list of adverse reactions as well as description of the adverse reaction: increased heart rate in section 4.8 'Undesirable effects'. In addition, the SmPC includes palpitations and orthostatic hypotension as effects of overdose of the Eladynos in section 4.9 'Overdose'. Risk minimisation measures for this risk are detailed in Part V. Moreover, section 5.3 on 'Preclinical safety data' describes the cardiovascular results from a safety pharmacology study.

Impact on the risk-benefit balance of the product:

Cardiovascular disease can cause significant disability and may negatively impact the patient's quality of life. Other than transient palpitations and tachycardia, the cardiovascular risk evaluated as MACE in subjects receiving abaloparatide has been demonstrated to be lower than that in the placebo population. Therefore, the impact on the risk-benefit is expected to be minimal.

Public health impact:

Minimal impact.

SVII.3.2. Presentation of the missing information

None.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Osteosarcoma Serious cardiovascular events (i.e. MACE, arrhythmia)
Missing information	None

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

III.1 Routine pharmacovigilance activities

All safety concerns will be monitored via routine pharmacovigilance activities.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for Osteosarcoma:

Purpose and Description: To identify reports of osteosarcoma from all sources in order to best capture all pertinent data

This follow-up questionnaire is presented in Annex 4.

Other forms of routine pharmacovigilance activities for Osteosarcoma and Serious cardiovascular events (i.e. MACE, arrhythmia):

Cumulative reviews of cases reporting osteosarcoma and cumulative reviews of cases reporting serious cardiovascular events (i.e. MACE, arrhythmia) will be included in each PBRER/Periodic Safety Update Report (PSUR).

The primary objective is to identify reports of osteosarcoma or serious cardiovascular events (i.e. MACE, arrhythmia) from all sources (clinical trials, spontaneous reports from healthcare professionals and patients, post-marketing surveillance, literature sources). In addition, FAERS, EudraVigilance, and the WHO VigiBase database will be queried every 6 months to identify any reported cases of osteosarcoma by healthcare providers or patients. This review will include interval and cumulative data of all cases in the PBRER/PSUR.

III.2 Additional pharmacovigilance activities

The Applicant will conduct an EU-based registry PASS to further evaluate a potential risk of serious cardiovascular events (i.e. MACE, arrhythmias) with abaloparatide.

Abaloparatide PASS summary

Study short name and title:

European non-interventional post-authorization safety study (PASS) to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide.

Rationale and study objectives:

Abaloparatide treatment is associated with transient increases in heart rate, which in the pivotal study BA058-05-003 were of mild to moderate severity. These transient increases in heart rate were not associated with an increased number of serious cardiovascular events (MACE) or arrhythmias, neither in the clinical developmental program, nor in the retrospective observational cohort study (BA058-05-028), nor from the five and half years of post-marketing experience.

However, due to the increase in heart rate associated with abaloparatide treatment, serious CV events of MI, stroke and arrhythmia are identified as potential safety risks in the EU-RMP for abaloparatide.

To evaluate the potential risk of serious CV events of MI, stroke, all-cause mortality including CV death and arrhythmias associated with the use of abaloparatide in routine clinical practice compared with other

available Osteoporosis (OP) medications, a European multi-national, multi-database, comparative PASS is planned and will be conducted as an additional pharmacovigilance activity.

Specific objectives of the study are as follows:

1. To assess the Incidence Rate (IR) of serious CV events (MI and stroke), all-cause mortality including CV death, and arrhythmias in abaloparatide users in the indicated population in Europe as per the SmPC, and in cohorts of users of other available OP medications, who would also fulfil the indication/contraindications for abaloparatide in Europe;

2. To assess the IR of serious CV events (MI and stroke), all-cause mortality including CV death, and arrhythmias in abaloparatide users in the indicated population in Europe as per the SmPC and amongst users of other available OP medications, similar to the indicated population for abaloparatide in Europe as per the SmPC, stratified by age, previous use of OP medications, and by prespecified key CV risk factors;

3. To assess the comparative risk of CV events (MI and stroke), all-cause mortality including CV death and arrhythmias in abaloparatide users in the indicated population in Europe as per the SmPC to users of an active comparator with similar baseline characteristics.

Study design:

This will be a non-interventional, multi-national, multi-database cohort study of new users of abaloparatide and new users of other available OP medications. The study period is expected to last for approximately 6 years (2023 to 2029).

Study population:

The study population comprises all postmenopausal women with severe osteoporosis who are dispensed or prescribed an OP medication of interest for the first time (new user) during the study period, who have been continuously registered in the participating data source for at least 12 months prior to the first recorded dispensing/prescription of the OP medication of interest, and are at least 50 years of age on the date of the first dispensing/prescription of the OP medication of interest. Women with a diagnosis of cancer (any except basal cell skin cancer) at any time before treatment initiation will be excluded. New users will be followed for a maximum of 19 months (18 months of treatment plus 1 month of follow-up) from index therapy initiation (index date).

Milestones:

The Applicant will provide the final PASS protocol within 3 months post abaloparatide approval in Europe. Interim reports will be provided on an annual basis, until the final study report is submitted. Upon the minimum sample size being reached, the comparative safety analysis will be conducted and reported as part of the next interim and/or final report/s.

Tabulated summary of planned, on-going and completed pharmacovigilance study programme is provided in Annex 2.

A synopsis of the planned PASS study is provided in Annex 3.

III.3 Summary Table of additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Abaloparatide PASS: European non-interventional post-authorization safety study (PASS) to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide. Planned	To evaluate the potential risk of serious CV events of MI, stroke, all-cause mortality including CV death and arrhythmias associated with the use of abaloparatide in routine clinical practice compared with other available OP medications	Serious cardiovascular events (i.e. MACE, arrhythmia)	Final PASS protocol submission	Within 3 months post abaloparatide approval
			Interim reports on an annual basis	For the entire study period until the final study report is submitted
			Final report	2029-2030

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies have been imposed.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
Osteosarcoma (Important potential risk)	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.2 and in Package Leaflet (PL) section 2 indicate that abaloparatide should not be used in children and adolescents less than 18 years because of safety concerns and that the maximum total duration of treatment with abaloparatide should be 18 months. SmPC section 4.3 and in PL section 2 include contraindications to the use of the product in the following situations: patients with unexplained elevations of serum alkaline phosphatase; patients with known risk for osteosarcoma such as those who have received prior external beam or implant radiation therapy involving the skeleton; patients with skeletal malignancies or bone metastases. SmPC section 4.4 and PL section 3 states that the maximum duration of treatment with abaloparatide should be 18 months and includes an additional statement that an increased risk of osteosarcoma was observed in rats following long-term administration of abaloparatide. SmPC section 5.3 includes preclinical safety data from a 2-year rat carcinogenicity study related to osteosarcoma. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.
Serious cardiovascular events (i.e. MACE, arrhythmia) (Important potential risk)	Routine risk communication: SmPC section 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.2 and PL section 3 include a statement about the appropriate administration. SmPC Section 4.4 and PL section 2 include warnings for orthostatic hypotension and increased heart rate describing the risk, indicating the measures to be assessed prior to beginning abaloparatide treatment and instruction for monitoring potential adverse events and action to be taken in case they occur. SmPC section 4.5 and PL section 2 include a statement about the concomitant medication affecting blood pressure. SmPC section 4.9 and PL section 3 include palpitations and orthostatic hypotension as effects of abaloparatide overdose that might be expected.

Safety concern	Routine risk minimisation activities
	SmPC section 5.3 describes the cardiovascular results from a safety pharmacology study. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine.

V.2. Additional Risk Minimisation Measures

All safety concerns can be mitigated or minimized via the information language provided in the EU SmPC and PL. Thus, no additional risk minimization measures are proposed at this time.

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Osteosarcoma (Important potential risk)	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 5.3. PL section 2, 3. Legal status: Prescription only medicine. Additional risk minimization activities: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for osteosarcoma. Other forms of routine pharmacovigilance activities for Osteosarcoma: Cumulative reviews of cases reporting osteosarcoma will be prepared and included in each PBRER/PSUR. Additional pharmacovigilance activities: None
Serious cardiovascular events (i.e. MACE, arrhythmia) (Important potential risk)	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5, 4.8, 4.9 and 5.3. PL sections 2, 3, 4. Legal status: Prescription only medicine Additional risk minimization activities: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Other forms of routine pharmacovigilance activities for Serious cardiovascular

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		events (i.e. MACE, arrhythmia): Cumulative reviews of cases reporting serious cardiovascular events (i.e. MACE, arrhythmia) will be prepared and included in each PBRER/PSUR. Additional pharmacovigilance activities: Abaloparatide PASS: European non-interventional PASS to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide. Final study report due date: 2029-2030

Part VI: Summary of the risk management plan

Summary of risk management plan for Eladynos 80 micrograms/dose solution for injection in pre-filled pen (abaloparatide).

This is a summary of the risk management plan (RMP) for Eladynos 80 micrograms/dose solution for injection in pre-filled pen. The RMP details important risks, how these risks can be minimised, and how more information will be obtained for risks and uncertainties (missing information).

Eladynos 80 micrograms/dose solution for injection in pre-filled pen's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Eladynos 80 micrograms/dose solution for injection in pre-filled pen should be used.

This summary of the RMP for Eladynos 80 micrograms/dose solution for injection in pre-filled pen 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 Eladynos 80 micrograms/dose solution for injection in pre-filled pen's RMP.

I. The medicine and what it is used for

Eladynos 80 micrograms/dose solution for injection in pre-filled pen is authorised for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. It contains abaloparatide as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Eladynos 80 micrograms/dose solution for injection in pre-filled pen’s benefits can be found in Eladynos 80 micrograms/dose solution for injection in pre-filled pen’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage https://www.ema.europa.eu/en/medicines/human/EPAR/eladynos.

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

Important risks of Eladynos 80 micrograms/dose solution for injection in pre-filled pen together with measures to minimise such risks and the proposed studies for learning more about Eladynos 80 micrograms/dose solution for injection in pre-filled pen's risks, are outlined below.

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

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

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

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

II.A List of important risks and missing information

Important risks of Eladynos 80 micrograms/dose solution for injection in pre-filled pen are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Eladynos 80 micrograms/dose solution for injection in pre-filled pen. 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	None
Important potential risks	Osteosarcoma Serious cardiovascular events (i.e. MACE, arrhythmia)
Missing information	None

II.B Summary of important risks

Important identified risk:

None.

Important potential risk 1: Osteosarcoma	
Evidence for linking the risk to the medicine	In the general population, osteosarcoma is the most common nonhematological primary bone malignancy, however its incidence is rare (Cipriani, 2012). The incidence of osteosarcoma has a biphasic trend by age, with a first peak around puberty and a smaller peak in subjects over 60 years of age (Cipriani, 2012). The number of cases per million per year ranges worldwide between 3 and 4.5 in childhood and adolescence, 2 in individuals 25 to 59 years old, and 1.5 to 4.5 in subjects over the age of 60 years. The exaggerated anabolic response in rats indicates a significant anabolic stimulus driving osteoblast activity, likely stimulating a proliferative response (or preventing osteoblast apoptosis) (Jilka, 1999; Schnoke, 2009), and leading to an abnormal accumulation of osteoblasts, and osteosarcomas, in rodents. The differences in bone metabolism between rodents and primates likely explain why the high incidence of osteosarcomas observed in rats has not been observed in monkeys and in humans. A limited number of monkeys have been exposed to abaloparatide during the development programme at doses up to 70 µg/kg (with a protocol defined reduction to 50 µg/kg) for 39 weeks and 5 µg/kg for 16 months. In these studies, no neoplasms were noted.

Important potential risk 1: Osteosarcoma	
	Studies in rats indicate an increased incidence of osteosarcoma with long-term administration of abaloparatide. The relevance of these rat findings to humans is uncertain, thus the use of abaloparatide should be avoided for patients at increased risk of osteosarcoma. During the post-marketing surveillance, no cases of osteosarcoma have been reported with abaloparatide treatment and no increase in the incidence of osteosarcoma has been identified with teriparatide treatment in the post-marketing studies.
Risk factors and risk groups	In elderly patients, osteosarcoma is often considered a secondary neoplasm attributed to the sarcomatous transformation of Paget's disease of bone (Mirabello, Troisi, & Savage, 2009). Exposures to radiation therapy, alkylating agents, could increase the chance of secondary osteosarcoma (Mirabello, 2009; Wu, 2012).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 and in PL section 2 indicate that abaloparatide should not be used in children and adolescents less than 18 years because of safety concerns. SmPC section 4.3 and in PL section 2 include contraindications to the use of the product in the following situations: patients with unexplained elevations of serum alkaline phosphatase; patients with known risks for osteosarcoma such as those who have received prior external beam or implant radiation therapy involving the skeleton; patients with skeletal malignancies or bone metastases. SmPC section 4.4 and PL section 3 states that the maximum duration of treatment with abaloparatide should be 18 months and includes an additional statement that an increased risk of osteosarcoma was observed in rats following long-term administration of abaloparatide. SmPC section 5.3 includes preclinical safety data from a 2-year rat carcinogenicity study related to osteosarcoma. Legal status: Prescription only medicine. Additional risk minimisation measures: None

Important potential risk 2: Serious cardiovascular events (i. e. MACE, arrhythmia)	
Evidence for linking the risk to the medicine	The prevalence of palpitations in elderly (60 to 94 years) has been reported as 8.3% (Lok, 1996). Transient increase in heart rate may occur with abaloparatide, which may resolve in few hours. In women with postmenopausal osteoporosis, adverse reactions of tachycardia, including sinus tachycardia, were reported in 1.6% of patients receiving abaloparatide and 0.4% of patients in the placebo group. In the QT/QTc study, abaloparatide has been associated with a dose-dependent increase in heart rate which developed within 15 minutes after injection and resolved in about 6 hours.

Important potential risk 2: Serious cardiovascular events (i. e. MACE, arrhythmia)	
	Although, abaloparatide treatment did not increase the risk of having a serious cardiovascular event (i.e. MACE, arrhythmia), the potential exists due to abaloparatide causing transient increase in heart rate.
Risk factors and risk groups	Patients with significant cardiovascular disease may be at increased risk of cardiac events.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 PL section 4. SmPC section 4.2 and PL section 3 include a statement about the appropriate administration. SmPC section 4.4 and PL section 2 include warnings for orthostatic hypotension and increased heart rate describing the risk, measures to be assessed prior to beginning abaloparatide treatment and instruction for monitoring potential adverse events and action to be taken in case they occur. SmPC Section 4.5 and PL section 2 include a statement about the concomitant medication affecting blood pressure. SmPC section 4.9 and PL section 3 include palpitations and orthostatic hypotension as effects of abaloparatide overdose that might be expected. SmPC section 5.3 describes the cardiovascular results from a safety pharmacology study. Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Abaloparatide PASS: European non-interventional PASS to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide .

Missing information:

None.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Eladynos 80 micrograms/dose solution for injection in pre-filled pen.

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

Abaloparatide PASS:

Study short name and title: European non-interventional PASS to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide .

Purpose of the study:

Abaloparatide treatment is associated with transient increases in heart rate, which in the pivotal study BA058-05-003 were of mild to moderate severity. These transient increases in heart rate were not associated with an increased number of serious cardiovascular events (MACE) or arrhythmias, neither in the clinical developmental program, nor in the retrospective observational cohort study (BA058-05-028), nor from the five and half years of post-marketing experience

However, due to the increase in heart rate associated with abaloparatide treatment, serious CV events of MI, stroke and arrhythmia are identified as potential safety risks in the EU-RMP for abaloparatide.

To evaluate the potential risk of serious CV events of MI, stroke, all-cause mortality including CV death and arrhythmias associated with the use of abaloparatide in routine clinical practice compared with other available OP medications, a European multi-national, multi-database, comparative PASS is planned and will be conducted as an additional pharmacovigilance activity.

Specific objectives of the study are as follows:

1. To assess the IR of serious CV events (MI and stroke), all-cause mortality including CV death, and arrhythmias in abaloparatide users in the indicated population in Europe as per the SmPC, and in cohorts of users of other available OP medications, who would also fulfil the indication/contraindications for abaloparatide in Europe;

2. To assess the IR of serious CV events (MI and stroke), all-cause mortality including CV death, and arrhythmias in abaloparatide users in the indicated population in Europe as per the SmPC and amongst users of other available OP medications, similar to the indicated population for abaloparatide in Europe as per the SmPC, stratified by age, previous use of OP medications, and by prespecified key CV risk factors;

3. To assess the comparative risk of CV events (MI and stroke), all-cause mortality including CV death and arrhythmias in abaloparatide users in the indicated population in Europe as per the SmPC to users of an active comparator with similar baseline characteristics.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Abaloparatide PASS: European non-interventional post-authorization safety study (PASS) to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide. Planned	To evaluate the potential risk of serious CV events of MI, stroke, all-cause mortality including CV death and arrhythmias associated with the use of abaloparatide in routine clinical practice compared with other available OP medications	Serious cardiovascular events (i.e. MACE, arrhythmia)	Final PASS protocol submission	Within 3 months post abaloparatide approval
			Interim reports on an annual basis	For the entire study period until the final study report is submitted
			Final report	2029-2030

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

A synopsis of the planned PASS study is presented as follows:

Title of Study: European non-interventional post-authorization safety study (PASS) to assess serious cardiovascular events of myocardial infarction (MI), stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide.	
Protocol number:	TBD
Version number:	TBD
Date of latest version of protocol:	TBD
EU PAS register number:	Study not registered, but will be registered upon approval of the protocol
Procedure number:	EMEA/H/C/005928/0000
Marketing Authorization Holder of Eladynos	Radius Health Ireland Limited
Phase of development:	IV, non-interventional study
Active substance:	Abaloparatide
Studied medicinal products:	Eladynos
Indication:	Treatment of osteoporosis in postmenopausal women at increased risk of fracture.
Rationale and background Abaloparatide treatment is associated with transient increases in heart rate, which in the pivotal study BA058-05-003 were of mild to moderate severity. These transient increases in heart rate were not associated with an increased number of serious cardiovascular events (MACE) or arrhythmias, neither in the clinical developmental program, nor in the retrospective observational cohort study (BA058-05-028), nor from the five and half years of post-marketing experience. However, due to the increase in heart rate associated with abaloparatide treatment, serious CV events of MI, stroke and arrhythmia are identified as potential safety risks in the European Union (EU)-Risk Management Plan (RMP) for abaloparatide. To further characterize these potential safety risks and the potential risk of arrhythmias for abaloparatide treatment, a post authorisation safety study is planned as an additional pharmacovigilance activity.	
Objectives: To evaluate the potential risk of serious cardiovascular (CV) events of myocardial infarction (MI), stroke, all-cause mortality including CV death and arrhythmias associated with the use of abaloparatide in routine clinical practice compared with other available osteoporosis (OP) medications, a European multi-national, multi-database, comparative PASS will be conducted. Specific objectives of the study are as follows: 1. To assess the incidence rate (IR) of serious CV events (MI and stroke), all-cause mortality including CV death, and arrhythmias in abaloparatide users in the indicated population in Europe as per the Summary of Product Characteristics (SmPC), and in cohorts of users of other available OP medications, who would also fulfil the indication/contraindications for abaloparatide in Europe; 2. To assess the IR of serious CV events (MI and stroke), all-cause mortality including CV death, and arrhythmias in abaloparatide users in the indicated population in Europe as per the SmPC and amongst users of other available OP medications, similar to the indicated population for abaloparatide in Europe as per the SmPC, stratified by age, previous use of OP medications, and by prespecified key CV risk factors; 3. To assess the comparative risk of CV events (MI and stroke), all-cause mortality including CV death and arrhythmias in abaloparatide users in the indicated population in Europe as per the SmPC to users of an active comparator with similar baseline characteristics;	
Study Design:	

This will be a non-interventional, multi-national, multi-database cohort study of new users of abaloparatide and new users of other available OP medications. The study period is expected to last for approximately 6 years (2023 to 2029).
Population: The study population comprises all postmenopausal women with severe osteoporosis who are dispensed or prescribed an OP medication of interest for the first time (new user) during the study period, who have been continuously registered in the participating data source (see "Data sources" below) for at least 12 months prior to the first recorded dispensing/prescription of the OP medication of interest, and are at least 50 years of age on the date of the first dispensing/prescription of the OP medication of interest. Women with a diagnosis of cancer (any except basal cell skin cancer) at any time before treatment initiation will be excluded. New users will be followed for a maximum of 19 months (18 months of treatment plus 1 month of follow-up) from index therapy initiation (index date). Two Follow-up Periods will be included for the estimation of CV IRs: an Exposure-based Follow-up Period and a Fixed (first exposure carried forward) Follow-up Period. For the Exposure-based Follow-up Period analysis, participants will be followed until first occurrence of the CV event of interest, discontinuation of the study drug of interest, switching or addition of any other OP medication (except calcium/vitamin D supplements), lost to follow-up, death, end of the 18 months after therapy initiation (as per the abaloparatide SmPC), or end of the study period/data extraction date. At the point of switching treatment a patient is censored for that arm of the study in this analysis. For the Fixed Follow-up Period, participants will be followed in their respective cohorts until first occurrence of lost to follow-up, CV event of interest, death, or end of the study period. In this analysis, patients are followed for up to 19 months regardless of whether they stop treatment or switch to a new treatment.
Variables: The OP medications of interest include abaloparatide and other available OP medications and a primary active comparator. Primary outcome is a major adverse cardiac event(s) (MACE-2), (first occurrence of death [all cause], MI, or stroke). Secondary outcomes are MI, stroke, death due to CV causes, all-cause mortality, and MACE-1 (first occurrence of death due to CV causes, MI or stroke). Third outcome is adverse events of arrhythmias which will be derived from medical visits and hospitalization records. Other covariates and potential confounding factors will be identified at cohort entry (index date) based on the patients' records in the previous 12 months (Baseline Period), and will include general patient characteristics, including alcohol and tobacco use, CV risk factors, markers of OP severity, use of other medications, and relevant family medical history regarding CV risk factors.
Data sources: This study is planned to be conducted using routinely collected data from different data sources, including countries that participate in the EU-ADR Alliance (Denmark, Italy, The Netherlands, Spain and UK), with the addition of databases from the UK (Clinical Practice Research Datalink [CPRD] GOLD), Germany (German Pharmacoepidemiological Research Database [GePaRD]), and France (Système National Des Données de Santé [SNDS] database). Participants from 7 European countries will provide heterogeneous and representative data on the safety of abaloparatide as well as ensuring sufficient precision of estimation for the study.
Study size: Feasibility estimates demonstrate the capability of the consortium and the data sources to capture a sufficient sample of patients in each OP medication group. The number of users of each OP medication needed to obtain a 95% confidence interval (CI) of the risk ratio of the incidence rates will be calculated. The precision for the 95% CI in a 1:1 (abaloparatide: teriparatide) matched cohort for different scenarios of incidence of CV events and risk ratio will be presented.

Data Analysis: The IRs of CV events of interest for each relevant OP medication will be calculated for the 2 Follow-up Periods. Incidence rates and 95% confidence intervals (CIs) of CV events of interest will be calculated for each study drug. For the Fixed Follow-up Period, IR of patients with CV events of interest will also be reported. The CV event/s rates (as in Objectives 1 and 2) for each study drug will be provided stratified by key CV risk factors. For Objective 3 (the comparative safety analysis), the Cox regression model stratified by matched sets will be used to calculate HRs and 95% CIs for each safety endpoint (MI, stroke, MACE-1 and MACE-2, and arrhythmias).
Milestones: The Applicant will provide the final PASS protocol within 3 months post abaloparatide approval in Europe. Interim reports will be provided on an annual basis, until the final study report is submitted. Upon the minimum sample size being reached, the comparative safety analysis will be conducted and reported as part of the next interim and/or final report/s.

Annex 4 - Specific adverse drug reaction follow-up forms

Specific adverse reaction follow-up questionnaire for Osteosarcoma:

Radius Health, Inc.

Targeted Osteosarcoma Questionnaire for Abaloparatide

Information on time to event onset from starting abaloparatide, pertinent positive or negative information (such as site of radiation exposure or lack thereof, Paget's disease or no history documented) and pathology reports are very helpful.

Please COMPLETE this questionnaire and return via email to PV@radiuspharm.com

PATIENT/REPORTER INFORMATION:

Patient Initials: _____ Date of birth: _____

Height: _____ circle in / cm Weight: _____ circle lb / kg

Gender: Male / Female circle Race/Ethnicity: _____

Reporter Type:

Patient ____ Patient's family ____ Physician ____ Nurse ____ Pharmacist ____ Other: _____

Name of healthcare professional _____

Location and contact information of healthcare professional: _____

_____

Date of Report: _____

Abaloparatide Administration Information						
Lot or batch number	Start date (DD/MMM/YYYY)	Stop Date (if applicable)	Start dose	Dose at time of AE	Restart date (if applicable)	Dose when restarted (if applicable)

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Event Details: Include adverse event of osteosarcoma and other adverse events (signs or symptoms) occurring at or around the same time					
Adverse event	**Date of onset**	**Date resolved**	**Confirmed diagnosis**	**Action taken with the drug**	**Outcome of adverse event**

ADDITIONAL QUESTIONS TO BE ANSWERED
1. Previous history of osteosarcoma? Yes _____ No _____ a. If yes, when was the diagnosis made?
2. Previous history of radiotherapy? Yes _____ No _____ a. If yes, which site was treated?
3. Previous history of Paget's disease of the bone? Yes _____ No _____ a. If yes, when was diagnosis made?
4. Previous history of unexplained elevations of alkaline phosphatase? Yes _____ No _____ If yes, when and for how long did the elevations last? Please provide elevated lab values.
5. Previous history of implant radiotherapy? Yes _____ No _____ a. If yes, what part of the body received the implant? When was treatment administered?
6. Has the patient taken any of the following chemotherapy agents: **If so Circle** Anthracyclines Methotrexate Dactinomycin Cyclophosphamide Ifosphamide Etoposide Somotropin
7. How was this diagnosis confirmed? (Summarize below and attach entire anonymized report)
8. Please summarize key findings from the biopsy report below, and attach the anonymized report.
9. Provide stage and grade of tumor and indicate staging system used.
10. History or presence of osteochondromas or any other bone lesions? Yes _____ No _____ a. If yes, describe the site, specific diagnosis of the lesion, and any treatments for the lesion
11. History of osteosarcoma or bone lesions among family members? Yes _____ No _____ a. If yes, please explain.
12. Other than abaloparatide, has the patient been exposed to any other bone anabolic agent e.g., rhPTH(1-34) [teriparatide, Forteo®], rhPTH(1-84) [parathyroid hormone, Natpara®; Yes ____ No ___ a. If so, when did the patient start use and stop use of the product?
Pathology Report
Summarize key findings from the pathology report and attach the anonymized report:

Name of the Treating Oncologist: _____
Contact information for Oncologist: _____
Permission to contact treating Oncologist: Yes:_____ No: _____

Relevant Medical History		
Medical History	**Date of Onset**	**Date Resolved**

Diagnostic Imaging		
TEST	**DATE**	**RESULT**
X-Ray:		
MRI:		
CT Scan:		
Pet Scan:		
Radionuclide bone scan:		
Other:		
Summarize key findings and attach the anonymized report:		

Family History of Cancer in first degree relatives (*including parents, siblings & children*)		
Type of Cancer	**Relation**	**Comments**

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

Not applicable.

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

Not applicable.

Annex 7 - Other supporting data (including referenced material)

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

Not applicable.