13 October 2022
EMA/857958/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eladynos

International non-proprietary name: abaloparatide

Procedure No. EMEA/H/C/005928/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ABL	abaloparatide
ABL-SC	abaloparatide subcutaneous
ABL-TD	abaloparatide transdermal
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ANMAT	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica
APD	action potential duration
AUC_∞	area under the concentration time curve extrapolated to infinity
AUC_t	area under the concentration time curve to the last measurable time point
AVA Study	Anabolic versus Antiresorptive Study
BFR	bone formation rate
BLQ	Below the limit of quantification
BMD	bone mineral density
BMI	body mass index
cAMP	cyclic AMP
CHMP	Committee on Human Medicinal Products
CI	confidence interval
CL	clearance
CT	computed tomography
s-CTX	C-terminal propeptide of type I procollagen in serum
CLCR	creatinine clearance
C_{max}	maximum concentration
CVA	cerebrovascular accident
DCGI	Drugs Controller General (India)
DDI	drug-drug interaction

Abbreviation	Definition
DSMB	Data Safety Monitoring Board
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EMA	European Medicines Agency
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FRAX	Fracture Risk Assessment Tool
GCP	Good Clinical Practice
hERG	human Ether-a-Gogo related gene
hPTH	human parathyroid hormone
hPTHrP(1-34)	human parathyroid hormone-related peptide (1-34)
HR	hazard ratio
HSA	hip structure analysis
IBD	international birth date
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	International Ethics Committee
IRB	International Review Board
ITT	intent-to-treat
IV	intravenous(ly)
LOCF	last observation carried forward
MAA	Marketing Authorisation Application
MABP	mean arterial blood pressure
MACE	major adverse cardiovascular events
MAR	mineral apposition rate
MBF	modelling-based formation
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction

Abbreviation	Definition
MOF	major osteoporotic fracture
MS/BS	mineralizing surface per unit of bone surface
MTD	maximal tolerated dose
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NVF	nonvertebral fracture
oMBF	overflow modelling-based formation
OVX	ovariectomised
s-PINP	N-terminal propeptide of type I procollagen in serum
PADER	periodic adverse drug experience report
PBRER	periodic benefit risk evaluation report
PD	pharmacodynamic(s)
P-gp	phospho-glycoprotein
PK	pharmacokinetic(s)
pOCT	peripheral quantitative computed tomography
PopPK	population pharmacokinetics
PP	per protocol
PT	preferred term
PTX	parathyroidectomised
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PTHR1	parathyroid hormone receptor 1
QALY	Quality of Life Years
R^0	G protein-independent conformation of PTHR1
RBF	remodelling-based formation
RG	G protein-coupled conformation of PTHR1
RIA	radioimmunoassay
RRR	relative risk reduction

Abbreviation	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous(ly)
SD	standard deviation
SERMs	selective oestrogen receptor modulators
sMTS	solid microstructured transdermal system
SmPC	Summary of Product Characteristics
SOC	system organ class
$t_{1/2}$	elimination half-life
TEAE	treatment emergent adverse event
TIA	transient ischaemic attack
t_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
VF	vertebral fracture
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Radius Health Ireland Ltd submitted on 4 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Eladynos, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 April 2021.

The applicant applied for the following indication: Treatment of osteoporosis in postmenopausal women at increased risk of fracture.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0307/2014 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance abaloparatide contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
24 June 2010	EMEA/H/SA/1604/1/2010/SME/III	*Fernando de Andrés Trelles, Hans Ovelgönne*

The applicant received Scientific Advice on one occasion, as mentioned in the table above for the development of Eladynos for treatment of osteoporosis. The Scientific Advice pertained to the following Pre-Clinical and Clinical aspects:

- General non-clinical strategy, including plans for carcinogenicity and bone quality studies
- Adequacy of Phase 2 clinical data to support Phase 3 studies
- Phase 3 programme: single pivotal study strategy, general design including placebo and active comparator arms, dose justification, study population, primary efficacy endpoint, measurement methodology for primary and secondary efficacy endpoints and the evaluation of safety.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder   Co-Rapporteur: Andrea Laslop

The application was received by the EMA on	4 November 2021
The procedure started on	25 November 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 February 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 February 2022
The CHMP Co-Rapporteur's Critique was circulated to all CHMP and PRAC members on	01 March 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 March 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 July 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 August 2022

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 September 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 September 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 September 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Eladynos on	13 October 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	13 October 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Osteoporosis is a common disease that presents with decreased bone strength that increases the risk of fractures (commonly vertebral fractures, forearm and hip fractures). Until a fracture occurs there are typically no symptoms. Chronic pain and a decreased mobility may be clinical consequences of fractures. Hip fractures have also been associated with increased mortality.

2.1.2. Epidemiology and risk factors, screening tools/prevention

With advancing age, bone mineral density (BMD) decreases and prevalence of osteoporosis increases. In the United States (US), Europe, and Japan, osteoporosis affects about 75 million people. Using the WHO criteria, 30% of postmenopausal Caucasian women have osteoporosis at the hip, lumbar spine, or distal forearm. By the age of 80 years, 70% of women are osteoporotic at the hip, lumbar spine, or distal forearm. The prevalence of osteoporosis, assessed by BMD and using the reference values from the young population, varies by region. In Sweden 6.3 % of men and 21.2 % of women aged 50 to 80 were classified as osteoporotic, whereas among individuals aged 80 to 84 years, 16.6 % of men and 47.2 % of women were osteoporotic. Osteoporosis causes about 9 million fractures annually worldwide and the risk of sustaining an osteoporotic fracture increases exponentially with age due to the decrease in BMD and the appearance of other age-related factors, e.g. increasing incidence of falls. Therefore, increasing life expectancy results in an increasing number of osteoporotic fractures (Szulc & Bouxsein, 2010). Osteoporosis represents a major non-communicable disease of today and is set to increase markedly in the future (Hernlund et al., 2013).

2.1.3. Aetiology and pathogenesis

Osteoporosis is characterised by reduced bone mass and disruption of bone architecture, resulting in increased risk of fragility fractures which represent the main clinical consequence of the disease. Fragility fractures are associated with substantial pain and suffering, disability, and even death for affected patients. Most osteoporotic fractures occur at the spine, wrist, and hip (Hernlund et al., 2013).

2.1.4. Clinical presentation and diagnosis

Osteoporosis is defined clinically on the level of BMD; on the basis of the relationship of fracture risk to BMD two thresholds of BMD have been defined by the WHO (2007):

• 'Osteoporosis' denotes a value for BMD that is equal to or less than 2.5 standard deviations (SDs) below the mean value for young adults (T-score ≤−2.5 SD).

• 'Severe' osteoporosis denotes osteoporosis as defined above in the presence of one or more documented fragility fractures

Clinically, bone strength is estimated by non-invasive assessment of BMD by dual-energy X-ray absorptiometry (DXA) since numerous epidemiologic studies confirm that low BMD is among the strongest risk factors for fracture. As endorsed by the WHO the clinical diagnosis of osteoporosis is based on BMD measurements and the presence of fractures. For these diagnostic criteria, BMD is transformed into a T-score, which reflects the number of standard deviations (SD) above or below the mean in healthy young adults. The thresholds for each category are shown in the Table 1 below (Szulc & Bouxsein, 2010).

Table 1. WHO criteria for clinical diagnosis of osteoporosis

BMD T-score	Diagnosis
T-score ≥ -1	Normal
-1 > T-score > -2.5	Low bone mass
T-score ≤ -2.5	Osteoporosis
T-score ≤ -2.5 with existing fracture	Severe osteoporosis

2.1.5. Management

The primary aim of pharmacological osteoporosis treatment is the reduction of the risk of osteoporotic fractures. Currently, there are two therapeutic approaches to the treatment of osteoporosis; one is to decrease bone loss with an antiresorptive drug and the other is to increase new bone formation and BMD with a bone anabolic therapy. Antiresorptive agents are e.g. oestrogens and selective oestrogen receptor modulators, anti-RANK ligand antibodies, and bisphosphonates. They inhibit the bone-resorbing activity of osteoclasts while an anabolic therapy like teriparatide and abaloparatide in contrast stimulates the production and activity of osteoblasts, increasing BMD by building new bone.

2.2. About the product

Human parathyroid hormone (hPTH) is a naturally occurring 84 amino acid hormone and is primarily a regulator of calcium homeostasis. When given intermittently at low doses, hPTH has a well-documented anabolic effect on bone. Abaloparatide is a chemically synthesised analogue of the first 34 amino acids of human parathyroid hormone-related peptide [hPTHrP(1-34)]. Due to the molecular modifications of specific amino acids enhancing PTH1 receptor RG/R0 selectivity, abaloparatide was claimed by the applicant to be more effective in patients with osteoporosis than hPTH(1-34) but with less bone resorptive effects and a reduced risk of hypercalcaemia. The finished product of abaloparatide is supplied as a 1.5 ml type 1 multi-dose cartridge that contains 3.0 mg of abaloparatide as free base. The cartridge is irreversibly installed into a multi-use pen for daily subcutaneous (SC) injection by the patient at a dose of 80 µg of abaloparatide in 40 µl of fluid (2 mg/ml). The pen used in Phase II and Phase III studies was manufactured by XXX while the to-be-commercialised pen will be manufactured by YYY.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as solution for injection in pre-filled pen containing 80 micrograms/dose of abaloparatide as active substance.

Other ingredients are: phenol, water for injections, sodium acetate trihydrate (for pH adjustment) and acetic acid (for pH adjustment).

The product is available in glass cartridge with a plunger (chlorobutyl rubber), crimp cap (bromobutyl rubber seal)/aluminium assembled into a disposable pen as described in section 6.5 of the SmPC.

The finished product is a solution for subcutaneous delivery using a multi-dose, fixed dose, disposable pen injection system.

2.3.2. Active Substance

2.3.2.1. General Information

The chemical name of the active substance, abaloparatide, is H-Ala-Val-Ser-Glu-His-Gln-Leu-Leu-His-Asp-Lys-Gly-Lys-Ser-Ile-Gln-Asp-Leu-Arg-Arg-Arg-Glu-Leu-Leu-Glu-Lys-Leu-Leu-Aib-Lys-Leu-His-Thr-Ala-NH_2 corresponding to the molecular formula $C_{174} H_{300} N_{56} O_{49}$. It has a relative molecular mass of 3961 Daltons and the following structure:

Figure 1. Active substance structure
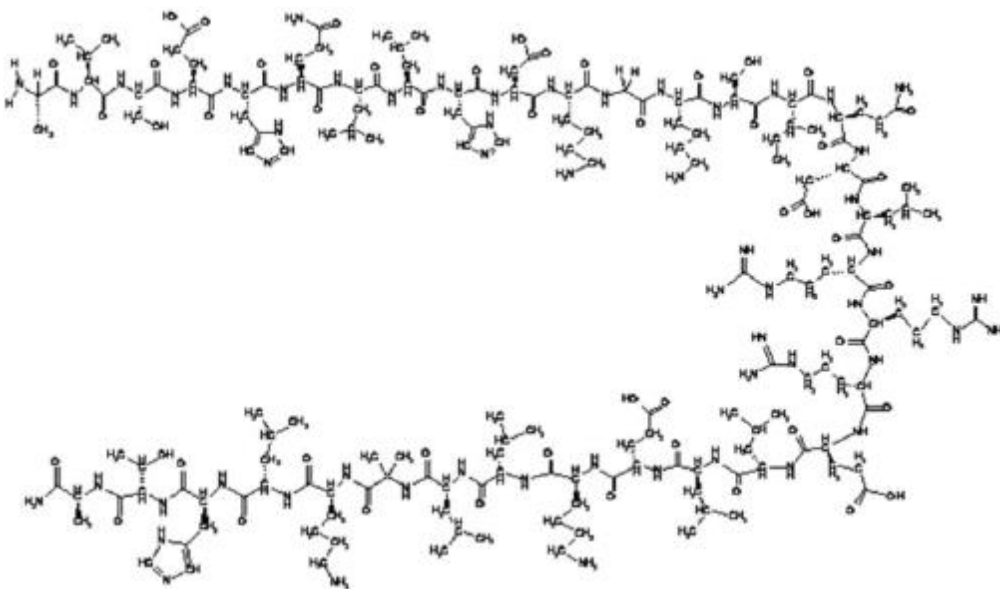
The chemical structure of active substance was elucidated by a combination of electrospray ionisation mass spectroscopy after trypsin digestion, N-terminal sequencing analysis with endopropteinase Lys-C digestion, chiral gas chromatography, 2D-NMR spectroscopy, UV spectroscopy, IR spectroscopy, circular dichronism (CD). Analysis of tertiary structure was performed with differential scanning calorimetry (DSC).

The active substance, abaloparatide, is a hygroscopic amorphous white to off-white powder, freely soluble in 0.1 N acetic acid and water. Abaloparatide is a synthetically manufactured peptide containing 34 amino acids.

The active substance has a chiral molecular structure. The chirality of the active substance is ensured by controlling the enantiomeric purity of the starting materials and is routinely controlled by a test for Specific optical rotation in the active substance specification.

Polymorphism has not been observed for the active substance.

2.3.2.2. Manufacture, process controls and characterisation

The synthesis of abaloparatide is described in 3 major steps; solid phase peptide assembly, deprotection and cleavage and purification and final isolation. The synthesis has been described in flow charts and a detailed narrative. The synthesis of the protected peptide is carried out by a stepwise solid phase method on a solid phase peptide synthesizer carrying Fmoc-Rink Amid MBHA Resin as solid support. The purification process is performed by preparative-scale HPLC. Two or three purification steps employing reversed phase preparative HPLC are part of the manufacturing process. Finally, the active substance is isolated by evaporation and lyophilisation. The parameters for purification and lyophilisation steps have been adequately described.

No reprocessing is anticipated during the course of the regular manufacturing process of abaloparatide. If reprocessing is necessary this will be performed via one or more of the validated purification, concentration, evaporation or lyophilization step, which is acceptable.

No class 1 solvents and no catalysts are used. Re-working, alternate processes and blending of batches are not mentioned.

Information on batch size is given.

Fmoc-protected amino acids are proposed as starting materials for the GMP synthesis of abaloparatide and these are considered acceptable. The starting materials can be considered as commodity chemicals and acceptable specification have been presented.

Reagents and solvents used in the synthesis of peptide-resin bond cleavage and in the purification and final isolation of the drug substance are listed. Appropriate specifications are provided for the raw materials.

Appropriate controls of critical steps are proposed.

The primary and secondary structure of the peptide has been characterised with appropriate methods including electrospray ionisation mass spectroscopy after trysin digestion, N-terminal sequencing analysis with endopropteinase Lys-C digestion, Chiral gas chromatography, 2D-NMR spectroscopy, UV spectroscopy, IR spectroscopy, circular dichronism (CD). Analysis of tertiary structure was performed with differential scanning calorimetry (DSC).

The applicant has discussed the potential of different types of impurities in the active substance. The applicant concludes that for the related impurities observed in abaloparatide do not contain structural alerts for genotoxicity. This information is acknowledged.

The active substance is packaged in bottles made of high-density polyethylene and closed by a polypropylene screw cap. Specifications for the materials have been provided.

Compliance with the EU regulation No. 10/2011 and No 202/2014 relating to plastic materials intended to come into contact with food stuff is informed. The provided information on the primary packaging material is acceptable.

2.3.2.3. *Specification, analytical procedures, reference standards, batch analysis, and container closure*

The active substance specification includes tests for appearance and colour, identification (LC-MS, UPLC), purity (UPLC), total and individual impurities (UPLC), API content (UPLC), acetic acid content (HPLC), TFA content (HPLC), water content (Ph.Eur.), residual solvents (Ph.Eur.), specific optical rotation (Ph.Eur.), endotoxins(Ph.Eur.), microbial purity (Ph.Eur.) and mass balance.

The active substance specification contains relevant parameters and the limits have been justified. Justifications for not including bioassay, elemental impurities and benzene in the specification are acceptable. The analytical methods have been described and validated in line with ICH Q2 guideline.

Batch analysis data is presented showing that the manufacturer can produce batches of acceptable quality.

2.3.2.4. *Stability*

Stability data from 8 production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (-20ºC), for up to 6 months under accelerated conditions (5ºC) and 3 batches up to 6 months under accelerated conditions (25°C / 60% RH), according to the ICH guidelines, were provided. Photostability testing following the ICH guideline Q1B was performed on one batch.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

The test results showed no change in appearance, acetic acid content, microbial contamination or bacterial endotoxins. Decrease in purity is observed at accelerated conditions but stays constant when stored at long term storage conditions (-20°C).

The proposed retest period of 60 months when the material is stored under the recommended storage condition of -20°C ±5°C can be accepted.

2.3.3. Finished Medicinal Product

2.3.3.1. *Description of the product and Pharmaceutical Development*

The finished medicinal product is a sterile solution for the subcutaneous delivery provided in a multi-dose, fixed dose, disposable pen injection system. Each injector is provided as a fully assembled unit, ready for use. Within the pen injector, the abaloparatide solution is contained in a glass cartridge with a rubber plunger closure at one end and a crimp seal with a rubber septum at the other end.

The cartridge is a siliconized glass cartridge of Type 1 Ph.Eur. glass with a plunger made of a chlorobutyl rubber. Additionally, the crimp seal has septum made of a bilayer of rubber consisting of bromobutyl rubber formulation (product contact side) and an isoprene rubber backing.

The development of the product has been a conventional development process and did not encompass any aspects of Quality by Design.

All used excipients are of compendial quality; monograph numbers are not indicated, however acceptable. No excipients of human or animal origin are used. A TSE/BSE statement from the manufacturer is provided. No novel excipients are used.

For the initial phase 1 clinical trial, a lyophilised formulation was developed and used, since it could be developed and tested more quickly than a solution formulation. Recognising that a lyophilised form would not be optimum for patient administration, a solution formulation delivered with a multi-dose injector would be the choice. All subsequent clinical studies were performed with the intended commercial formulation, a solution. Different types of administration devices were used in the clinical trials.

Since the finished product is intended for multi-dose administration a preservation system was evaluated. Phenol was concluded to be the most suitable preservative since it was effective in maintaining peptide content and preservative content, it is easy to use in manufacturing (readily soluble) and it met the antimicrobial effectiveness criteria. The compatibility of phenol has been demonstrated on stability studies both in formulation development as well as clinical and registration stability studies in which both phenol and abaloparatide have been shown to be stable at the formulation pH. The choice of phenol has been justified.

During development abaloparatide was administered to patients by syringe, and by a pen.

The clinical and to-be-marketed pens have similar appearance and dimensions. The clinical pen was approximately 15.8 cm long and 1.6 cm wide, and the to-be marketed pen is 17.2 cm long and 1.95 cm wide. The same needles and cartridges are used in both pens. The major difference is that the user places the cartridges into the clinical pen, while the to-be marketed pen is provided with the cartridge permanently fitted into the pen. The pen with cartridge is disposed of after use. Both pens were multiple-dose injectors.

The clinical pen had 2 fixed dose settings, 0.020 and 0.040 mL. The to-be marketed pen has 1 fixed dose, 0.040 mL. The method of injection for both is a manually driven piston. The clinical pen and to-be marketed pen have the same dose accuracy.

The development of the commercial manufacturing process had been described and compatibility of the finished product with equipment materials but also with excipients (in solution at 2-8°C) has been shown. The choice of the sterilisation method has been justified by the fact that the finished product is sensitive to higher temperatures and thus does not support autoclaving. This can be accepted.

No overage is used. An overfill volume (0.3ml) is used for priming of the pen. This is accepted and also correctly described in the SmPC.

The container closure system consists of a glass cartridge fitted with an aluminium crimp cap on one end and a grey, chlorobutyl rubber plunger on the other end. The crimp cap contains a septum of bromobutyl rubber formulation 4780/40 which is in contact with the drug solution. The plunger consists of the chlorobutyl rubber formulation 4432/50. The filled glass cartridge is permanently fitted into a pen assembly.

The suppliers, specifications and drawings are presented for the materials.

Compliance with Ph.Eur. requirements are presented for materials in contact with the drug product.

The pen is a disposable administration device intended for the subcutaneous injection of multiple doses. It is a "dial and push" type fixed-dose multiple-dose disposable pen-injector. The disposable pen-injector (pen) and the drug product form a single integral product, intended exclusively for use in combination.

The pen corresponds to system designation C of ISO 11608-1:2014 "*Needle-based injection systems for medical use – Requirements and test methods*" which describes a needle-based injection device with integrated non-replaceable container.

The pen-injector is used with sterile injection pen needles, although the needles are not provided with the pen. The pen is compatible with 8 mm, 31-gauge needles Clickfine Pen Needles (CE marked, CE 0123).

No assembly of the pen or loading of the finished product is required at the point of clinical use. The drug product can be inspected through the opening in the cartridge holder. A sterile needle is attached to the cartridge holder tip. The single dose is set by turning the dose knob until the "80" (corresponding to 80 µg dose) shows in the display window on the pen housing. A dose is administered by pressing the injection button. For the first use of a new pen, the pen is primed. The pen cannot be dialed to "80" if not enough volume remains in the cartridge. The needle does not retract. The outer needle cap is scooped back onto the needle, the needle is removed, and the pen cap replaced. After 30 doses the entire product is disposed.

2.3.3.2. Manufacture of the product and process controls

The finished product manufacturing and testing sites are listed in the dossier and QP release is performed by Cilatus Manufacturing Services Ltd, Dublin, Ireland. The batch formula is provided.

The overall manufacturing process consists of compounding of excipient solution and drug product solution, sterilisation by filtration and aseptic filling into cartridges. Finally, the pens are assembled. Suitable in-process controls are proposed. The process is considered to be a non-standard manufacturing process.

The manufacturing process has been acceptably validated with four batches. The batches were manufactured in May-July 2015 with batch sizes of 40-80 litres. The proposed holding times have been validated and are thus acceptable. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.3.3.3. Product specification, analytical procedures, batch analysis

The finished product specification comprises tests for filled cartridges and assembled pens including appearance (Ph.Eur.), clarity (Ph.Eur.), colour (Ph.Eur.), pH (Ph.Eur.), sub-visible particles (Ph.Eur.), extractable volume (Ph.Eur.), phenol content, assay (HPLC), identity (LC/MS, HPLC), total and individual impurities (HPLC), sterility (Ph.Eur.), bacterial endotoxins (Ph.Eur.), content uniformity (USP), break loose and glide forces.

The tests and limits have been appropriately justified.

The shelf-life limit for the degradant has been justified by toxicological qualification.

The analytical methods have been described and validated. The validations are considered acceptable.

Acceptable batch analysis data is presented.

The justification for the omission of bioassay for drug product is acceptable.

A risk assessment concerning elemental impurities in accordance with ICH Q3D has been provided.

A nitrosamine impurity risk assessment has been performed and concluded that based on the assessments from abaloparatide active substance, excipients, finished product manufacturing process, packaging

materials, degradation pathway and the screening results, the nitrosamine impurity risk in abaloparatide injection is low and no additional control is needed.

Regarding used reference standards or materials, reference to S.5 is made which is accepted.

2.3.3.4. Stability of the product

The applicant proposes the following shelf-life and storage restriction:

> 3 years when stored in a refrigerator (2-8°C). Do not freeze.

> After first use, or once removed from the refrigerator, the drug product can be stored for up to 30 days at temperatures up to 25°C.

Stability data from 6 production scale batches of finished product stored for up to 36 months under long term conditions (5ºC / ambient RH), up to 24 months under accelerated conditions (25ºC / 60% RH) and from 3 batches up to 6 months under stressed conditions (40ºC / 75 % RH), according to the ICH guidelines, were provided. The batches of medicinal product are identical to those proposed for marketing (naked cartridges, no pen, horizontal position) and were packed in the primary packaging proposed for marketing. In addition, stability results from 6 annual batches stored at 5 °C for up to 36 months were presented. These batches are with both naked cartridges and assembled pens.

Samples were tested for in line with the shelf life specifications outlined above. The analytical procedures used are stability indicating.

Significant changes, out of specification results for the specified degradant impurity, occur between 3- and 6-months' testing in accelerated and stressed conditions. Therefore, the proposed shelf-life is based on real time data at long-term conditions (5ºC / ambient RH) where acceptable results were provided.

Data regarding photostability has been provided and it can be concluded that no storage restriction with respect to light is needed. The drug product will not be exposed to light as it is enclosed with the pen holder.

Three batches on long-term stability studies were also studied for in-use stability. At defined timepoints (5 months+3 days, 11 months+30 days, 23 months+30 days and 35 months+30 days) samples were analysed. A defined number of these samples were punctured 30 times to mimic patient use and the remaining were left un-punctured. Both sets of samples were then stored at 25°C/60% RH for 30 days and then tested. The samples were analysed for appearance, visible and sub-visible particles, peptide content and peptide impurities, sterility, pH, extractable volume, phenol content, antimicrobial effectiveness, break lose and glide forces.

No trends were observed except for the degradant that increases. It was thus found within specification limits when stored at 5°C for up to 35 months and 30 days at 25°C/60% RH.

The shelf-life and storage statements above have been acceptably justified.

2.3.3.5. Regional information (CTD module 3.2.R):

A Notified Body Opinion Report from Radius Health (Ireland) Limited for the drug product Eladynos is provided. The provided Notified Body Opinion is in line with Article 117 of the Medical Devices Regulation (EU) 2017/745. Conformity of the device part of Eladynos Drug-Device combination to the relevant GSPRs in Annex 1 of the Medical Devices Regulation is stated.

The biological safety evaluation is compliant with ISO 10993-1 and includes the adequacy of the material characterization, the rationale for selection and/or waiving of tests, the interpretation of existing data and results of testing, the need for any additional data to complete the biological evaluation. No CMR or endocrine disrupting substances were stated to be present.

Appropriate specifications, requirements, and intended performance have been demonstrated through the full lifetime in normal use. Claimed 5 years of shelf-life is fully covered by accelerated aging tests and partially (up to 1 year) by real time testing. Visual inspection and dose accuracy were tested to support the claimed shelf-life. Sample size was appropriate. Evaluation of the data is considered satisfactory and the data provided supports the shelf life claims, however no real-time studies were available at the time of review.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product (solution for injection in prefilled pen) has been presented in a satisfactory manner. There were no major objections raised on quality, and all other concerns have been addressed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Pharmacology

Abaloparatide is a chemically synthesised peptide corresponding to the first 34 amino acids of human PTH related peptide (hPTHrP) with 8 amino acid modifications, among them the non-proteinogenic and atypical amino acid aminoisobutyric acid. PTHrP is different from PTH, as it is the product of a different gene with partial amino acid sequence homology and with different biological functions. PTH and PTHrP show structural homology within the 1–13 and 29–34 amino acid sequences of both polypeptides and both peptides interact with the common PTH1 receptor.

A number of binding and cellular *in vitro* as well as *in vivo* studies have been conducted to characterize the pharmacological activity of abaloparatide.

2.4.1.1. Primary pharmacodynamic studies

In vitro studies

In vitro binding studies using HEK cells stably expressing hPTH1 and hPTH2 receptors demonstrated that abaloparatide is a potent (EC_{50} 0.2nM), and selective agonist of the human PTH1 receptor, with no affinity for human PTHR2 ($\geq$ 100 nM). Abaloparatide had a comparable potency to hPTH(1-34) (EC_{50} 0.26 nM) and hPTHrP(1-34) (EC50 0.21 nM) at enhancing cellular metabolic activity, and was about 2-fold more potent than the native peptides in stimulating downstream cAMP production (EC_{50} of 0.17 $\pm$ 0.06 versus 0.40 $\pm$ 0.16 and 0.48 $\pm$ 0.13 nM, for PTH and PTHrP, respectively). In the in vitro experiments the human and the rat form of the PTH1 receptor was investigated. However, *in vitro* characterisation of abaloparatide in dog and monkey was not provided. As a stretch of the PTH1 receptor involved in hormone binding shows identical amino acid sequence in humans, dogs and monkeys and as similar pharmacologic effects of abaloparatide were seen in humans and in dogs and monkeys, the lack of *in vitro* binding data for dog and monkey PTH1 receptors is considered acceptable. For the PTH1 receptor two high affinity conformations, termed RG and R^0 have been identified. The RG conformation is the G-protein dependent conformation leading to transient cAMP signalling. The R^0 conformation is G-protein independent and leads to prolonged cAMP signalling responses in cells, presumably because the ligand remains bound. Investigation of binding specificity of abaloparatide for the PTHR1 conformations RG and R^0 demonstrated that abaloparatide binds with similar affinity (IC_{50}=0.20 nM) as PTH (IC_{50}=0.33 nM) and PTHrP (IC_{50}=0.32 nM) to the RG conformation of the PTHR1. Abaloparatide exhibited the greatest selectivity for the RG versus R^0 conformation, as the selectivity for the RG vs R^0 conformation was 1,600-fold for abaloparatide, 12-fold for PTH and 110-fold for PTHrP, respectively. In a cAMP time-response assay, abaloparatide showed a slightly more transient (i.e. ~2-fold shorter duration) of the cAMP signalling responses as compared to PTH and PTHrP. The ability of abaloparatide to activate downstream ERK-1/2 signalling was, however, found to be similar to hPTH(1-34) and hPTHrP(1-36) in the same cell system (GP-2.3 cells).

In vivo studies

Comparison of abaloparatide and hPTH(1-34) (teriparatide) activity

1. Calcium mobilization in rat plasma

In calcium-deficient, parathyroidectomised (PTX) rats, abaloparatide produced at or above therapeutic doses (5 to 80µg/kg, SC) similar calcium mobilising activity as the native peptides hPTH(1-34) and hPTHrP(1-34), with no significant difference in plasma calcium levels between the treatment group. However, when experimental data from two separate studies were pooled together, abaloparatide had less calcium mobilising activity at a high supra-therapeutic dose (320 µg/kg, SC) than hPTH(1-34).

2. Efficacy in ovariectomised (OVX) rats

The OVX-induced osteopenia model is considered to represent clinical features of oestrogen deficiency-induced (or postmenopausal) bone loss in the adult human. A dose-related increase in bone mineral density (BMD) was observed in proximal femur and femur metaphysis regions, which contain a high percentage of trabecular bone, after 4-weeks of daily administration of hPTH(1-34) and abaloparatide (0.039 to 40 µg/kg, SC).

Based on ED50 calculations, abaloparatide was stated to be ~2-fold more potent in restoring BMD than hPTH(1-34), with ED_{50} values: 1.75 µg/kg for hPTH(1-34) and 0.87 µg/kg for abaloparatide, respectively.

However, the potency data should be interpreted cautiously, since no statistical analysis was performed to demonstrate a difference between the two treatments. Thus, both compounds demonstrated that they are similar efficacious anabolic agents capable of fully restoring BMD at comparable doses in OVX rats.

Given that both abaloparatide and teriparatide were anabolic agents capable of fully restoring BMD in OVX rats at comparable doses, that there was no significant difference in calcium plasma levels at therapeutic doses of abaloparatide compared to hPTH1-34 and hypercalcemia was observed at clinically relevant exposure levels in repeat-dose toxicity studies, the non-clinical evidence supporting the hypothesis that RG selectivity of abaloparatide per se would offer differential effects of abaloparatide compared to teriparatide is considered weak.

Anabolic effects of abaloparatide in rats and non-human primates

The 6-week rat study included a longer bone-depletion period following OVX of 8 weeks compared to 5 weeks in the 4-week rat study. Groups of sham operated vehicle treated and OVX vehicle treated animals were compared to OXV animals treated with 5 or 20 µg/kg bw/day of abaloparatide SC. The evaluation included DXA, microCT and biomechanical testing. DXA showed significant increases in femur, whole and cortical, and lumbar vertebral BMD. MicroCT revealed at the high abaloparatide dose at the femur metaphysis relative bone volume (BV/TV) and bone density values not significantly different from sham controls and at the lumbar vertebrae even higher than sham controls with increases in trabecular number and thickness.

All investigated biomechanical values increased in abaloparatide treated groups in the three tests employed (3-point bending of the femoral shaft, femoral neck cantilever compression test and lumbar compression test) compared to vehicle treated OVX animals, often statistically significantly, and often compared to sham vehicle treated animals as well.

The 12 months rat study included an even longer bone-depletion period following OVX of 3 months and the doses of abaloparatide administered SC were 1, 5, or 25 µg/kg bw/day. In this study, evaluation by peripheral quantitative computed tomography (pQCT), histomorphometry and biochemical markers of bone turnover was included. Treatment with abaloparatide at 5 or 25 µg/kg bw/day increased bone formation markers (s-P1NP or s-OC) whereas bone resorption markers, s-CTX and u-DPD, remained unaffected. In vivo DXA showed that abaloparatide treatment resulted in marked increases in bone mineral concentration (BMC) and BMD relative to sham controls at all dose levels and at all sites evaluated: whole body, lumbar spine, femur and tibia, in trabecular and cortical bone compartments. Regarding whole body BMD, abaloparatide dose-dependently restored OVX-induced bone loss to sham control levels at 1 µg/kg bw/day by Week 12/13, and earlier at 5 and 25 µg/kg bw/day. In vivo pQCT showed that treatment of OVX rats with abaloparatide at all dose levels reversed the OVX-induced decreases in total slice BMC and BMD at the proximal tibia metaphysis with positive bone gains at all time points and all dose levels compared to sham controls. The 3-point bending test of the femur revealed that treatment with abaloparatide at all dose levels reversed OVX-induced effects on bone strength. Histomorphometry of cortical bone showed that treatment with abaloparatide reversed the OVX-induced static cortical changes at all dose levels and histomorphometry of cancellous bone showed increases in all bone formation parameters at abaloparatide doses of ≥1 µg/kg bw/day. Within physiological ranges slight increases in serum calcium levels were noted in the high dose group. At the minimum effective dose (1 µg/kg, SC) a C_{max} of 396 pg/mL and 884 pg/mL was observed at Day 1 and Day 358, respectively. For comparison, the human C_{max} at the recommended daily dose of 80 µg/kg is 812 pg/mL.

For the 10-months monkey study a bone depletion period of 10 months after OVX was followed by SC abaloparatide treatment with 1 or 10 µg/kg bw/day for another 10 months. A third group received a treatment of 0.1 µg/kg bw/day for 7 months followed by weekly injection of 10 µg/kg bw/week. Total alkaline phosphatase activity did not change during abaloparatide treatment. In and ex vivo BMD measurements of lumbar spine using DXA showed that abaloparatide treatment at 1 and 10 µg/kg bw/day induced an increase of the lumbar BMD. Other BMD measurements (femur, radius, tibia) did not yield significant differences between OVX control, sham and abaloparatide treated animals. Only relatively few histomorphometric parameters responded to abaloparatide treatment. Biomechanical testing did not reveal significant differences between sham and abaloparatide-treated animals for any of the biomechanical parameters evaluated in this study. For the 16-month monkey study a bone depletion period of 9 months after OVX was followed by SC abaloparatide treatment with 0.2, 1 or 5 µg/kg bw/day for another 16 months and monkeys were obviously older than those ones used in the 10 months study.

Treatment with abaloparatide at all doses increased the bone formation marker s-P1NP but without any significant increase in the biochemical markers of bone resorption. In vivo DXA showed that treatment with abaloparatide resulted in significant dose-dependent increases in BMD in most evaluated areas. Except distal radius, distal femur and proximal tibia, depending on abaloparatide dose and treatment duration restoration of bone mass to sham controls was seen. In vivo pQCT revealed full restoration of bone mass at the tibial total proximal metaphysis at ≥1 µg/kg bw/day near study end, but abaloparatide induced only partial restoration at the proximal tibia diaphysis. MicroCT did not reveal significant differences regarding cortical regions but showed generally increases in bone mass at trabecular sites.

Biomechanical testing at the femur (3-point bending test) showed trends for increases in several evaluated parameters. Statistically significant values for biomechanical parameters were reached in vertebral body and even more so in the lumbar vertebral core compression test with values generally similar to sham controls. Regression analysis of biomechanical parameters vs. BMC and/or BMD showed increases in bone mass were positively and significantly correlated with bone strength parameters. In the histopathological evaluation abaloparatide treated OVX monkeys demonstrated a lower incidence and severity of decreases in cancellous/cortical bone when compared to OVX controls, consistent with abaloparatide -related reversal of the OVX-related bone loss.

2.4.1.2. Secondary pharmacodynamic studies

Across the 229 molecular targets tested, four were identified, where a 10 µM concentration of abaloparatide inhibited the radioligand binding to its receptor by >50%. These targets were the bombesin receptor, N-formyl peptide receptor-like receptor, orexin receptor and the vasoactive intestinal peptide receptor. Overall, abaloparatide was demonstrated to be selective for the PTHR1, with at least a 7,000-fold margin (based on the ratio K_i/human C_{max}) to the other 229 molecular targets at the clinical dose (80 µg/kg/day).

In order to address potential cardiovascular effects of abaloparatide and investigate efficacy in indications besides osteoporosis in postmenopausal women, additional studies were submitted.

HL-1 cardiomyocytes were used to evaluate the influence of abaloparatide or PTHrP(1-36) on viability and survival kinase (AKT and ERK) expression under normoxic and simulated ischemia-reperfusion conditions as well as with co-administration of a MEK-ERK inhibitor (PD98059).

Under normoxic conditions Abaloparatide did not have any effect on cell survival at a concentration range from 0.1 to 100 nM. Under ischemia-reperfusion conditions Abaloparatide had beneficial effects on cell survival as compared to the control group with the highest cell survival observed at the 10 nM concentration.

Similar results were obtained with PTHrP(1-36) that was tested at concentrations of 10 and 100 nM. When both compounds were analysed in parallel in the same assay, no difference was noted under normoxic conditions. Under ischemia-reperfusion conditions cell survival with 10 nM Abaloparatide was statistically significantly higher than with 10 nM PTHrP(1-36) and 100 nM Abaloparatide or PTHrP(1-36). Under ischemia-reperfusion conditions expression of phospho-AKT and phospho-ERK were higher in cells incubated with 10 nM Abaloparatide than with 10 nM PTHrP(1-36).

PD98059 outweighed the beneficial effect of Abaloparatide and PTHrP(1-36) on cell survival under ischemia-reperfusion conditions to the level of vehicle control. A similar effect was observed on the expression of survival kinases.

Overall, both abaloparatide and PTHrP(1-36) can be considered protective to cardiomyocytes under the conditions investigated above.

In a porcine coronary artery occlusion model PTHrP(1-36) statistically significantly reduced the size of necrotic areas (3 hours post infarction) as compared to controls when administered at a dose of 1 µg/kg for four days in advance to induced infarction. No differences in heart rate or blood pressure were noted during the experiment. No difference was detected in terms of ERK phosphorylation. According to the applicant, differences in ERK phosphorylation could only have been noted within 10 minutes after infarction which was experimentally not feasible. Overall, the significance of the study employing PTHrP(1-36) only is questionable.

The efficacy of abaloparatide was also tested in orchidectomised rats. Doses of 5 and 25 µg/kg/day administered for 8 weeks had a positive effect on the restoration of bone mass and bone mineral density as compared to controls and sham operated rats.

Ovariectomised rabbits with glucocorticoid-enhanced osteoporosis were treated with 5 or 25 µg/kg abaloparatide and BMD was assessed after 4, 8 and 12 weeks. The 25 µg/kg/day dose was capable to prevent bone marrow density loss as compared to untreated ovariectomised rabbits and ovariectomised + GC-treated rabbits. Also, in comparison to the 5 µg/kg/day dose, which lead to comparable results as ovariectomised controls, only the 25 µg/kg/day dose had beneficial effects on BMD. Of note, in contrast to rabbits a dose of 5 µg/kg was efficacious in other species included in the non-clinical development of abaloparatide.

2.4.1.3. Safety pharmacology programme

Safety pharmacology was extensively studied according to the ICH S7A and S7B guidelines in 16 studies (3 *in vitro* studies and 13 *in vivo* studies in rats and dogs) to assess the effects of abaloparatide SC and intravenous (IV) administration on the cardiovascular, central nervous, respiratory, renal/urinary, gastrointestinal, and haematological systems. No safety pharmacology studies comparing the profile of abaloparatide and hPTH were provided by the applicant. Abaloparatide was generally well-tolerated over a wide range of doses in 3 species, rats, dogs, and monkeys: single doses were studied in rats up to 625 µg/kg, and in dogs up to 10 µg/kg; repeat doses were studied in rats up to 25 µg/kg/day for 12 months, and in monkeys up to 10 µg/kg/day for 10 months and up to 5 µg/kg/day for 16 months.

Central nervous system

The influence of abaloparatide on the central nervous system was investigated in female Wistar rats following subcutaneous and intravenous application. In the Irwin test subcutaneous administration of up to 625 µg/kg

did not induce behavioural alterations. Intravenous administration resulted in a non-dose dependent manner after 15 to 30 minutes in signs of excitation accompanied by stereotypies such as sniffing and body licking in every dose group. Abaloparatide did not show significant long-lasting effects on spontaneous locomotive activity (up to 125 µg/kg; SC). However, in the first minutes a decrease of activity was noticed and may be attributed to the cardiovascular effects of abaloparatide. Barbital-induced sleeping time test (up to 125 µg/kg; SC), shock induced tonic convulsion test (up to 125 µg/kg; SC), and the pentylenetetrazole-induced seizure test (up to 125 µg/kg) were unaffected by abaloparatide administration. The applicant concludes a no-observed-effect level (NOEL) of abaloparatide in the central nervous system of 125 µg/kg/day subcutaneously which appears to be acceptable.

Cardiovascular system

Haemodynamic effects of abaloparatide have been investigated in in-vitro and in in-vivo studies in dogs. The in vitro studies consisted initially of one study investigating the arrhythmogenic risk in Purkinje fibres of rabbits, one non-GLP compliant study investigating hERG currents in human embryonic kidney (HEK) cells and one GLP compliant hERG assay. Significant effects on APD60 and APD90 were noticed after 30 minutes for 0.3 µM abaloparatide, whereas for 10 µM the increase failed to reach significance. All other parameters investigated did not show relevant effects. One EAD was noticed in the highest dose group at a pacing rate of 12 puls/min. The applicant concludes that the most likely cause of these effects may be a weak blockade of the delayed rectifier potassium channels. Alternatively, these findings could be indicative of an activating effect on the calcium channels, which could then be concordant with the increase in contractile movements observed in the Purkinje fibres in the presence of abaloparatide at these two concentrations.

In the non-GLP study, abaloparatide slightly blocked the hERG current without showing evidence for a dose response. No significant effects were observed at 0.1 and 0.3 µM and the applicant concludes a no effect concentration of 0.3 µM. The second GLP-compliant study indicates an IC_{50} for abaloparatide > 30 µM. The applicant argues furthermore that the maximum plasma concentration (C_{max}) obtained in clinical study BA058-001B was 0.205 nM (812 pg/mL) and that the safety margin would be between 400 (based on results obtained with Purkinje fibres) and 1500-fold (based on results obtained with HEK cells). This appears to be a rather conservative approach since the plasma protein binding of approximately 70 to 75% was not considered. Taking this into account the safety factors appear to be rather 600 to 1600-fold. Based on the in vitro studies presented an arrhythmogenic risk of abaloparatide appears to be unlikely.

The haemodynamic and cardiovascular effects of abaloparatide following IV and SC treatments have been evaluated both in anaesthetised and in conscious dogs. The significance of these studies is hampered by the lack of abaloparatide exposure data and plasma calcium levels.

Haemodynamic effects of abaloparatide were evaluated in anaesthetised dogs at IV bolus ascending doses of 0, 0.03, 0.1, 0.3, 1 and 3 µg/kg in 3 males and 3 females. Starting from 0.1 µg/kg, abaloparatide exerted dose-dependently a peripheral arteriolar vasodilatation (maximal decrease in mean arterial blood pressure [MABP] of 45%) and a direct marked positive chronotropic and inotropic effect, leading to increased cardiac output. Abaloparatide did not affect cardiac work and the haemodynamic efficiency of the heart, although some preliminary and marginal signs of myocardial depression were detected at the highest dose of 3 µg/kg. It did not cause a deleterious effect on pulmonary and renal circulation.

Abaloparatide, administered at doses of 0, 1, 3 and 10 µg/kg SC to the conscious dog had marginal effects 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 by 68%, 82% and 120% at 1, 3 and

10 µg/kg, respectively. The effect occurred shortly following the administration and recovery to the initial values was achieved within about 3 hours. Associated with the heart rate increase, abaloparatide shortened the PR interval at 3 and 10 µg/kg and the QT interval by 18% to 27% at all doses. Changes in the PR and the QT intervals were closely linked to the changes in heart rate. Abaloparatide had only marginal effect on the QTc interval although a non-significant tendency towards a decrease was observed at 3 µg/kg (decrease of 11% at maximum). No arrhythmia or other changes in the morphology of the electrocardiogram which could be attributed to abaloparatide were detected during the study. The applicant has tried to establish a safety margin based on allometric scaling predicting a margin ≤ 4.61 for the risk of QT changes.

The applicant concludes that due to the effects observed on the heart rate, the NOEL in this study was <1 µg/kg SC and argues further, that the SC dose of 3 µg/kg at which decreased MABP and a heart rate increase by 82% were observed in Study BA058-131 corresponds to a human equivalent dose (HED) of 1.67 µg/kg in humans, i.e. to 108 µg, 1.4-fold the therapeutic dose (considering an allometric scaling factor of 1.8 for dogs and a patient weight of 65 kg).

Considering the repeated dose studies in cynomolgus monkeys (BA058, Study 7801-125), there was a non-significant trend towards a shortening of uncorrected QT intervals, similar to the observation in the dog cardiovascular study. Nevertheless, there was no apparent correlation with plasma calcium levels and the QT-interval findings in monkeys. Shortening of the QT interval or changes in QTc were not observed in human. Furthermore, the cardiovascular effects observed in dogs may be consistent with a transient and reversible increase in heart rate observed in some patients. Applying the same factors as given above to the animal dose of <1 µg/kg SC this would result in a HED of below 0.6 µg/kg. As the clinically intended dose is 1.2 µg/kg (80 µg dose for a 65 kg patient) the "safety" factor for this effect is smaller than 1. The observed cardiovascular effects may reflect a potential pharmacodynamic response (vasodilatation) of vascular smooth muscle cells (Halaplas et al. 2003) to abaloparatide exposure. Similar effects have been observed with comparable substances such as teriparatide. From the non-clinical point of view additional cardiovascular safety studies are not considered necessary; any remaining uncertainties should be addressed clinically.

Respiratory system

Effects of abaloparatide on the respiratory system were evaluated in freely moving female rats by plethysmography and doses of up to 125 µg/kg subcutaneously did not modify significantly any respiratory parameters up to 240 min after administration.

Supplemental safety pharmacology studies

Supplemental safety pharmacology studies were conducted in rats investigating renal, haematological and gastrointestinal system.

Renal function

In conscious female rats, abaloparatide (5, 25, and 125 µg/kg, SC) displayed no significant effect on urinary volume, pH, or potassium, creatinine, or phosphate excretion, but urinary sodium excretion was increased (at the intermediate dose of 25 µg/kg), and urinary calcium excretion was increased (at the 2 highest doses of 25 and 125 µg/kg).

Haematologic system

Abaloparatide increased non-significantly the bleeding time of female rats at 25 and 125 µg/kg, which is in agreement with the increased prothrombin time (PT) and APTT observed during the toxicology studies. No notable changes were, however, observed in the clinical studies for albumin, platelet counts, APTT, and PT. Haematological effects including decreases in haemoglobin and leukocytes were observed at high doses in both rats and monkeys, which were stated to be secondary to the marked bone formation effects observed in the marrow.

Gastrointestinal system

The gastrointestinal tests (transit, ulcerogenic activity and changes in gastric fluid volume and gastric acid secretion) revealed no significant effects. Since the gastric acid secretion was increased at the highest dose tested the NOEL of abaloparatide for the gastrointestinal system was therefore 25 µg/kg subcutaneously.

2.4.1.4. Pharmacodynamic drug interactions

No pharmacodynamics drug interaction studies were conducted. Although abaloparatide has been shown to act specifically via the PTH1 receptor, as bisphosphonates are a common therapeutic drug in osteoporotic women, the applicant was initially asked to comment on the possibility of pharmacodynamic drug interactions between abaloparatide and bisphosphonates. According to recent literature (Cosman et al. [2014] osteoporosis Int 25, 2359-2381) it is common to follow teriparatide treatment with an antiresorptive agent. Abaloparatide treatment followed by alendronate treatment is subject to clinical observation. Conduct of non-clinical pharmacodynamic interaction studies is not considered necessary.

2.4.2. Pharmacokinetics

Methods of analysis

The bioanalytical methods described for rat and monkey seem appropriate. However, the applicant has not provided validated methods for measuring abaloparatide levels in dog plasma and serum. Moreover, there are no results on the pharmacokinetic profile of abaloparatide in the dog despite the compound being evaluated in GLP-compliant safety pharmacology studies in dogs (study BA058-130, BA058-131). Since a clinically relevant risk for cardiovascular safety was already identified, it is concluded that a proper method validation in dogs as required otherwise is not necessary.

Absorption

Absorption of abaloparatide was investigated in rats and cynomolgus monkeys. Doses up to 300 µg/kg day in rats and 450 µg/kg day in cynomolgus monkeys were applied. Four single dose and eleven repeated dose studies were performed with abaloparatide only. Three additional studies in rats and cynomolgus monkeys concern the specified degradant impurity.

Bioavailability of abaloparatide was determined in rats after subcutaneous administration of 10 µg/kg bodyweight and was 27 % in females and 39 % in males. The applicant points out that a similar result was obtained for humans (bioavailability 40% in clinical study BA058-05-10).

Systemic exposure was investigated in rats and cynomolgus monkeys in ovariectomised and naive animals. After single dose (first dose) administration abaloparatide peak plasma exposure (T_{max}) was reached quickly between 15 to 30 minutes, with no notable differences between healthy animals and ovariectomised rats or monkeys in all dose groups. Exposures (C_{max} and AUC) were approximately dose proportional in rats and monkeys independent of gender or health status (ovariectomised or not). No significant differences were detected between ovariectomised and intact animals.

After repeated dose administration a time and dose dependent increase of exposure (AUC) was observed in naive rats at doses above 15 µg/kg day after 4 weeks and after 26 weeks above 1 µg/kg day. The picture in non-human primates was less consistent although a trend for increasing AUCs during study duration can be seen. At week 13 (~Day 91) a remarkable increase of the AUC compared to Day 1 was noticed in females was not apparent later on. The reason is unknown.

The applicant points out that since the observed increase in exposure was observed with ascending dose only the relevant dose range in ovariectomised animals should be considered only. The intended therapeutic dose of 80 µg /day equals a daily dose of 1.2 µg/kg bodyweight for a 65 kg patient. By applying the conversion factors for a allometric scaling for rat and non-human primates of 6.2 and 3.1 as given by the relevant guiding documents this would result in a human equivalent dose of 7.4 µg/kg day (rat) and a human equivalent dose 3.7 µg/kg day (monkey) and that these doses would be covered by the dosing range of approximately 1 to 5 µg/kg bodyweight in ovariectomised rats and of round about 5 µg/kg in non-human primates. Considering this aspect, the ratio of increase is about 2 in rats and between 0.5 and 2.7 in monkeys. The applicant concludes that in humans no drug accumulation has to be anticipated. Although this argumentation may be valid during the development of the medicinal product, a comparison of the exposure obtained in clinical studies and animal data may be of additional interest.

According to the tabulated overview provided by the applicant the C_{max} obtained in clinical use is 0.7 ng/mL and the AUC_{0-t} is 1.25 ng·h/ml which equals a dose of 1 to 5 µg/kg day in ovariectomised rats. In ovariectomised monkeys the highest dose applied (5 µg/kg day) does not reach the AUC levels which have to be anticipated for clinical use. However, in naïve monkeys much higher doses have been applied which show, that a comparable AUC would be reached below a dose of 10 µg/kg day. In study BA058-119 pharmacokinetic parameters in cynomolgus monkeys were obtained after 88 days of 10 µg/kg/day showing a heterogeneous response with one group of animals showing an increase of exposure which is indicated by a basal exposure with abaloparatide before the daily administration and a second group of animals which do not show this effect. Considering this aspect, an accumulation of abaloparatide cannot be completely excluded based on non-clinical data. The applicant tries to explain these results by the appearance of anti-drug antibody (ADA) formation, which may stabilise abaloparatide /abaloparatide fragments which were measured therefore in the analytical assays. However, since no clear information regarding the homology between the non-clinical species and humans is provided it remains unclear if similar effects have to be anticipated in humans.

The applicant summarizes that the elimination was independent of dose with half-lives in the range of approximately 0.2 to 1.3 hours with doses from 10 to 300 µg/kg SC in rats and of approximately 0.6 to 1.3 hours with doses from 10 to 450 µg/kg SC in monkeys and further points out that half-lives of the OVX animals were slightly lower near the HED (5 µg/kg for OVX rats and monkeys), being around 0.3 hours for both species, and lower than in humans (1.3 hours) after single dose administration. The applicant further points out that mean residence times are coherent with the half-lives with dose-independent values between 0.3 and 1.0 hour in rats and 1.0 and 2.2 hours in monkeys. In relation with the short half-life, the clearance of abaloparatide given SC is high with values of 2.6 to 8.1 L/h/kg for rats and 1.1 to 13 L/kg/h for monkeys.

The volumes of distribution (Vz/F) range from 1.9 to 6.9 L/kg in rats and from 1.4 to 15 L/kg in monkeys. Despite high clearance and Vz/F values for females at the dose of 200 μg/kg in Study BA058-119, there is no evident increase of either clearance or Vz/F values with dose in monkeys. Unfortunately, the applicant does not take the repeated dose toxicokinetic data into account. In general, the groups showing basal (resident) abaloparatide levels exhibit an increased elimination half-life and a decreased plasma clearance. It remains unclear whether or not this can be attributed to ADA formation and if this results in an increased pharmacodynamic effect or toxicity.

Distribution

Distribution was investigated in two tissue distribution studies in rats and one in-vitro protein plasma binding study. One tissue distribution study was performed using ^{125}I-Tyr attached terminally to abaloparatide. Although not elucidated in depth it becomes clear that the molecule becomes de-iodinated shortly after application and that the obtained data will most likely reflect the fate of the iodide in the organism. The other distribution studies were performed with ^{125}I labelled abaloparatide with a more protected label using the positions 5, 9 and 30 of the peptide. An in-vitro assay confirmed the pharmacodynamics activity of the labelled test substance.

The highest radioactive concentrations in the blood were observed at 0.25 to 0.50 hours post administration. The plasma radioactivity declined steadily to 72 hours and fell below the limit of quantification (BLQ) by 120 hours. The apparent plasma elimination half-life was 6.61 hours (males) and 8.07 hours (females). The ratio of blood to plasma radioactivity was generally less than 1, suggesting little preferential association of radioactivity with the cellular compartment of blood.

The tissue distribution of radioactivity following SC administration of ^{125}I-abaloparatide was maximal at the injection site, kidneys and pancreas, 0.5 hours after administration. Liver, brown fat and blood radioactivity also peaked at this time with values slightly above 100 ngEq/g. After 2 hours, the highest radioactive concentration was in urine. Radioactive concentration peaked at this time in almost all the other organs, with values generally not exceeding 121 ngEq/g. The radioactivity declined and was generally cleared by 72 to 120 hours in these organs.

The applicant points out that the results are consistent with a rapid distribution ^{125}I-abaloparatide, followed by rapid clearance and a renal route of elimination. From the Assessor´s point of view this study does not show a marked binding of abaloparatide to the target bone tissues since no specific binding can be seen. In comparison to the results obtained with RIA assays the elimination half-life is markedly prolonged from approximately 1 hour to 7 to 8 hours and the results obtained may indicate rather the fate of the liberated [125]Iodide within the organism than the distribution of abaloparatide within the body. No drug-related radioactivity was detectable in the eye or skin at 120 hours. However, the applicant did not evaluate distribution of radioactivity in pigmented rats. Thus, it is not possible to assess potential melanin binding. Since abaloparatide does not absorb the visible wavelengths (290 to 700 nm), this deficiency is not considered crucial.

The binding of abaloparatide to plasma proteins was evaluated in dogs, monkeys and humans. The free fraction of abaloparatide was similar in dogs (26% in males and 29% in females) and in humans (26% in males and 30% in females) and was slightly higher in monkeys (43% in males and 53% in females). The free fraction in rats could not be determined. These data suggest that abaloparatide does not appear to be highly bound to plasma proteins and that at doses equivalent to the therapeutic dose, abaloparatide may be slightly more pharmacologically active in monkeys than in humans and dogs.

Metabolism was investigated in four in-vitro studies. One study evaluated in vitro the degradation of ^{125}I-Tyr0-abaloparatide by rat kidney and liver homogenates, as well as by the purified enzymes chymotrypsin and cathepsin B. Abaloparatide was quickly transformed in all preparations, the rate of transformation being kidney homogenate > chymotrypsin > liver homogenate > cathepsin B, with 97%, 94%, 73% and 56% of transformed abaloparatide after 30 minutes. Liver and kidney homogenates led to the same metabolites, which were not found following incubation with chymotrypsin and cathepsin B. Additionally, kidney homogenates led to an additional metabolite, however the specific peptide sequence of these metabolites was not elucidated during this study. A metabolite profile of urine and faeces collected during the in vivo study did not allow the determination of the metabolites other than one, hypothesized to be free iodine eliminated via the urine.

In a second in vitro study the degradation of abaloparatide in the presence of human liver and kidney homogenates was investigated. Six peptide fragments were identified after 1-hour incubation, consistent with a non-specific degradation of abaloparatide into multiple peptide fragments. The potential activity of the metabolites was investigated in the rat osteosarcoma cell line UMR-106 expressing the PTH1 receptor. Ten potential abaloparatide fragments were tested, only one had agonistic activity (fragment 1-31) and one (fragment 20-31) had a weak antagonistic activity in presence of abaloparatide. The results of the studies indicate that the metabolic pathway of abaloparatide is consistent with non-specific proteolytic cleavage, both in rat and in human liver and kidney preparations. This resulted in the formation of inactive peptide fragments. The potential elimination of abaloparatide via proteolytic degradation and elimination via the kidneys appeared greater than that of the liver. In conclusion, abaloparatide was rapidly metabolised *in vitro* and *in vivo* into smaller peptide fragments, however no clearly defined pathway was identified.

Excretion

Excretion was investigated in two studies. One study was considered to be of minor interest because of the suspected liberation of the radioactive iodide as discussed above. In the second study 91% and 102% of the radioactivity was excreted within the first 48 hours in males and females respectively. Faecal excretion was minimal, and 168 hours after administration, 82% ± 13% and 94% ± 9% of the radioactivity were excreted in urine and 4.8% ± 1.3% and 4.5% ± 1.7% were excreted in the faeces of male and female rats, respectively. The results obtained are in accordance with a renal elimination as main route of excretion. However, as already suggested the results may reflect rather the elimination of iodide out of organism than the elimination of abaloparatide. Most likely there will be a break-down of abaloparatide by the plethora of proteases. This will result in smaller peptides or single amino acids will take part in the anabolic and katabolic processes within the body. Under this aspect urea would be the final excretion product. This view is supported by the simple fact that no unchanged abaloparatide was found in the urine. The excretion into milk was not studied, because of the lack of relevance for the intended patient population (postmenopausal women). Considering the results obtained within the biodistribution studies specific studies would most likely reflect the transmission of the labelled iodide and not the excretion of abaloparatide into the milk. Further studies are therefore not required.

2.4.3. Toxicology

The toxicity profile of abaloparatide was characterized in GLP-compliant single-dose studies in mice and rats, and repeat-dose toxicity studies in rats and cynomolgus monkeys, up to 6- and 9-month duration, respectively. No in vitro potency data for these species was submitted (see Pharmacology); however,

abaloparatide was shown to be pharmacologically active in both rats and monkeys; thus, the choice of species is endorsed. Abaloparatide was administered by SC injection in all in vivo toxicity studies. This is the same administration route as the intended clinical route. The doses chosen for the studies are considered appropriate to characterize the toxicity of abaloparatide.

2.4.3.1. Single dose toxicity

Single-dose studies were performed in mice and rats, using IV and SC administration of abaloparatide at a dose of 42 mg/kg bw. Transient hypoactivity and neurological signs were observed after IV, but not SC, injection. The approximate lethal dose for both species was > 42 mg/kg bw. The margins to human therapeutic dose are in the range of 3000-6000x. In conclusion, the acute toxicity of abaloparatide is considered low.

2.4.3.2. Repeat dose toxicity

The majority of treatment-related findings in repeat-dose toxicity studies with abaloparatide in rats and monkeys were due to exaggerated pharmacology (agonism of PTHR1). The toxicity findings can be divided into primary effects on bone and secondary effects. Main target organs of toxicity were the bone, bone marrow, kidney and heart.

In the 4-week study in rats with abaloparatide doses of 0, 15, 70 and 300 µg/kg bw/day, no mortalities occurred and clinical signs were limited to transient tachypnoea and vasodilation-caused reddening of parts of the body. Reddish colour of the extremities and skin was observed in all three repeat-dose toxicity studies, at doses of $\geq$ 10 µg/kg. The effect was transient, sometimes associated with tachypnoea, and considered possibly due to a peripheral vasodilatory effect of abaloparatide. No similar findings were present in monkeys. Effects on investigated parameters mainly reflected exaggerated pharmacological effects including bone formation caused by a decrease in bone marrow spaces, signs of anaemia/thrombocytopenia and extramedullary haematopoiesis and increases in serum and urine Ca^{2+}. Obviously related to stress, there was a non-dose dependent slight decrease in thymus weight, correlated with involution in one female, at ≥15 µg/kg. As in the rat studies of longer durations, coagulation time was shortened and, as seen in the monkey studies , the albumin/globulin ratio was decreased. A decreased albumin/globulin ratio was observed in all rat studies, at doses of $\geq$ 10µg/kg, and in cynomolgus monkeys at $\geq$ 100 µg/kg. The applicant did not discuss the mechanism behind this finding. It is possible that it may be linked to calcium homeostasis, since both albumin and globulin can bind to calcium. The low dose of 15 µg/kg bw/day may with limitations be considered the no-observed-adverse-effect level (NOAEL) of this study, as already at this low dose slight secondary effects were observed.

Similarly, in the 13-week rat study (abaloparatide doses 10, 25, 70 µg/kg bw/day) no deaths occurred and transient vasodilation was seen. Apart from effects attributable to exaggerated pharmacological action on bone metabolism and subsequent consequences, among them effects on blood count, extramedullary haematopoiesis, increased spleen weight and Ca^{2+} homeostasis, coagulation time was shortened, albumin/globulin ratio was decreased and kidney weights were increased. In high dose, males serum Ca^{2+} was increased transiently 3 hours after abaloparatide administration. Due to the kidney effect, with limitations a NOAEL of the low dose of 10 µg/kg bw/day may be considered, although already at this low dose slight secondary effects were observed.

In the 26 weeks study in rats with identical abaloparatide doses as in the 13-week rat study one high dose female died to reasons obviously unrelated to abaloparatide (lymphosarcoma). Effects seen in this study are in line with those seen in the rat toxicology studies of shorter duration mirroring mainly exaggerated pharmacological effects of abaloparatide. Transient vasodilation was observed as in the other rat studies of shorter duration but also shortened coagulation time and decreased albumin/globulin ratio. Minimal to slight vacuolation of the zona glomerulosa was observed at ≥10 µg/kg, being associated with increased weight of the adrenal gland at 70 µg/kg. This finding was not associated with any necrosis or inflammation in the adrenal gland and is thus not considered to be adverse. Due to mineralisation of the renal pelvis, with limitations a NOAEL of the low dose of 10 µg/kg bw/day may be considered, although already at this low dose slight secondary effects were observed.

A 3 days dose range finding study in cynomolgus monkeys compared abaloparatide with hPTH(1-34) [consistent with teriparatide]. Serum Ca^{2+} increased after administration of 0.75 µg/kg bw/day of hPTH(1-34) similarly as after 7.5 µg/kg bw/day of abaloparatide (in males slightly above maximum pretest values).

In another dose range finding study in monkeys of 2 weeks duration with abaloparatide doses of 0, 3.5, 10, 50, 150, 450 and 1000 µg/kg bw/day (one animal of each sex/dosing group) the high dose female was sacrificed Day 11 in moribund state due to marked renal tubular necrosis. This female showed obviously stress-related moderate adrenal cortical hypertrophy. Apart from exaggerated pharmacological effects of abaloparatide on bone and subsequent consequences starting from 450 µg/kg bw/day clinical signs (decrease in food consumption and bw) and in females, renal effects were noted.

In the 4-week study with daily doses of 0, 100, 200 and 450 µg/kg bw no deaths occurred but 1of 3 high dose males presented in a poor condition. The effects noted in this study appear to be caused mainly by the pharmacodynamic effects of abaloparatide. One of 3 high dose males showed an increased kidney weight corresponding histopathologically to peritubular fibrosis and mineralization. As the pharmacodynamic effects at the low dose are of low magnitude and as a decrease in albumin/globulin ratio seen in this study at the low dose is low and not of statistical significance (although dose-dependent), 100 µg/kg bw/day may with limitations be considered NOAEL of this study.

In the 13 week study in cynomolgus monkeys with daily doses of 0, 10, 50 and 200 µg/kg bw and a recovery period of 2 weeks two high dose animals died after 8 and 9 weeks due to renal tubule-interstitial nephropathy with mineralisation and myocardial degeneration with necrosis and mineralisation.

Apart from exaggerated pharmacological effects of abaloparatide another female presented tubulo-interstitial nephropathy and kidney weights were increased in high dose animals. Low and medium dose animals showed after abaloparatide administration transient serum Ca^{2+} increases mostly within physiological ranges. After the recovery period (2 animals / sex / group) obviously neither findings of any toxicological significance nor the presence of subendosteal fibroblast proliferation, osteoblasts, osteoclasts or woven bone is any longer reported. The medium dose of 50 µg/kg bw/day is accepted as the NOAEL.

In the 39 weeks study in cynomolgus monkeys with abaloparatide doses of 0, 10, 25 and 70 µg/kg bw/day (lowered to 50 µg/kg bw/day at week 21) and a recovery phase of 2 weeks 4 animals died due to hypercalcaemia-caused morbidity (mineralisation of kidney tubules, myocardium, lung, stomach epithelium, salivary glands): one low dose male at week 20, one high dose male and two high dose females at weeks 7, 7 and 15, respectively. Several preterminally euthanized animals showed obviously stress-related lymphoid depletion in the thymus and/or spleen. Kidney weights were increased starting at the medium dose (statistically significant in high dose males).

Mineralisation was seen to different degrees in several organs of all dosed animals. Increases in serum Ca^{2+} are only reported for 1 of 4 females of the medium dose group and in 2 of 5 females of the high dose group. Therefore, apparently an increase in serum Ca^{2+} does not necessarily precede mineralisation of organs. The applicant was initially asked to discuss how abaloparatide can be safely used in patients without exposing patients to the risks of organ mineralisation. Occurrence of tissue mineralization in nonclinical animal studies is considered a class effect for PTH1 receptor agonists and was observed in nonclinical studies with teriparatide as well. Regarding teriparatide this effect in nonclinical studies translated apparently not into tissue mineralization in patients during clinical use. A renal CT Scan Sub-study did not yield evidence of increased mineralization in the subset of patients who underwent renal CT scans in clinical study BA058-05-003 with dosing of abaloparatide (80 µg SC/day), teriparatide (20 µg SC/day) or placebo over 18 months. The risk of organ mineralization (calcification) is in response to an initial clinical question included in the Summary of safety concerns in the Risk Management Plan. In response to a request, the applicant amended SmPC section 5.3 Preclinical safety data appropriately in order to add information regarding organ mineralisations in non-clinical studies and AUC based exposure ratios to the intended clinical exposure.

Regarding bone (femur, vertebra, other bone) no microscopic findings are reported (therefore, bone metabolism is obviously not increased). Emesis and non-formed or liquid faeces were observed in all pivotal studies in monkeys at doses of $\geq$ 10 µg/kg. The emesis was probably the cause of decreased food consumption and associated lower body weight in males at $\geq$ 10 µg/kg in the 39-week study. Emesis appears to be clinically relevant, since 'nausea' is listed in the adverse reactions table in section 4.8 of the SmPC, with frequency common. It is considered that the study did not identify a NOAEL.

Toxicokinetics

In several of the repeat-dose studies in rats and monkeys, plasma exposure to abaloparatide increased more than expected from Day 1 to the end of the study, indicating accumulation. This was particularly evident in the 13-week monkey study, where it was suggested that the development of anti-drug antibodies (ADA) was associated with an increased exposure, resulting from a prolonged extravascular clearance of the drug. On the other hand, the assay used for antibody determination was considered unreliable by the applicant, due to high unspecific binding. Thus, the reason for the increased exposure in the 13-week study, as compared with the 39-week study, remains unclear.

Exposure margins

Safety margins between NOAELs in repeated dose toxicity studies and intended human clinical exposure are extremely small or nearly non-existent: for the rat C_{max} based (13 weeks study, Day 86) 1.052, AUC based (same study, Day 1) 1.153 (which is similar to 1.177 [26 week study, Day 1] or 1.8 [same study, Day 182]), or less than 1.682 (rat 2 years carcinogenicity study, Day1). In the latter study already at the lowest dose of 10 µg/kg bw/day tissue mineralization was found in the major arteries and kidneys. In the 39 weeks repeated dose toxicity study in monkeys of the longest duration (and therefore of main importance) no NOAEL could be determined due to obviously hypercalcaemia caused death of one male animal in the low dose group. Safety margins resulting from this study are below 3.5 based on AUC.

2.4.3.3. Genotoxicity

Abaloparatide was tested in the standard battery of genotoxicity assays according to ICH S2 (R1) consisting of a bacterial gene mutation assay, and an in vitro and in vivo assay for chromosome damage. There was no evidence for a mutagenic potential of abaloparatide.

2.4.3.4. Carcinogenicity

Abaloparatide was investigated for its carcinogenic potential in rats in a 2-year bioassay with a comparator arm treated with hPTH(1-34). This is accordance with the ICH S6 (R1) and rat is considered a pharmacologically relevant species.

Abaloparatide was administered via once daily SC injection at 0, 10, 25 and 50 µg/kg to Fischer 344 rats. The comparator group was treated with 30 µg/kg hPTH(1-34). Based on broadly similar margins to human therapeutic exposure with the mid-dose abaloparatide group (14-20x for abaloparatide, 14-25x for hPTH), this comparison is considered relevant.

Mortality rate in drug-treated rats was increased compared to controls, due to increased incidences of osteosarcoma and osteoblastoma at $\geq$ 10 µg/kg abaloparatide, and at 30 µg/kg PTH(1-34). In females the incidence of bone tumours in mid dose females was similar to that in females treated with hPTH(1-34) whereas the incidence was slightly higher in male rats compared to hPTH(1-34).

Osteosarcomas originated from different bones with tibia being the most frequently affected. Males were more affected than females, showing higher incidences of osteosarcoma and associated clinical signs (limited usage or paralysis of hind legs). The incidence of palpable masses (mainly bone tumours) was increased in rats treated with abaloparatide compared to hPTH(1-34), however the time of onset did not differ significantly between the groups. Osteosarcoma metastases to soft tissues were frequent and comparable between abaloparatide and PTH (1-34). There were no other treatment-related neoplastic findings in the study.

Exposure at the lowest abaloparatide dose where osteosarcoma occurred (10 µg/kg/day), was 3.6x the human therapeutic exposure. However, there was no neoplastic NOAEL.

Non-neoplastic bone changes observed in the abaloparatide and hPTH(1-34) groups, included osteoblast hyperplasia, hyperostosis and osteofibrous dysplasia. Treatment related soft tissue mineralization in the heart (vessels) and kidney (pelvis) was observed in abaloparatide and PTH(1-34)-treated rats. Increased incidence of extramedullary haematopoiesis in the spleen, and increased incidence of alveolar histiocytosis, was observed in all abaloparatide-treated groups and in the PTH(1-34)-treated group, and considered secondary effects to the obliteration of the bone marrow space and osteosarcoma lung metastases respectively. Dilatation, haemorrhage and/or inflammation of the urinary bladder were observed at a slightly increased incidence in abaloparatide-treated males at > 25 µg/kg/day. These findings were probably secondary to the presence of osteosarcoma localized in the spine or pelvis, which may have interfered with the neural control of micturition. Overall, there was no significant difference in incidence or severity of non-neoplastic findings between the abaloparatide 25 µg/kg group and the hPTH(1-34) group.

2.4.3.5. Reproductive and developmental toxicity

Since the intended patient population is postmenopausal women with osteoporosis, the reproductive and developmental toxicology program was limited to a male fertility and early embryonic development study in

rats with dosing of males only. A female fertility study, embryo-foetal development studies in rats and/or rabbits and a prenatal and postnatal development toxicity study were not performed. This is acceptable. Treatment with abaloparatide at doses of 10, 25 and 70 µg/kg/day for 2 weeks before mating, throughout the mating period and 2 weeks after, did not cause any effects on mating performance, sperm parameters, pregnancy index, uterine and litter parameters.

2.4.3.6. Local Tolerance

The applicant conducted 2 local tolerance studies with venous, perivenous and subcutaneous administration in rabbits, which did not indicate a local irritating potential for abaloparatide. The abaloparatide concentration of the clinical formulation is by a factor of approx. 40 or 20 times higher, respectively, than those ones used in the preclinical local tolerance studies. Furthermore, the composition of the formulations is different. Therefore, the findings of these nonclinical local tolerance studies may underestimate the potential local tolerability in humans. As the meanwhile gathered clinical experience with the clinically intended formulation with repeat administration in Phase 2 and Phase 3 studies supports the tolerance in patients up to 18 months of treatment, conduct of non-clinical local tolerance studies with the clinically intended formulation is considered neither necessary nor appropriate.

2.4.3.7. Other toxicity studies

Antigenicity

Occurrence of ADA was investigated in multiple repeated dose studies, among them the 12 months and 16 months pharmacology studies in rats (Study 10RAD029) and monkeys (Study 10RAD030), the carcinogenicity study (Study 10RAD032), and the 39 weeks repeated dose toxicity study in monkeys (Study 7801-125) using validated normalised assay cut-point (NACP) and RIA methods. There was a large variation in antibody response between the studies, ranging from < 2% to 39%, without any apparent correlation to dose or duration of exposure.

In long-term rat and monkey studies, where ADA detection was performed with more validated assays, the number of ADA-positive animals was low, both in rats and monkeys, and there was an apparently higher abaloparatide exposure in ADA-positive rats, but this was not the case in the single ADA positive monkey. The bioanalytical method used by the applicant for determination of serum abaloparatide levels did not distinguish between free vs. antibody bound abaloparatide. Therefore, no information is available regarding the level of free, pharmacologically active abaloparatide in anti-abaloparatide antibody positive animals.

The low number of ADA-positive animals in long-term animal studies is in contrast to the situation in patients, where 49% developed ADA following 18 months of treatment (pivotal phase III study), and ADA formation correlated with a decrease in abaloparatide exposure. Thus, the non-clinical results do not reflect the clinical situation and are considered of limited value for human risk assessment.

Abaloparatide is a synthetic peptide with homology to the N-terminal part of human PTHrP. The amino acid sequence of rat, monkey and human PTHrP is identical and, therefore, abaloparatide shares the same degree of amino acid identity (76%) to the endogenous PTHrP of rats, monkeys and humans. The difference in immunogenicity across species cannot be explained only by the degree of amino-acid sequence identity.

Immunotoxicity

The observation of increased spleen weights, changes in white blood cell counts and formation of osteosarcomas and osteoblastomas in rats are related to the pharmacological effect of abaloparatide, namely the reduction of the bone marrow canal secondary to bone formation and the direct anabolic effect on bone. Therefore, these effects are of no immunotoxicological significance and the conduct of additional immunotoxicity studies with abaloparatide is not considered necessary.

Impurities

A degradation product of abaloparatide, appearing during long term storage, and its toxicological profile was evaluated in molecular potency and target binding screens, 2- and 4-week toxicity studies in rats, and in a complete genotoxicity package (gene mutation test in bacteria, chromosomal aberration test *in vitro*, bone marrow micronucleus test *in vivo*). The results of these studies showed that this impurity was 10-fold less potent than abaloparatide and did not inhibit molecular targets at clinically relevant doses. The genotoxicity studies showed negative results. There were no new or additional toxicological findings associated with this impurity, following abaloparatide/degradant administration at 65/5 µg/kg/day or 21/49 µg/kg/day, for 4 weeks. The applicant suggests a specification limit for the impurity of abaloparatide at the end of shelf life. Exposure to this impurity in the rat toxicology studies, which did not demonstrate any new or exaggerated toxicological findings, was up to around 600-fold compared to the human exposure to this impurity with the 80 ug dose at the proposed specification. At the NOAEL in a 2-week repeated dose toxicity study in rats exposure to this impurity was 155-fold compared to the human exposure to this impurity with the 80 ug dose at the proposed specification limit. The specification limit proposed by the applicant is considered toxicologically qualified.

Phototoxicity

As abaloparatide does not absorb visible wavelengths and as no evidence for accumulation in organs exposed to light was seen, abaloparatide does not raise concerns regarding phototoxicity.

2.4.4. Ecotoxicity/environmental risk assessment

Table 2. Summary of main study results

Substance (INN/Invented Name): abaloparatide			
CAS-number (if available):			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, default or refined (e.g. prevalence, literature)	4.0×10^{-4}	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)	N/A	N/A	N/A

2.4.5. Discussion on non-clinical aspects

In vitro studies showed that abaloparatide is acting specifically via the PTH1 receptor. The non-clinical *in vivo* pharmacology program demonstrated that daily SC injections of abaloparatide stimulated the formation of bone and restored bone mineral density (BMD) at vertebral and nonvertebral sites in OVX, osteopenic rats and monkeys as compared to relevant vehicle controls. The provided non-clinical *in vivo* studies do not, however, convincingly show that abaloparatide displays a differentiating profile compared to hPTH(1-34) (teriparatide). Notably there was no significant difference in calcium plasma mobilization at therapeutic doses of abaloparatide compared to hPTH1-34 *in vivo*, whereas hypercalcemia was in fact observed at clinically relevant exposure levels of abaloparatide in repeat-dose toxicity studies. Furthermore, both compounds were similarly efficacious anabolic agents capable of fully restoring BMD at comparable doses in OVX rats.

In safety pharmacology studies performed in conscious dogs, SC administration of abaloparatide dose-dependently and significantly increased heart rate (68-120% max increase at 1-10 µg/kg) while the QT interval was markedly shortened at all doses (max decrease ~60 ms). The observed increase in heart rate is believed to be of clinical relevance and should be investigated clinically, whereas an influence on QT intervals appears to be not likely.

Pharmacokinetic data revealed no unexpected findings regarding a synthetic peptide with SC administration. However, the pharmacokinetic profile of abaloparatide was not established in all species tested *in vivo* (i.e. PK results were absent in the dog). However, the relevance of this deficiency for the safe use of the product appears to be low. Further studies are not considered necessary.

Repeat-dose toxicity studies with abaloparatide in rats and monkeys identified the bone, bone marrow, kidney and heart as main target organs for toxicity. The observed effects were due to exaggerated pharmacology (agonism of PTHR1). The anabolic effect on bone was overall more pronounced in rats than in monkeys and occurred at lower doses and exposure levels as well. The reason for this difference between species is probably a more osteoblast-driven, proliferative response to PTH agonists in rats as compared with monkeys, where PTH appears to stimulate bone remodelling.

The major non-clinical finding that is considered of potential concern for patients is tissue mineralization, with or without associated hypercalcaemia. In long term animal repeated dose studies mineralisation of organs was seen at low dosages and at exposure ranges close to the clinically intended exposure.

The non-clinical data suggests that tissue mineralization can occur even without persistent hypercalcaemia, as evidenced by the transient or (in 26-week rats) non-detectable changes in serum calcium levels. Furthermore, mineralization in monkeys occurred also in the heart and other organs apart from the kidneys. Calcium deposition was associated with degenerative/necrotic and inflammatory lesions in the heart and kidney and was not reversible in the 39-week study. Hypercalcaemia has been observed in the clinical setting as well.

In a two-year bioassay in rat, abaloparatide induced the formation of osteosarcoma at every tested dose. Due to the high incidence of osteosarcomas there was a resulting lower survival, especially in males. There is a theoretical risk that the lower survival rate may have obscured less pronounced carcinogenic effects in other tissues. However, there is no evidence for carcinogenicity in other tissues than bone.

The carcinogenic potential of abaloparatide in rats is qualitatively comparable to hPTH(1-34). Quantitative differences observed (e.g. higher incidence of bone tumours in males treated with abaloparatide versus hPTH(1-34)) are difficult to assess due to the lack of exposure data for hPTH(1-34). Both molecules are activators of hPTH1R and the carcinogenic potential in rats is probably a class effect for hPTH1R agonists. The

potential reasons for the rodent specific development of osteosarcomas are exaggerated response of rat bones to constant hPTH1R activation and osteoblast stimulation and the differences in bone metabolism in rodents and humans.

The effect in rodents is predominated by bone formation whereas in primates the main effect is remodelling including bone resorption and reconstruction. The species differences between rats versus monkeys and humans in terms of bone anabolic response are well documented in scientific literature. There is broad scientific consensus on these species' differences. Nevertheless, osteosarcoma must remain as an important potential risk for patients treated with abaloparatide and – similar to rhPTH(1-34) – appropriate risk mitigation and follow up measures are necessary.

The applicant has performed a Phase I assessment, as specified in the ERA guideline. The Log K_{OW} values for abaloparatide, and LogP values for the non-natural amino acid 2-aminoisobutyric acid, which is a part of abaloparatide, were not experimentally determined. Normally this would be required; however, considering that abaloparatide is a peptide the predicted values can be accepted.

Abaloparatide PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log K_{OW} does not exceed 4.5. Therefore, abaloparatide is not expected to pose a risk to the environment.

2.4.6. Conclusion on the non-clinical aspects

From non-clinical point of view, there are no objections against approval of Marketing Authorisation of abaloparatide.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 3. Clinical studies

Study No, Phase No, Sites, Country(ies)	Study Design Treatment Duration	Clinical Pharmacology Endpoints	Study population, Gender M/F Median Age (Range)	Dosage Form, Treatment: Dose, Route & Regimen	No. randomised	N° batch ABL
2-52-52127-001 Phase 1 1 in Germany	Part A: Randomised, Double-blind, Dose escalation, Placebo-controlled, Single dose Part B: Randomised, Open-label, Two-period Cross-over, Single dose	- PK analysis ABL (dose escalation and BA) - Change in serum total and ionised calcium, phosphorus, cAMP, creatinine - change in urine calcium, phosphorus, cAMP	Part A: Healthy subjects 43M/37F Median age: 61 (55-73) Part B: Healthy subjects 8M/8F Median age: 60 (55-69)	Part A: ABL (lyophilised): SC 2, 5, 7.5, 10, 15, 20, 40, 60, 80, and 100 µg Placebo Part B: IV & SC administration sequence randomised. ABL (lyophilisate) -IV 2.5 µg ABL (lyophilisate) -SC 15 µg	Part A (total 80): 6/ABL dose group 2 Placebo Part B (total 16): Randomised/ dosed 16	MBPY, NBLC, NBNC, NBNB
BA058-05-001 Phase 1 1 in Canada, 1 in USA	Randomised, Double blind, Placebo-controlled, Parallel group, Dose escalating 7 days	- PK profile ABL - change in serum total and ionised calcium, phosphorus, PTH(1-84), 1,25 dihydroxy vitamin D - change in urine calcium, phosphorus, cAMP and creatinine - change in serum bone markers (s-PINP and s-CTX)	Healthy PMW Median age:59 (50-73)	ABL (lyophilised): SC 5, 20, 40, and 80 µg, QD Placebo: SC, QD	39 8/ABL dose group 7 placebo	PBQZ
BA058-05-001B Phase 1 1 in Canada	Randomised, Double blind, Placebo-controlled, Parallel group, Dose escalating 7 days	- PK profile ABL - change in serum total and ionised calcium, phosphorus, PTH(1-84), 1,25 dihydroxy vitamin D - change in urine calcium, phosphorus, cAMP and creatinine - change in serum bone markers (s-PINP, PICP, BSAP, osteocalcin and s-CTX)	Healthy PMW Median age: 60 (52-74)	ABL: SC 80, 100, and 120 µg QD (160 µg not enrolled) Placebo: SC, QD	30 8/ABL dose group 6 placebo	643004

Study No, Phase No, Sites, Country(ies)	Study Design Treatment Duration	Clinical Pharmacology Endpoints	Study population, Gender M/F Median Age (Range)	Dosage Form, Treatment: Dose, Route & Regimen	No. randomised	N° batch ABL
BA058-05-010 Phase 1 1 in USA	Cohort 1 (BA): randomised, open-label, single-dose, 2-treatment (SC and IV abaloparatide), 2-sequence crossover study. Cohorts 2-5 (MTD): randomised, double-blind, placebo-controlled, single ascending dose of abaloparatide SC in healthy subjects (MTD determined for the QTc study).	- analysis of ABL (BA and MTD)	Healthy subjects Cohort 1 Healthy subjects 19 total 11M/8F Median age: 34 (20-54) Part B Healthy subjects 40 18M/22 F Median age: 32 (20-53)	Cohort 1: ABL 80 µg SC and ABL 40 µg IV over a 2-hour continuous infusion. Cohort 2: ABL 120 µg SC placebo Cohort 3: ABL 240 µg SC placebo Cohort 4: ABL 320 µg SC placebo Cohort 5: ABL 400 µg SC placebo	Cohort 1: 19 Cohort 2-5: 8/ABL dose groups 2 placebo groups (total: 40)	D28382/BEKL05 (for both SC and IV ABL)
BA058-05-011 Phase 1 4 in Poland	Open-label, parallel group, single-dose study to evaluate the PK, PD and safety of a single dose of abaloparatide in subjects with varying degrees of renal function Single dose	- PK profile ABL - change in serum total and ionised calcium, phosphorus, cAMP - change in urine calcium, phosphorus, cAMP and ratio urine Ca/urine Cr, ratio urine Pi/urine Cr, ratio urine cAMP/urine Cr	Subjects with renal impairment 32 total 18M/14 F Median age: 59 (26-77)	ABL 80 µg, SC Group 1-mild $CL_{CR} \geq 60$ to <90 mL/min Group 2-moderate $CL_{CR} \geq 30$ to <60 mL/min Group 3-severe $CL_{CR} \geq 15$ to <30 mL/min Group 4-normal $CL_{CR} \geq 90$ mL/min	32 8/ABL dose group	20871004-01B - E07274; 20871004-02B - E07274; 20871004-03B – VVNJ24; 20871004-04B - E07274; and 20871004-05B
BA058-05-012 Phase 1 1 in USA	Randomised, partially double-blind (to ABL and placebo), single dose, positive controlled and placebo-controlled, 4-way cross-over study to evaluate the effects of abaloparatide on the QT/QTc interval in healthy subjects Single dose	- change from baseline in QTc, - placebo-adjusted and corrected for HR based on QTcI	Healthy subjects 32 M/23 F Median age: 34 (18-54)	ABL 80 µg, SC ABL 240 µg, SC Moxifloxacin 400 mg PO Placebo SC	4-way cross-over, n=55	E07274

Study No, Phase No, Sites, Country(ies)	Study Design Treatment Duration	Clinical Pharmacology Endpoints	Study population, Gender M/F Median Age (Range)	Dosage Form, Treatment: Dose, Route & Regimen	No. randomised	N° batch ABL
BA058-05-002 Phase 2 10 in Argentina, 6 in India, 4 in UK, 10 in USA	Randomised, Double-blind (for abaloparatide/Placebo), Placebo-controlled, Parallel group, Dose finding 6 months of treatment	- change in BMD of the spine, hip and wrist - change in serum levels of s-PINP, PICP, BSAP, osteocalcin, s-CTX and (urine) levels of NTX	PMW with osteoporosis 222F Median age: 64 (54-84)	ABL 20, 40, 80 µg SC, QD Placebo Teriparatide 20 µg SC QD	222 (43/43/45/46/ 45)	6430004, 644006, 65007
BA058-05-002 extension Phase 2 1 in USA, 7 in Argentina, 3 in India	Extension of Study BA058-05-002 to provide longer term safety and efficacy data 1. 6 months of treatment	- change in BMD of the spine, hip and wrist - change in serum levels of s-PINP, PICP, BSAP, osteocalcin, s-CTX and (urine) levels of NTX	PMW with osteoporosis 55F Median age: 66 (55-83)	ABL 20, 40, and 80 µg SC, QD Placebo SC Teriparatide 20 µg SC QD	55 (13/10/7/11/ 14)	6430004, 644006, 65007
BA058-05-007 Phase 2 3 in USA, 3 in Denmark, 1 in Estonia, 2 in Poland	Randomised Double-blind (for TD, ABL/Placebo) Placebo-controlled Parallel Group Dose-finding 6 months of treatment	- change in BMD-spine, hip and forearm - change in serum bone markers (s-PINP, PICP, BSAP, osteocalcin, s-CTX)	PMW with osteoporosis 51 F (ABL) Median age: 66 (56-84) 50 F (Placebo TD) Median age: 66 (44-84)	ABL 80 µg SC, QD Placebo TD (ABL TD not presented in this submission)	101 (51/50)	D28382
BA058-05-003 Phase 3 14 in EU, 5 in Brazil, 1 in Argentina, 1 in Hong Kong, 5 in USA	Randomised Placebo-controlled Comparative Safety and Efficacy study 18 months of treatment	- change in BMD-spine, hip and forearm - change in serum bone markers (s-PINP, BSAP, osteocalcin, s-CTX)	PMW with osteoporosis 2070 F Median Age: 69 (50-86)	ABL 80 µg SC, QD Teriparatide 20 µg SC, QD Placebo SC	2070 (688/696/686)	BEJH08, BEJH09, BEJJ12, BEKF02, BEKL05, BELD06
BA058-05-005 (extension of BA058-05-003) Phase 3 13 in EU, 5 in Brazil, 1 in Argentina, 1 in Hong Kong, 3 in USA	Open-label extension of Study BA058-05-003 to provide longer term safety & efficacy data after alendronate treatment (integrated analysis for BA058-05-003/005 with 24 months of treatment) Controlled Comparative Safety and Efficacy – Extension Phase 3 study	Same as BA058-05-003	Same as BA058-05-003 963 F Median Age: 69 (50-86)	Alendronate 70 mg oral once per week	963 (469 ABL/alendronate; 494 Placebo/alendronate) All subjects randomised to ABL/PBO in Study BA058-05-003 and who are candidates for alendronate treatment	Not applicable

Study No, Phase No, Sites, Country(ies)	Study Design Treatment Duration	Clinical Pharmacology Endpoints	Study population, Gender M/F Median Age (Range)	Dosage Form, Treatment: Dose, Route & Regimen	No. randomised	N° batch ABL
ITM-058-301 Phase 3 21 in Asia (Japan)	Randomised, Double-blind Placebo-controlled Parallel-group Confirmatory Safety and Efficacy study 18 months of treatment	- change in BMD-spine, hip and forearm - change in bone metabolism markers (PINP, PICP, BALP, osteocalcin, CTX and TRACP 5b	PMW with osteoporosis and men with osteoporosis 192 F 20 M Median Age: 68 (56-85)	ABL 80 µg SC, QD Placebo SC	213 (141/72)	ITM058001 ITM058002
BA058-05-020 Phase 1ª 4 in USA	Open-label Single-arm Histomorphometry study 3 months of treatment, Substudy: 6 months of treatment	- trans-iliac bone biopsies - change in s-PINP and s-CTX	PMW women with osteoporosis 23 F Median Age: 65 (54-85)	ABL 80 µg SC, QD	23	RP011A03 RQ031B01

Table 4. Description of clinical efficacy studies

Study No. Phase No. No. subject by region	Study Design Treatment Duration	Primary Efficacy Endpoint	Study population, Gender M/F Median Age (Range) in years	Dosage Form, Treatment: Dose, Route & Regimen	No. randomised
Study BA058-05-003 Phase 3, 983 in EU, 387 in Asia, 661 in South America, 39 in North America	Randomised, double-blind, placebo-controlled Safety and Efficacy study 18 months of treatment	Incidence of new vertebral fracture and nonvertebral fractures	PMW with osteoporosis 2070 F Median Age: 69 Age range: 50-86	Placebo, SC ABL 80 µg QD, SC Teriparatide 20 µg QD, SC	688 696 686
Study BA058-05-005 *Extension of Phase 3 study BA058-05-003* 441 in EU, 204 in Asia, 302 in South America, 16 in North America	Open-label, 24-month extension of Study BA058-05-003 to provide longer term safety & efficacy data after alendronate treatment 24 months of treatment	Incidence of new vertebral fracture and nonvertebral fractures	Same as BA058-05-003 963 F Median Age: 69.2 Age range: 50-86	Alendronate 70 mg oral once per week	469 (prior-abaloparatide-SC) 494 (prior-Placebo)
Study 3D-DXA Appendix to 3D-DXA Analysis *Post-hoc sub-analysis of Phase 3 Study BA058-05-003*	Retrospective post-hoc analysis in a randomly selected sub-population of Study BA058-05-003	Changes in volumetric BMD and cortical thickness by 3D-DXA at 6, 12, 18 months compared to baseline	Subset of 624 randomly selected subjects from BA058-05-003§	Same as BA058-05-003: Placebo, SC ABL 80 µg QD, SC Teriparatide 20 µg QD, SC	(subgroups randomly selected from existing treatment groups: placebo 208 abaloparatide 207 teriparatide 209

Study No. Phase No. No. subject by region	Study Design Treatment Duration	Primary Efficacy Endpoint	Study population, Gender M/F Median Age (Range) in years	Dosage Form, Treatment: Dose, Route & Regimen	No. randomised
Study ITM-058-301 Phase 3 21 in Japan	Randomised, double-blind, placebo- controlled Confirmatory Safety and Efficacy study 18 months of treatment	Percent change in lumbar spine (L1 L4) BMD at the last visit	PMW with osteoporosis (and men with osteoporosis) Median Age: 68 Age range: 56-85	Placebo, SC ABL 80 µg QD, SC	72 141
Study BA058-05-**002** Phase 2 14 in USA, 147 in Argentina, 49 in India, 12 in UK	Randomised double-blind (for abaloparatide-SC/Placebo) Placebo-control Parallel group Dose finding 6 months of treatment	Change in BMD-spine Change in serum bone markers (s- PINP, PICP, s-BALP, s- OC)	PMW with osteoporosis 221 F Median age: 64 (range: 54 –84)	ABL 20 µg QD, SC ABL 40 µg QD, SC ABL 80 µg QD, SC Placebo, SC Teriparatide 20 µg QD, SC	43 43 45 45 45
Extension of Study BA058-05-002 (Amendment 5) Phase 2 1 in US, 43 in Argentina, 11 in India	Extension of Study BA058-05-002 to provide longer term safety & efficacy data 6 months of treatment	Change in BMD-spine Change in serum bone markers (s- PINP, PICP, s-BALP, s- OC)	PMW with osteoporosis 55 F Median age: 66 (range 55-83)	ABL 20 µg QD, SC ABL 40 µg QD, SC ABL 80 µg QD, SC Placebo, SC Teriparatide 20 µg QD, SC	13 10 7 11 14
Study BA058-05-007 Phase 2 13 in US, 52 in Denmark 15 in Estonia 21 in Poland	Randomised double-blind (for ABL-sMTS/ Placebo) Placebo- controlled Parallel Group Dose-finding 6 months of treatment	Change in BMD-spine, hip and forearm Change in serum bone markers (s- PINP, PICP, BALP, osteocalcin, s-CTX1)	PMW with osteoporosis 51 F (abaloparatide) Median age: 66 (range: 56-84)	ABL 80µg QD, SC Placebo, SMTS	51 50
Study BA058-05-020 (Dempster et al., 2021) (PD study) 4 in US	Open-label, single-arm, multicentre 3 months of treatment	Change from baseline in dynamic indices of bone formation in relevant bone envelopes (cancellous, endocortical, intracortical, periosteal) – Mineralizing surface (MS/BS) – Mineral apposition rate (MAR) – Bone formation rate (BFR/BS)	PMW with osteoporosis 23 F Median age: 67.4 (range: 54-85)	ABL 80µg QD, SC	23
Study BA058-05-028 Post approval	Retrospective observational cohort study 18 months	Time to the first incidence of nonvertebral fracture (hip,	PMW with osteoporosis 23,232 F		No randomisation, but PS-matched

Study No. Phase No. No. subject by region	Study Design Treatment Duration	Primary Efficacy Endpoint	Study population, Gender M/F Median Age (Range) in years	Dosage Form, Treatment: Dose, Route & Regimen	No. randomised
		pelvis, shoulder, radius or ulna, wrist, femur, tibia or fibula, ankle) within the 18 months after treatment initiation.	Median age: 67 (range: 50-80)	ABL, SC Teriparatide, SC Both in alignment with US FDA prescribing information (real-world data)*	cohorts from database: 11,616 11,616

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

The clinical pharmacology of abaloparatide was evaluated in healthy subjects, subjects with renal impairment, and postmenopausal women with osteoporosis. Six Phase I studies (including single and multiple ascending dose studies, and a bioavailability study), as well as one dose-finding Phase II study, one supportive Phase II study, and one pivotal Phase III study were conducted. Additionally, a confirmatory Phase III study was conducted in Japanese subjects. A tabular listing of all clinical studies is provided in Table 3.

The PK evaluations of abaloparatide were carried out as part of clinical studies denoted as: 2-52-52127-001, BA058-05-001, BA058-05-001B, BA058-05-010, BA058-05-011, BA058-05-012, BA058-05-002, BA058-05-007 and BA058-05-003. In the latter study (pivotal Phase III Study), a population PK analysis was conducted.

The first two Phase I studies (2-52-52127-001 and BA058-05-001) were conducted with an initial lyophilised abaloparatide formulation (i.e., Formulation 1) that was discontinued. Subsequently, liquid formulation (i.e., Formulation 2) has been developed for the use with a multi-dose prefilled cartridge and pen delivery device. Formulation 2 (to-be-commercialised formulation) was used in the subsequent Phase I, Phase II and Phase III studies.

Study 2-52-52127-001 was a single-dose PK and bioavailability clinical trial in healthy male and female subjects >55 years of age, study BA058-05-001 was a repeated dose 7-day PK/PD study in 39 healthy postmenopausal women from 50 to 73 years of age, study BA058-05-001B was a repeated dose 7-day PK/PD study in 30 healthy postmenopausal women from 52 to 74 years of age investigating a new liquid formulation presented as prefilled multi-dose cartridge for use in a pen injector device, study BA058-05-010 was a single-dose PK and bioavailability study in healthy male and female subjects 20 to 54 years of age, study BA058-05-011 was a single dose study to evaluate the effects of varying degrees of renal impairment on abaloparatide PK, and study BA058-05-012 was a four way crossover thorough QT/QTc in healthy subjects.

Methods

Abaloparatide was detected in serum using radio-immune assay (RIA) detection after solid-phase extraction. The method was transferred to different laboratories three times, each site performing further development and re-validation of the assay. The method has been appropriately validated with a measuring range of 20 to 800 pg/mL and 20 to 1600 pg/ml, for sample volumes of 1.2 mL and 0.6 mL, respectively.

A tiered assay approach to identify the presence (Tier 1), specificity (Tier 2), and titer (Tier 3) of ADA responses has been used. Anti-abalaparatide antibodies were detected directly from human serum by RIA. Cut-offs specific for the target population has been employed. A cell based neutralising antibody (Nab)-assay was developed and validated, using abaloparatide ability to increases levels of intracellular cAMP.

Further assays for detecting ADAs with PTH and PTHrP cross-reactivity were developed and validated in a similar way as for abaloparatide, i.e. a RIA method for ADA-detection and a cell based Nab-assay based on intracellular levels of cAMP.

Population pharmacokinetic analysis

A population pharmacokinetic analysis was performed with the objectives to establish a structural PK model, identify significant covariates on PK parameters and perform simulations for patients with varying degree of renal impairment. The analysis was based on data from six phase 1 studies in healthy volunteers (BA058-05-004, BA058-05-006, BA058-05-008, BA058-05-010, BA058-05-011, BA058-05-012) and one phase 3 study in patients (BA058-05-003). The database included 5232 measurable concentrations from 967 subjects following IV and SC dosing (40-320 µg).

A standard workflow was used to develop the final model, consisting of a two-compartment model with linear elimination. The model structure was considered overall reasonable; however, empirical implementations were present in the final model. This included an estimated time-varying infusion rate considered necessary to describe the IV data, despite the study protocol specifying a constant infusion rate. In addition, a visit-dependency in bioavailability among patients was included, without a clear biologic explanation.

A standard stepwise procedure was used for the covariate analysis and identified several covariates, including dose on bioavailability, dose on Vc, a patient factor on bioavailability and creatinine clearance on CL. In addition, time-constant ADA was an influential covariate on CL and Vc where the estimates suggested a considerable alteration of abaloparatide at ADA positive status. According to the MAA, limited recovery of abaloparatide in plasma samples with presence of ADAs (due to assay interference) may contribute to the estimated effect of ADAs.

Body weight, BMI, BSA, age, race, the presence of Nab, markers of liver function (bilirubin, albumin, AST, and ALT) were not identified as significant covariates. The parameter estimates (see Table 5) and their uncertainties were overall reasonable. The final model described the observed data overall well according to visual predictive checks.

Table 5. Final Population PK parameters of abaloparatide

Parameter	Estimate	BSV%	Shrinkage
CL (L/h)	48.7 x 1.59 if ADA titer ≤1:1) x 2.92 if ADA titer >1:1) x $(CRCL/79)^{0.371}$	27.9%	32.4%
Vc (L)	12.3 x 2.46 if ADA Low (≤1:1) x 14.9 if ADA High (>1:1) x $(DoseSC/80)^{0.350}$	63.5%	52.9%
CLp (L/h)	20.7	0, Fixed	NA
Vp (L)	30.2	49.2%	48.8%
Ka (h^{-1})	1.57	44.4%	33.4%
F	0.532 x $(DoseSC/80)^{-0.250}$ x 0.83 if Healthy Subjects x 1.17 if Visit 4 (Patients) x 1.19 if Visit 5 (Patients) x 1.06 if Visit 6 (Patients) x 0.98 if Visit 8 (Patients)	27.8%	38.3%
Infusion Model			
InfRate0 (µg/h)	7.01	0, Fixed	NA
InfRateMax (µg/h)	15.9	0, Fixed	NA
InfDur50 (h)	0.38	0, Fixed	NA
Hill	5.6	0, Fixed	NA
Error Model			
Log Error	0.429	NA	NA

CL: clearance, Vc: central volume of distribution, CLp: peripheral clearance, Vp: peripheral volume of distribution, Ka: rate constant of absorption, F: bioavailability, InfRate0: the infusion rate at time 0, InfRateMax: maximum infusion rate, InfDur50: duration of infusion associated with 50% of the maximum infusion rate. BSV: Between-subjects variability.

For Study BA058-05-003 and BA058-05-005, at the request of the Committee on Human Medicinal Products (CHMP), data from two sites in Europe were excluded from analysis due to GCP issues that were raised at the previous 2015 MAA. Therefore, all data from these two European investigative sites were excluded from all data analyses presented.

A sensitivity analysis was performed by re-estimation of the final model with exclusion of two excluded EU sites which resulted in comparable parameter estimates. An updated PopPK analysis was performed, where ADA was explored as a time-varying covariate which resulted in overall comparable estimates for the ADA coefficients (data not shown).

The final model was used to perform simulations to determine the effect of creatinine clearance (CL_{CR}) on key PK parameters. A typical patient (postmenopausal woman with osteoporosis) with normal or moderate renal impairment is expected to have AUC_{0-24}, C_{max}, and elimination half-life values within 22% of that observed in a patient with mild renal impairment. A typical patient with severe renal impairment is expected to have AUC_{0-24}, C_{max}, and elimination half-life values 57%, 23% and 20% higher than that observed in a typical patient with mild renal impairment, respectively.

Absorption

The bioavailability of the to-be-marketed formulation of abaloparatide was determined following a single dose of 80 µg SC injection, and a single dose of 40 µg IV administered over a 2-h continuous infusion, which were

administered to healthy volunteers of both genders. Abaloparatide was rapidly absorbed with median T_{max} of 0.4 h and 1.8 h for SC and IV administration, respectively, while mean $t_{\frac{1}{2}}$ were 1.9 h and 0.9 h, respectively. Following SC injection C_{max} reached 467.3 ± 143.83 pg/mL. Thereafter abaloparatide plasma concentrations declined in a multiphasic manner until 3 h for SC administration, which was (for most of the study subjects) the last time-point with data above the LLOQ. Clearance and the apparent volume of distribution (Vz/F) were greater after SC than after IV administration. Bioavailability for abaloparatide 80 µg SC was 39.44% (90% CI: 32.6 to 47.8%).

Figure 2. Mean (±SD) abaloparatide plasma concentrations after 80 µg SC injection and 40 µg IV 2-hours infusion (N=18); the BA arm (Cohort 1) of Study BA058-05-010
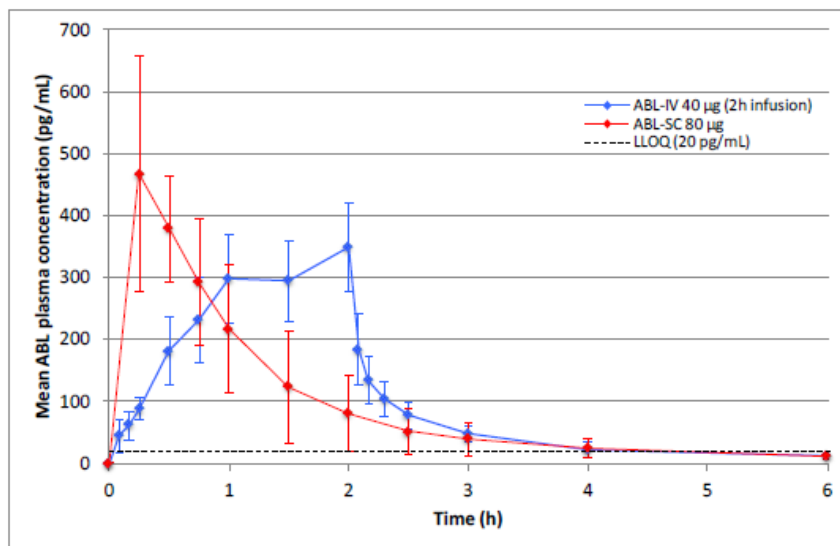
According to the applicant, except for the first two Phase I studies in humans, the same liquid formulation of abaloparatide in a multi-dose prefilled cartridge has been used to be applied with a pen delivery device in all pivotal clinical studies. Therefore, all relevant PK and PD data have been generated with this final to-be-commercialised abaloparatide formulation. Thus, no bioequivalence data are required. Moreover, abaloparatide is to be administered SC and therefore no studies to evaluate the effect of food on PK have been conducted.

Distribution

Human plasma protein binding of abaloparatide *in vitro* is about 70% (i.e., fraction unbound of about 30%). The apparent volume of distribution Vss was estimated to be 42.5 L in the Phase III PopPK analysis.

Elimination

Clinical PK data indicated that abaloparatide has a rapid elimination ($t_{1/2}$ of about 1h after SC administration), and that it is primarily excreted in urine. Metabolism of abaloparatide has been investigated in preclinical studies only, which is acceptable for a compound comparable to an endogenous protein. Abaloparatide appears to be rapidly degraded by multiple proteases into shorter peptide fragments which are then renally excreted.

There are no clinical data available regarding the fraction excreted in urine (i.e., the applicant has not quantified the unchanged parent drug in human urine). Lack of the human urine PK data hinders the exact

estimation of abaloparatide renal clearance. It is worth noting that in a preclinical mass-balance study in rats (Study 15RAD105), no full-length parent 125I-abaloparatide was found in urine (i.e., only smaller peptide fragments were detected in urine). Furthermore, in vitro studies (TNED-09-0198 and BA058-145) indicated that kidney tissue homogenates had a larger metabolic capacity for abaloparatide (faster abaloparatide degradation) than the respective liver tissue homogenates, which suggests that kidneys could also play an important role in the metabolism of abaloparatide and not just in its excretion. Overall, based on the currently available data it can be concluded that kidneys play an important role in the elimination of abaloparatide through its metabolism and/or excretion, as well as the main route for the excretion of its metabolites (i.e., excretion of smaller peptide fragments).

Dose proportionality and time dependencies

Based on the available PK data from different Phase I studies, the systemic exposure of abaloparatide increased with the increasing abaloparatide SC doses over the dose range from 5 µg to 240 µg. However, it is also worth noting that there was a general slight tendency towards the less than dose-proportional increases over the mentioned dose range. Moreover, further increase in abaloparatide SC doses to 280 µg and 320 µg resulted in no further increase in its systemic exposure. The lack of further increases in the systemic exposure (beyond 240 µg abaloparatide dose) could potentially be attributed to a saturation of its absorption from the SC injection site.

Abaloparatide does not seem to exhibit the time dependent pharmacokinetics since mean PK parameters were in general comparable between Day 1 and Day 7. Furthermore, the mean accumulation index after repeated dosing observed in Study BA058-05-001B was from 1.11 to 1.25. ADA development may occur in patients over time and may lead to differences in observed PK parameters which was indicated based on the PopPK analysis (see section 'Population Pharmacokinetic analysis').

Special populations

The pharmacokinetics of abaloparatide in subjects with impaired renal function has been investigated in a dedicated Phase I study (BA058-05-011). Abaloparatide is primarily excreted in urine, and the systemic exposure increased with decreasing renal function. The ratio of AUC_{0-inf} in BA058-05-011 study was 1.17 (0.81, 1.68), 1.68 (1.15, 2.45), and 2.13 (1.49 – 3.06) in mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function (see table below).

Table 6. Summary of Primary Abaloparatide Plasma Pharmacokinetic Parameters by Renal Status– Study BA058-05-011

PK Parameter (unit)		Mild (N=8)	Moderate (N=7)	Severe (N=8)	Normal (N=8)
C_{max} (pg/mL)	n	8	7	8	8
	Mean	444.0	574.9	639.0	431.0
	SD	153.37	135.59	270.58	142.04
	%CV	34.54	23.59	42.35	32.96
	Median	415.0	512.0	543.0	451.0
	Min, Max	214, 636	426, 772	338, 1140	198, 668
	Geo Mean	418.7	561.6	593.2	408.0
AUC_{0-inf} (hr*pg/mL)	n	8	7	8	8
	Mean	652.1	955.6	1240.5	576.4
	SD	201.67	306.82	514.90	213.62
	%CV	30.93	32.11	41.51	37.06
	Median	725.5	945.0	1244.5	607.0
	Min, Max	349, 895	556, 1341	568, 1923	194, 802
	Geo Mean	619.5	911.2	1134.8	530.5
CL/f (L/hr)	n	8	7	8	8
	Mean	137.3	92.4	78.1	169.5
	SD	55.2	32.4	39.5	104.0
	%CV	40.21	35.07	50.54	61.37
	Median	110.4	84.7	64.3	132.2
	Min, Max	89.4, 229.2	59.7, 143.9	41.6, 140.8	99.8, 411.9
	Geo Mean	129.1	87.8	70.5	150.8

It is worth emphasizing that the target population for treatment with abaloparatide are postmenopausal women with osteoporosis and not healthy young subjects. Thus, the target population is in general more likely to have a certain degree of renal functional impairment. In comparison to subjects with mild renal impairment (representing the true Phase III population), the $AUC_{0-\infty}$ increased 1.47-fold and 1.90-fold for subjects with moderate and severe renal impairment, respectively. Abaloparatide plasma C_{max} concentrations increased 1.29-fold and 1.44-fold in subjects with moderate and severe renal impairment, respectively, compared to the mild renal impairment group representing the target population. Overall, the available clinical data do not indicate need for dose adjustments/restrictions for patients with mild to moderate renal impairment.

No dedicated pharmacokinetic studies in subjects with hepatic impairment were performed which is considered acceptable. As a compound comparable to an endogenous protein, abaloparatide is expected to be eliminated via proteolytic degradation, and not considerably eliminated via hepatic metabolic mechanisms (e.g., no CYP enzyme involvement). Furthermore, results of the population pharmacokinetic analysis in the pivotal phase III trial demonstrated no evidence for a potential correlation with the hepatic function.

Based on the scarce data available, no significant influence of gender on the PK parameters of abaloparatide has been identified. PK data are primarily available in female subjects, which is acceptable since abaloparatide is only indicated in women.

Pharmacokinetics of abaloparatide in children has not been studied. An overview of all subjects included in PK clinical trials by the age group is presented in the table below.

Table 7. Subjects in PK trials by age group (all subjects with PK data)

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	565/1135	159/1135	1/1135

Pharmacokinetic interaction studies

No dedicated *in vivo* drug-drug interaction (DDI) studies have been conducted with abaloparatide. The applicant considered the potential for DDI to be low. It was argued that abaloparatide is a potent and selective ligand for PTHR1 with no known significant affinity to PTHR2 or other molecular targets; the likelihood of abaloparatide-mediated calcium mobilisation drug-drug interactions was thus considered low.

Abaloparatide is rapidly degraded by proteases in serum and has a relatively short half-life of only about 1h. There was no inhibiting or inducing effects on the metabolising CYP enzymes *in vitro*, and the drug was not an inhibitor of relevant drug transporters *in vitro* (OAT1, OAT3, OCT2, OATP1B1, OATP1B3, P-gp and BCRP). Overall, based on the available data it can be concluded that there is no clinically relevant DDI risk for abaloparatide to act as a potential "perpetrator" or "victim" of DDIs.

Pharmacokinetics using human biomaterials

In vitro "perpetrator" aspects

Repeated administration of the proposed therapeutic dose of 80 µg abaloparatide once daily SC, yielded to abaloparatide estimated C_{max} of 635 ± 188 pg/mL in females with osteoporosis (parameter value based on the Phase III study BA058-05-003). The fraction unbound of abaloparatide was estimated *in vitro* to be 30%. Abaloparatide MW is 3960.7 g/mol. Therefore, abaloparatide systemic concentration cut-off which is used to determine potential clinical relevance of *in vitro* enzyme and transporter inhibition data, based on EMA guideline on the investigation on drug interactions (CPMP/EWP/560/95/Rev. 1) is calculated as 50 x $C_{max, unbound}$ = 0.0024 µM = 2.4 nM.

Since abaloparatide is intended only for the SC administration, no additional concentration cut-offs were relevant for the interpretation of *in vitro* DDI results. Overall, all "perpetrator" DDI *in vitro* experiments investigated sufficiently high abaloparatide concentrations.

Abaloparatide was investigated as a direct/competitive and a time-dependent inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5 *in vitro*. In addition, abaloparatide was investigated as an *in vitro* inhibitor of human transporters, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, P-gp and BCRP. Overall, no relevant inhibition was observed.

The *in vitro* induction study in hepatocyte indicated no risk for CYP induction of abaloparatide for CYP1A2, 2B6, and 3A4 enzymes. A slight decrease of the CYP mRNA levels compared to the vehicle control was observed, which was however not concentration dependent.

In vitro "victim" aspects

The metabolism of abaloparatide is consistent with non-specific proteolytic degradation into smaller peptide fragments (i.e., no CYP-mediated metabolism), and therefore no clinically relevant enzyme-mediated interactions are expected.

Based on the overall PK data available, active secretion of abaloparatide in the kidneys cannot be ruled out. Therefore, *in vitro* study 17RAD102 investigated abaloparatide as a potential substrate of renal transporters (OAT1, OAT3, OCT2, MATE 1 and MATE2-K), that could be involved in a potentially present active secretion of abaloparatide in kidneys. Based on the results of this study, the applicant has concluded that abaloparatide was not a substrate of renal transporters. In addition, the applicant has conducted two *in vitro* studies denoted as 21RAD127 and 22RAD132 which confirmed that abaloparatide is not a substrate of OAT3 transporter nor P-gp transporter.

2.5.2.2. Pharmacodynamics

Pharmacodynamic studies in relation to the claimed indication evaluated primarily abaloparatide's effects on bone turnover markers and BMD in patients receiving abaloparatide-SC and teriparatide, and in healthy volunteers (i.e., postmenopausal women and men included in Phase I studies). The repeated dose Phase I studies as well as the efficacy studies in postmenopausal women with osteoporosis determined that abaloparatide had a hypercalcaemic effect and induced early changes in a bone formation marker (s-P1NP). Serum 1,25-dihydroxyvitamin D rose in response to drug exposure. Since PTH and PTHrP stimulate the conversion of 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D in the kidney, this is an expected pharmacodynamic response to abaloparatide-SC administration. There were transient decreases in serum PTH(1-84) and phosphorus levels.

Bone metabolism markers

Integrated analysis of the bone turnover markers shows consistent increases in both anabolic (s-P1NP, BSAP, Osteocalcin) and resorption marker (s-CTX) in both abaloparatide-SC and teriparatide groups compared to placebo (Study BA058-05-003)

Table 8. Mean (SD) percentage change from baseline in serum bone turnover markers (study BA058-05-003, bone metabolism population n=500)

Marker	Month	Placebo (N=156)	ABL [a] 80 μg (N=164)	Teriparatide [a] (N=180)
s-PINP	1	-8.3±16	114±130	97±87
	3	-16±26	127±245	124±168 [b]
	6	-17±36	158±298	198±197 [c]
	12	-12±36	140±254	201±182 [d]
	18	-1.5±45	90±208	142±160 [e]
BSAP	6	-11±19	20±56	37±55 [f]
	12	-9.3±18	19±61	45±51 [g]
	18	-2.7±22	9.5±44	31±47 [h]
Osteocalcin	6	-15±20	74±102	121±129 [i]
	12	-13±21	67±116	124±119 [j]
	18	-6.6±24	52±103	104±104 [k]
CTX	1	-5.2±20	0.3±37	9.7±38 [l]
	3	-5.0±26	43±99	64±72 [m]
	6	-19±30	39±102	87±123 [n]
	12	-9.6±37	35±109	87±120 [o]
	18	-1.1±40	18±87	68±113 [p]

[a]Statistically significant (p value <0.0001) increases in % change from baseline vs. Placebo for all timepoints and all markers, except for CTX at Month 1 and Month 18 in abaloparatide group.
[b]Statistically significant (p value <0.0001) increases in % change from baseline between teriparatide vs. ABL
ABL=abaloparatide; BSAP=bone specific alkaline phosphatase; CTX=C-terminal telopeptide; PINP=N-terminal propeptide of type I procollagen; s=serum; SD=standard deviation

Upon initiation of alendronate treatment at Month 19 for both the abaloparatide-SC and placebo groups, a marked decline of all bone markers is observed. These results are consistent with the known effects of bisphosphonates (Study BA058-05-005).

Table 9. Mean (SD) percentage change from baseline in serum bone turnover markers (studies BA058-05-003/005, bone metabolism population, N=288

Marker	Month	Placebo (N=140)	ABL 80 µg (N=148)
s-PINP	1	-7±15	115±135 [a]
	3	-15±27	134±255 [a]
	6	-16±37	169±310 [a]
	12	-11±37	148±264 [a]
	18	-2±44	96±216 [a]
	19	-5±44	15±73
	25	-60±27	-60±22
	43	-59±27	-50±28 [a]
BSAP	6	-11±19	22±58 [a]
	12	-9±18	22±64 [a]
	18	-3±20	11±46 [a]
	19	12±29	21±48
	25	-30±20	-30±19
	43	-35±19	-29±24
Osteocalcin	6	-15±20	77±106 [a]
	12	-12±21	71±121 [a]
	18	-7±24	55±106 [a]
	19	-14±21	18±70 [a]
	25	-48±16	-43±19
	43	-52±17	-41±21 [a]
s-CTX	1	-6±19	-0.1±35
	3	-5±25	45±103 [a]
	6	-19±30	44±105 [a]
	12	-9±38	38±110 [a]
	18	-1.1±40	16±76
	19	-1.5±38	18±62 [a]
	25	-71±21	-64±28 [a]
	43	-64±29	-51±34

[a]Statistically significant (p value <0.0001) increases in % change from baseline vs. Placebo
ABL=abaloparatide; BSAP=bone specific alkaline phosphatase; CTX=C-terminal telopeptide; PINP=N-terminal propeptide of type I procollagen; s=serum

Similar results were seen in Study ITM-058-301.

Bone remodelling

The early effects of abaloparatide on bone remodelling were assessed in a histomorphometry study in postmenopausal women with osteoporosis (BA058-05-020). The study was an open-label, single-arm study and was designed to measure the early effects of abaloparatide on tissue-based bone formation and

resorption variables based on samples obtained by iliac crest bone biopsy after fluorochrome labelling. A total of 23 postmenopausal women with osteoporosis were enrolled.

Figure 3. Mineralizing Surface (MS/BS) (%) at Baseline and 3 Months by Relevant Bone Envelope (Bone-Biopsy Population)
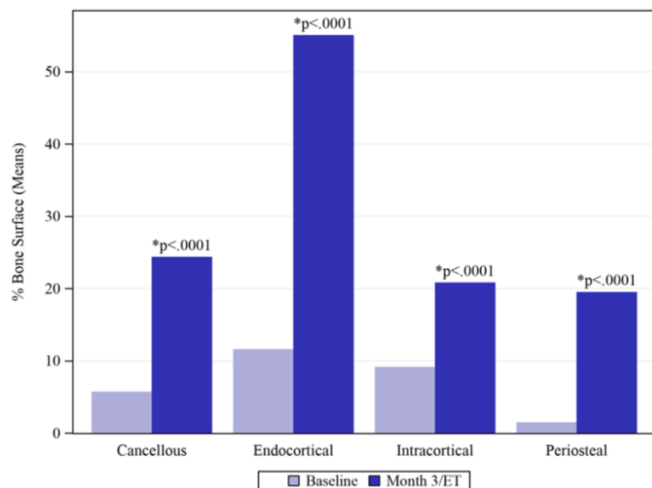
* p-value for MS/BS comparing 3 months to baseline.

The primary endpoint, change from baseline to 3 months in MS/BS in the cancellous envelope, was met. Statistically significant increases from baseline were also found for the MS/BS of endocortical, intracortical, and periosteal envelopes (p<0.0001 for all mean changes from baseline to 3 months)

Other Parameters: Hypercalcaemic effect, Serum 1,25-dihydroxyvitaminD increase, serum PTH(1-84) decrease, phosphorus decrease:

In line with the known mechanism of action, hypercalcaemic effect, serum 1,25-dihydroxyvitamin D increase, serum PTH(1-84) decrease and phosphorus decrease have been identified in clinical studies. The hypercalcemia and hypercalciuria are discussed in detail in the safety section.

Secondary pharmacology has not been specifically investigated. There were higher incidences of adverse events such as palpitations, nausea, and dizziness for abaloparatide compared to teriparatide and a higher percentage of subjects discontinued treatment due to orthostatic hypotension adverse events in the abaloparatide compared to the teriparatide group; this may suggest that abaloparatide has secondary pharmacodynamic effects besides the increase in calcium levels. However, the available data indicate that abaloparatide is selective for the PTH1 receptor with no currently known secondary targets. Changes observed in the cardiovascular system included positive chronotropic and inotropic effects. Abaloparatide did not bind to or activate the PTH2 receptor.

Abaloparatide is neither expected to affect pharmacodynamic properties of concomitantly administered drugs nor are concomitant drugs expected to affect pharmacodynamic properties of abaloparatide; no studies on pharmacodynamic interactions with other medicinal products or substances have been conducted which is acceptable.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics of abaloparatide was evaluated in healthy subjects, subjects with renal impairment, and in postmenopausal women with osteoporosis; the latter included a population PK analysis. Human plasma protein binding of abaloparatide *in vitro* is about 70%. The apparent volume of distribution is estimated to be 42.5 L in the Phase III PopPK analysis. Clinical PK data indicate that abaloparatide has a rapid elimination ($t_{1/2}$ of about 1h after SC administration), and that it is primarily excreted in urine. Metabolism of abaloparatide has been investigated in preclinical studies only, which is acceptable for a compound comparable to an endogenous protein. Abaloparatide appears to be rapidly degraded by multiple proteases into shorter peptide fragments which are then renally excreted. Based on the available PK data from different Phase I studies, the systemic exposure of abaloparatide increased with increasing abaloparatide SC doses over the dose range from 5 µg to 240 µg, however with a general tendency towards less than dose-proportional increases.

The available clinical data after repeated dosing of abaloparatide do not indicate time-dependent pharmacokinetics. Moreover, a slight increase in C_{max} and AUC_{0-t} was observed after once daily SC administration of 80 µg abaloparatide for 7 days (C_{max}: 702±175 pg/mL at day 1 and 812±118 pg/mL at day 7; AUC_{0-t}: 1248±485 pg.h/mL at day 1 and 1546±618 pg.h/mL at day 7). However, the observed increase was relatively small (mean values are covered within the respective SD), and it was not observed with once daily administration of 120 µg SC dose. Considering the very rapid elimination ($t_{1/2}$ of about 1h) of abaloparatide, drug accumulation is not expected with the repeated dosing.

The popPK analysis showed that ADA was an influential covariate for abaloparatide PK, and thus, it is possible that differences in pharmacokinetic parameters may occur over time in case a subject develops ADAs. The methods employed for bioanalysis or detection of ADAs are considered principally adequate for their purpose. In the validation process the presence of Anti-abaloparatide antibodies (ADAs) leads to a reduction in bioanalytical recovery of abaloparatide (antibody interference, especially noticed at higher concentrations of ADAs). This might influence the results when Anti-abaloparatide is present in samples such as in the phase 3 study where samples with low concentrations of abaloparatide may be more affected. However, considering the mostly very low titers of ADAs detected in the clinical trials this may not be a major issue. Still the applicant argues that this interference might explain at least some of the effect seen with ADAs on the PK of abaloparatide in the popPK analysis and this is further discussed below.

Due to the described interference of ADAs with the concentration assay for abaloparatide, results regarding PK in subjects with confirmed presence of ADAs are not fully conclusive. As a consequence, no reliable data on a potential influence of ADAs on drug exposure are available. Following the compromised results from concentration analysis in ADA positive subjects, also the construction of the popPK model might be compromised by the inclusion of measures from ADA positive subjects. Furthermore, ADAs were included as time independent covariate, based on ADA status after 12 months. In this context, and in order to make predictions of the popPK model more reliable for potential future use (including the covariate analyses other than ADAs), the applicant should explore the possibility to construct the popPK model in a way that data from ADA positive subjects are excluded. Considering the time-dependent occurrence of ADAs as well as the applied sampling schedule in study BA058-05-003 (i.e. a single serum sample post-dose after daily administration), this exclusion does not need to affect all measures that were collected from an individual that became ADA positive during treatment, but can be restricted to the time points starting from the first positive ADA signal. In case the model is to be used for future predictions, the applicant is strongly advised to use a revised model excluding measures from ADA positive subjects.

For the current model, time-constant ADA was an influential covariate and positive subjects were predicted to have considerably higher CL and Vc, compared to ADA negative subjects. Assay interference and/or abaloparatide clearance by ADAs may be responsible for apparent changes in CL and Vc; however, no firm conclusions can be drawn.

The dataset used to develop the population PK model included SC and IV data from 6 different Phase I studies and one Phase III study. This is considered a relevant database to develop the model. A considerable proportion of the observed data was below the lower limit of quantification and the MAHs handling of BLQ using M6 is acceptable.

A standard workflow was used to develop the final population PK model which was a two-compartment model with linear elimination. The final model structure is considered overall reasonable, however, the visit-dependent bioavailability in patients, and the empirical time-varying infusion rate are considered limitations of the model. As the model has limited impact and is primarily used for descriptive purposes, these limitations are considered acceptable. Of note, simulations of PK over time in patients outside the design of the Phase III study is not possible without making assumptions regarding the visit-dependent bioavailability.

The stepwise covariate analysis is considered a relevant approach and overall relevant covariates were identified and included in the final model. The estimated covariate-parameter coefficients were mostly considered reasonable; however, it was noted that ADAs had considerable influence on abaloparatide PK based on the magnitude of the ADA coefficients (1.59-2.46 and 2.92-14.9 for low and high titer, respectively). Antibody interference may have an apparent effect on the magnitude of the ADA coefficients, however, no firm conclusions can be drawn. Furthermore, ADA was implemented as a time-constant covariate; ignoring the time-varying nature of ADAs is a limitation which may cause bias in the estimated ADA coefficients. The MAH confirmed that an updated PopPK analysis has been conducted with ADA implemented as a time-varying covariate. The updated analysis with time-varying ADA resulted in comparable estimates for the ADA coefficients. Therefore, also the time-constant ADA implementation is acceptable.

The final population pharmacokinetic model gave acceptable description of the observed data and the presented parameters had reasonable uncertainty.

Abaloparatide systemic exposure increases with decreasing renal function. Patients with severe renal impairment should not take abaloparatide and patients with moderate renal impairment should be closely monitored, as mentioned in the SmPC. However, no dose adjustment is required for patients with mild to moderate renal impairment. No dedicated pharmacokinetic studies in subjects with hepatic impairment were performed, which is considered acceptable.

The applicant has not initially investigated abaloparatide as a potential P-gp substrate *in vitro*. P-gp transporter is also expressed in the kidney tissue and thus could potentially be involved in the disposition of abaloparatide. Therefore, upon the EMA request, the applicant has conducted an additional *in vitro* experiment (denoted as 22RAD132). Results of this new study indicated the lack of P-gp involvement in the disposition of abaloparatide.

Human parathyroid hormone (hPTH) is a naturally occurring 84 amino acid hormone and is primarily a regulator of calcium homeostasis. When given intermittently at low doses, hPTH has a well-documented anabolic effect on bone. Abaloparatide is a synthetic 34-amino acid peptide analogue of hPTHrP, with molecular modifications of specific amino acids. Abaloparatide has enhanced PTH1 Receptor RG/RO selectivity and has demonstrated retention of the potent anabolic activity of PTH, with reduced bone resorption and calcium-mobilizing potential.

Integrated analysis of the bone turnover markers from clinical studies show consistent increases in both anabolic (s-P1NP, BSAP, Osteocalcin) and resorption marker (s-CTX) in both abaloparatide-SC and teriparatide groups compared to placebo in the main study BA058-05-003. Increases in both formation and resorption seem somewhat more pronounced in the teriparatide group compared to abaloparatide. Therefore, the conclusion of the applicant that the data on bone turnover markers would strongly support abaloparatide being more bone formation selective than teriparatide is not fully agreed. In study 301 the same bone turnover markers were measured and included PICP and TRACP-5b. All markers increased from baseline until approximately week 24, after which the percent change decreased again. Although the methods for the analyses might differ between the studies, the percent increase and pattern during time seems to be similar.

Overall, analysed bone turnover markers show dynamic responses with an initial increase followed by a decline until Month 18 in study BA058-05-003 and study ITM-058-301. The time of peak serum concentration during daily abaloparatide treatment varies slightly across investigated bone markers.

Upon initiation of alendronate treatment at Month 19 for both the abaloparatide-SC and placebo groups, a marked decline of all bone markers is observed. These results are consistent with the known effects of bisphosphonates.

The early effects of abaloparatide on bone remodelling were assessed in a histomorphometry study in postmenopausal women with osteoporosis (BA058-05-020) as well as in a subset of patients in the Phase 3 study (BA058-05-003).

In study BA058-05-020 iliac crest bone biopsies of all four bone envelopes (cancellous, endocortical, intracortical, and periosteal) were examined in 23 postmenopausal women with osteoporosis using quadruple tetracycline labelling with markers of bone turnover. However, the clinical relevance and contribution to the claimed MoA of results with biopsy quadruple markers remains vague and the open-label, non-controlled character of this study does not support robust conclusions. Results on serum bone markers (s-PINP and s-CTX) as well as BMD were principally comparable to other studies.

The other pharmacodynamics bone markers, PTH(1-84) and 1,25-dihydroxy vitamin D, showed expected changes in response to abaloparatide-SC exposure: Serum PTH values were observed to fall, serum 1,25-dihydroxy vitamin D levels rose, elevations in serum calcium were observed. Hypercalciuria did not increase in studies with healthy volunteers.

Some preclinical safety studies indicated the potential for abaloparatide to affect QT prolongation. A thorough QTc study (Study 012) has been performed and is described in the safety section. In a clinical trial of abaloparatide-SC at doses of 20 µg, 40 µg, and 80 µg administered to postmenopausal women with osteoporosis (study BA058-05-002), overall findings showed no clinically significant effect of abaloparatide-SC on cardiac conduction, and specifically on QT interval.

Transient and reversible tachycardia and hypotension occurred following subcutaneous (SC) doses of abaloparatide in preclinical and clinical phase1 studies. See safety section for detailed results in clinical studies in the targeted patient population.

2.5.4. Conclusions on clinical pharmacology

Overall, the available pharmacokinetic data are considered sufficient for the purpose of this application.

The pharmacodynamic principles have been sufficiently described by the applicant.

2.5.5. Clinical efficacy

The clinical efficacy in the application is based on one phase 2, dose-ranging, 24 weeks study in postmenopausal women with osteoporosis (BA058-05-002), one phase 3, pivotal clinical trial of abaloparatide in postmenopausal women with osteoporosis to prevent the occurrence of vertebral and non-vertebral fractures (Study BA058-05-003) and its extension (BA058-05-005), one phase 3 clinical trial in postmenopausal women and men with osteoporosis in Japan (ITM-058-301), and one retrospective observational cohort study using US claims data (BA058-05-028).

2.5.5.1. Dose response study(ies)

Study BA058-05-002 was a dose-response study. It assessed the efficacy of 20, 40, and 80 µg abaloparatide-SC in postmenopausal patients with osteoporosis in terms of change in bone mineral density (BMD) from baseline to the end of the 6-month treatment period. Co-primary endpoint consisted of changes in serum bone markers. An extension of care for a further 6 months was offered to patients who had not had any treatment-related SAE, who were within 14 days of their last study drug administration and who had not shown deterioration in BMD during the initial 6 months of treatment.

Single doses up to 400 µg SC were given in phase 1 trials. A thorough QT/QTc study in healthy male and female volunteers concluded that a 240 µg was the maximal tolerated dose. In phase 1 trial 127-001, the maximum tolerated dose of abaloparatide-SC was determined to be 80 µg as in the subjects treated with 100 µg, 50% experienced non-serious drug related AEs with moderate intensity (nausea).

Consequently, the dose of Abaloparatide-SC 80 µg daily was the highest dose studied in the dose-response study BA058-05-002.

Efficacy Results study BA058-05-002

Among the 831 patients screened, 270 patients entered a pre-treatment period, 222 were randomized at 30 study sites, and 221 patients (intent-to-treat (ITT) and Safety Populations) received at least one dose of study treatments. A total of 184 patients (83%) completed 6 months of treatment, 55 patients (25%, from 11 sites) continued treatment beyond 6 months and the majority of them (48/55, 87%) completed 12 months of treatment (Extension Population).

Across all patients, treatment groups were comparable with regard to demographic and baseline characteristics, including age, race, height, weight, and BMI.

BMD at Week 24:

Mean percent changes from baseline in **lumbar spine BMD** at Week 24 increased with abaloparatide-SC dose (1.6%, 2.9%, 5.2%, and 6.7% in the placebo, abaloparatide-SC 20 µg, 40 µg, and 80 µg groups, respectively) for the ITT Population. The test for a linear trend (dose response) was statistically significant ($p<0.001$). Mean percent change in the teriparatide group at this visit was 5.5%.

At Week 24, mean percent changes in **femoral neck BMD** for the ITT Population were 0.8%, 2.7%, 2.2%, and 3.1% in the placebo, abaloparatide-SC 20 µg, 40 µg, and 80 µg groups, respectively.

At Week 24, mean percent changes in **total hip BMD** for the ITT Population were 0.4%, 1.4%, 2.0%, and 2.6% in the placebo, abaloparatide-SC 20 µg, 40 µg, and 80 µg groups, respectively.

At Week 48, a continued treatment effect in terms of BMD was observed over an additional 6 months of treatment in the subset of patients who entered the extension period of the study. The mean percent changes from baseline were highest for the abaloparatide-SC 80 µg dose group (for all anatomical sites) and the mean percent change from baseline in the teriparatide group was always similar to the abaloparatide-SC 40 µg group.

Markers of bone formation rose in a dose-dependent manner, with the earliest rise seen in the abaloparatide-SC 80 µg.

Most AEs showed no evidence of dose-dependency among the abaloparatide-SC patient groups. There were no serious adverse events related to treatment with abaloparatide-SC. A lower dose of abaloparatide-SC, specifically the 40 µg dose, demonstrated no additional safety advantage when compared to abaloparatide-SC 80 µg, while abaloparatide-SC 80 µg induces greater BMD response without increasing the risk of hypercalcemia or other safety events. The safety data of abaloparatide-SC 80 µg compared to the lower doses was therefore considered acceptable by the applicant. The choice of abaloparatide-SC 80 µg daily as the phase 3 study dose is endorsed.

2.5.5.2. Main study(ies)

BA058-05-003: A randomized, double-blind, placebo-controlled, comparative Phase 3 multicenter study to evaluate the safety and efficacy of BA058 for injection for prevention of fracture in ambulatory postmenopausal women with severe osteoporosis and at risk of fracture.

BA058-05-005 (Study BA058-05-005): was a multi-center, multinational, open-label **extension of Study BA058-05-003** to collect additional safety and efficacy data in patients transitioned to alendronate therapy.

A total of 652 patients from two EU sites were excluded from the final analysis. Addendums to the final study reports were provided, which included analysis of efficacy and safety excluding data from these two sites

ITM-058-301 (Study 301) was a randomised, double-blind, placebo-controlled confirmatory study investigating the efficacy and safety of abaloparatide for 18 months in Japanese subjects.

BA058-05-003 and extension BA058-05-005

Figure 4. Design of study BA058-05-003 and extension BA058-05-005
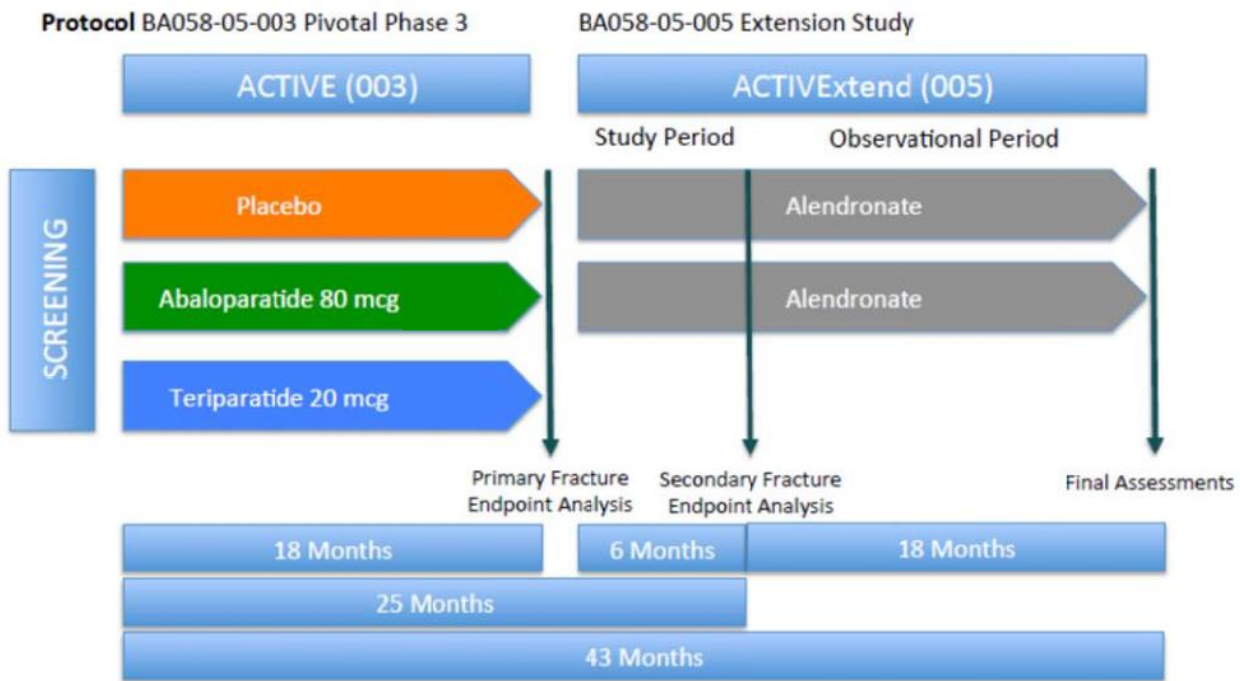
The design of the pivotal Phase 3 study (Study BA058-05-003) and its extension (Study BA058-05-005) were discussed with the EMA SAWP. The duration of abaloparatide-SC treatment was determined to 18 months (due to potential long-term safe concerns of this anabolic treatment). In order to provide 24 months of fracture assessment data, and to conform with the current guidelines, abaloparatide-SC and placebo subjects enrolled in Study BA058-05-003 were to be treated with additional 24 months of alendronate (study BA058-05-005), from which the first 6 months are added to the original 18 month trial data for a total of 24.

This design was considered acceptable as 24 months is available for the main comparisons abaloparatide vs placebo. However, the teriparatide arm was lost for any comparisons at 24 months. No data is available on patients who did not continue on alendronate treatment after abaloparatide treatment.

Methods (BA058-05-003 and BA058-05-005)

- **Study Participants**

Among the inclusion and exclusion criteria, the following could be considered as more important:

Inclusion:

-Be a healthy ambulatory postmenopausal woman from 50 to 85 years of age (inclusive) with osteoporosis.

-Have a BMD T score ≤2.5 and >-5.0 at the lumbar spine (L1-L4) or hip (femoral neck) by dual energy x-ray absorptiometry (DXA) and radiological evidence of 2 or more mild or one or more moderate lumbar or thoracic vertebral fractures, or history of low trauma forearm, humerus, sacral, pelvic, hip, femoral, or tibial

fracture within the past 5 years. Postmenopausal women older than 65 who met the above fracture criteria but had a T-score ≤2.0 and >-5.0 could be enrolled. Women older than 65 who did not meet the fracture criteria could be enrolled if their T-score was ≤3.0 and >-5.0.

-Albumin-adjusted serum calcium, PTH (1-84), serum phosphorus and alkaline phosphatase values all within the normal range during the Screening Period. Patients with minor elevations or reductions in serum calcium could be enrolled if serum ionized calcium was normal. Any patient with an elevated alkaline phosphatase (AP) value, and who met all other entry criteria, needed a normal bone-specific AP result to be enrolled.

-Serum 25-hydroxyvitamin D values above 15 ng/mL and within 3 times the upper normal (ULN) range.

-Resting 12-lead electrocardiogram (ECG) obtained during screening showing no clinically significant abnormality and a QTc ≤470 msec (Bazett's correction).

-Systolic blood pressure: ≥100 and ≤155 mmHg, diastolic blood pressure: ≥40 and ≤ 95 mmHg, and heart rate: ≥45 and ≤100 beats per minute (bpm) (sitting or supine).

-No clinically significant abnormality of serum haemoglobin (Hgb), haematocrit (Hct), white blood cells (WBC) and platelets, or usual serum biochemistry: electrolytes, renal function, liver function and serum proteins.

Exclusion:

-History of more than 4 spine fractures, mild or moderate, or any severe fractures.

-History of bone disorders (e.g., Paget's disease) other than postmenopausal osteoporosis.

-Unexplained elevation of serum AP.

-History of radiotherapy (radiation therapy), other than radioiodine.

-History of chronic or recurrent renal, hepatic, pulmonary, allergic, cardiovascular, gastrointestinal, endocrine, central nervous system, hematologic or metabolic diseases, or immunologic, emotional and/or psychiatric disturbances to a degree that would interfere with the interpretation of study data or compromise the safety of the patient.

-History of Cushing's disease, hyperthyroidism, hypo- or hyperparathyroidism or malabsorptive syndromes within the past year. History of nephrolithiasis or urolithiasis within the past five years.

-History of significantly impaired renal function (serum creatinine >177 µmol/L or >2.0 mg/dL. If the serum creatinine was >1.5 and ≤2.0 mg/dL, the calculated creatinine clearance (Cockcroft-Gault) must have been ≥37 mL/min.

-History of any cancer within the past 5 years (other than basal cell or squamous cancer of the skin) or history of osteosarcoma at any time.

-Decrease of 20 mmHg or more in systolic blood pressure or 10 mmHg or more in diastolic blood pressure from supine to standing (5 minutes lying and 3 minutes standing) and/or any symptomatic hypotension at screening (The Consensus Committee of the American Autonomic Society and the American Academy of Neurology, 1996; Lipsitz LA, 1989).

-Prior treatment with bisphosphonates*, fluoride or strontium in the past five years or prior treatment with gallium nitrate, or with as yet unapproved bone-acting investigational agents at any time (Black et al, 2006). (*Patients who had a short course of bisphosphonate treatment (3 months or less) and were intolerant of the treatment were not excluded from study participation.)

-Prior treatment with denosumab, calcitonin, SERMs (such as raloxifene or tamoxifen), tibolone, or anabolic steroids in the past 12 months. Oestrogens administered as hormone replacement therapy (HRT), with or without progestins, were not exclusionary.

-Treatment with anticonvulsants that affect vitamin D metabolism (phenobarbital, phenytoin, carbamazepine or primidone) or with chronic heparin within the 6 months prior to the Screening Period.

-Daily treatment with oral, intranasal or inhaled corticosteroids within the 12 months prior to the Screening Period. Occasional use of corticosteroids (for seasonal allergies or asthma) was not exclusionary.

-Abnormal nutritional status (abnormal diets, excessive or unusual vitamin or herbal intakes, malabsorption, significant recent weight change), vitamin D intake of ≥4,000 IU/day or vitamin A intake of ≥10,000 IU/day1.

- **Outcomes/endpoints**

1. **Primary Endpoint**

The primary efficacy endpoint of this study was the percentage of patients with one or more incidents of new vertebral fracture according to Genant's method (Genant et al, 1993) from the baseline spine X-rays until post-baseline spine X-rays (over the study treatment period up to 18 months) in abaloparatide-SC-treated patients when compared to placebo.

Secondary Efficacy Endpoints

2. **Key secondary efficacy endpoint:** nonvertebral fracture

• The time to the first incident NVF by the Follow-up Visit (Visit 10). NVF was source-document verified and adjudicated according to "BA058-05-003 Clinical and Nonvertebral Fracture Verification and Adjudication Process".

3. **Additional Key Secondary Efficacy Endpoint:** Bone mineral Density

• The % change from baseline in lumbar spine BMD through end of 18-month treatment.

• The % change from baseline in total hip BMD through end of 18-month treatment.

• The % change from baseline in femoral neck BMD through end of 18-month treatment.

Other Efficacy Endpoints

4. The change and % change in vertical (standing) height from baseline to end of 18-months of treatment. Vertical height was measured in the standing position using a medical stadiometer and standardized procedures at each visit.

5. The severity of incident new and/or worsening vertebral fractures over the study treatment period up to 18 months in abaloparatide-SC-treated patients when compared to placebo. The severity was categorized as an increase from baseline in semi-quantitative (SQ) grade ≥2 versus <2 with or without prevalent fractures at baseline.

6. The % change in distal 1/3 radius BMD from baseline through end of 18-month treatment in a subset of patients.

7. The % change in serum P1NP, BSAP osteocalcin and CTX in a subset of patients.

8. The incidence of one or more incident new vertebral fractures over 18 months of treatment in teriparatide-treated patients when compared to placebo.

Safety Endpoints

• Incidence of hypercalcemia (albumin-corrected serum calcium value ≥10.7 mg/dL or ≥2.67 mmol/L) in abaloparatide-SC-treated patients when compared to teriparatide

• Incidence of AEs and SAEs

• Vital signs and ECGs

• Incidence of hypercalciuria

• Clinical laboratory parameters for chemistry (sodium, potassium, chloride, Inorganic phosphorus, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, AP, total bilirubin, LDH, cholesterol, triglycerides and total calcium), haematology and urinalysis.

• Renal safety

• Bone histomorphometry

The primary endpoint of study BA058-05-003 is in line with the EMA guideline on osteoporosis 2006, which states that the primary variable should be assessed as incidence of patients with new fractures, which may be expressed as vertebral fractures. The key secondary endpoint- non-vertebral fracture- was pre-defined according to Cummings et al 2009 and Kreg and Wan 2012, which is considered acceptable.

The other pre-defined endpoints are considered acceptable.

The endpoints for study BA058-05-005 were similar to those reported for Study BA058-05-003 with a few exceptions. The radius BMD and teriparatide were not studied in Study BA058-05-005. In the analyses at month 25 in study BA058-05-005, clinical fractures and major osteoporotic fractures were stated to be pre-defined endpoints. However, the amendment was done after unblinding the BA058-05-003 study results.

- **Sample size**

For study BA058-05-003 it was determined that a sample size of 622 patients per treatment group would provide 90% power at a 2-sided alpha of 0.05 to detect a difference of 4% between treatments, assuming a vertebral fracture rate of 7% in placebo patients and 3% in abaloparatide-SC-treated patients. To ensure 622 patients in the analysis, an overall sample size of 800 patients per treatment arm was to be recruited, anticipating that approximately 20% of patients might not have a second evaluable radiograph available for analysis.

Besides being powered for the primary comparison, power calculations were seemingly performed also for a number of secondary (BMD) endpoints although not for the non-vertebral fracture endpoint. Identified as a concern by CHMP/SAWP within a scientific advice procedure (EMEA/H/SA/1604/1/2010/SME/III), this was clarified by the applicant ("Clarification letter" procedure) that stated that the study was adequately powered to detect a clinical significant relative risk reduction also in incidence in non-vertebral fractures rates (based on a placebo fracture rate of 5-7%); i.e. in principal based on the similar assumptions as had been made for the vertebral fracture endpoint.

- **Randomisation and Blinding (masking)**

On Day 1 of the Treatment Period (Visit 3, baseline) eligible patients were randomised 1:1:1 to treatment with abaloparatide-SC (80 µg), placebo, or teriparatide (20 µg) and received their first dose of study medication. The randomisation procedure seems acceptable.

The primary comparison, abaloparatide-SC vs. placebo, was performed on data collected under double-blind conditions. Treatment with the active control was open-label. All fracture and BMD endpoint assessments were however performed by independent third-party blinded reviewers. A second reviewer was to confirm the assessment of the first reviewer only for patient radiographs in which an incident fracture had been identified. This implies that the fracture event rate may have been underestimated compared to if instead two independent assessors had viewed and assessed all patient radiographs. Considering the primary objective being superiority versus placebo this can be considered conservative and therefore of no concern.

As pointed out within the scientific advice procedure (EMEA/H/SA/1604/1/2010/SME/III), with this design, inter-rater and intra-rater reliability are a matter of importance. With only one assessor viewing all radiographs with a second assessor only to confirm the fractures found by the first, an assessment of inter-rater reliability within the trial is not possible. However, as clear from the submitted "Charter for Independent Imaging Assessment" (Synarc, Inc.), inter-reader and intra-reader variability for vertebral fracture is assessed annually in a reader qualification process. The inter-reader agreement was evaluated according to the "Imaging Charter". The primary reader identified 48 incident vertebral fractures of which the secondary reader confirmed 45 but also found 1 new fracture. Based on a third adjudication the final total number of incident vertebral fractures in study BA058-05-003 was identified as 47. With the procedure used the number of vertebral fractures (first event) could only be underestimated. The number of patients with ≥1 new vertebral fracture in the primary analysis was 40.

In study BA058-05-005, all patients and investigators remained blinded to the previous BA058-05-003 double-blind treatment assignment through the first 6 months (Visit 3), which is endorsed.

Previous treatment in study BA058-05-003 was thus unblinded with 18 months left in study BA058-05-005. The radiographs and scans were however still analysed in a blinded fashion.

- **Statistical methods**

Study BA058-05-003

The primary efficacy endpoint comparison was performed using a modified intent-to-treat population (mITT). All other efficacy analyses were performed using the Intent-to-Treat (ITT) Population including all randomised patients. The mITT Population included all ITT patients who had both a pre-treatment and a post-baseline evaluable radiologic assessment (spine X-ray). For both populations, treatment classification was based on the randomised treatment. A Per-Protocol (PP) population was defined for supportive analyses. The PP population used to support the primary mITT analysis included patients in the mITT population who complied with treatment and did not have any protocol violations.

The analysis of the primary endpoint was to be based on both scheduled (at Visit 1 and Visit 9) and unscheduled (e.g., at early termination) X-ray. The percentage of patients who had at least one new vertebral fracture and 95% CI was estimated for each treatment group using the Wilson's score method. The Fisher's exact test was used to compare Abaloparatide-SC and placebo. A sensitivity analysis on the primary efficacy endpoint was performed based on the ITT population using a multiple imputation (MI) method. A logistic regression model was used to impute missing primary efficacy outcomes for ITT patients who were

excluded from the mITT population. The imputation approach assumes that those subjects excluded from the ITT population are missing at random (MAR).

Following the test of the primary efficacy endpoint of vertebral fracture, a hierarchical approach was employed to control the overall type-I error rate at the 2-sided significance level of 5% for testing the multiple hypotheses on the secondary efficacy endpoints of non-vertebral fracture and BMD. To claim statistical significance at the 2-sided level of 5%, the 9 fixed-sequence tests were performed in a sequential order. At any step, if the treatment difference was not statistically significant at the 5% level then the p-values for the subsequent comparisons were to be generated as nominal for exploratory purposes only.

P-values for treatment comparisons of all other efficacy endpoints or time points were to support the study findings for exploratory purposes without further multiplicity adjustment.

The statistical method to analyse NVF was changed from the planned analysis in the protocol (Fishers exact). Instead, the log-rank test was used for the primary analysis to compare time to first non-vertebral fracture between Abaloparatide-SC and placebo using the ITT population. The analysis of NVF was based on all data collected through the end of the Follow-Up visit (i.e., Visit 10) in the study with time estimated from day of randomisation to the first incidence of a non-vertebral fracture. If a patient did not experience any non-vertebral fracture over the 18 months of treatment plus the 30-day follow-up (for a total of 19 months), the patient was considered censored at the last known day in the study. The Cox proportional hazard model was used to calculate the hazard ratio and corresponding 95% CI. The Kaplan-Meier method was used for graphical display and to estimate incidence rates at 19 months (Visit 10). The analysis of NVF was also performed using the PP population to support the findings from the ITT population. For data display, the Kaplan-Meier curve for the teriparatide group was added to the plot of Abaloparatide-SC vs. placebo together with the estimated p-value from a log-rank test comparing Abaloparatide-SC with teriparatide.

Regarding the analyses of the additional key secondary efficacy endpoints based on Bone Mineral Density (BMD), BMD was measured at 3 post-baseline visits (6, 12 and 18 month). The primary population for the analysis of BMD data was the ITT population for those patients who had baseline and at least one post-baseline BMD data. An analysis of covariance (ANCOVA) model was used to compare treatment groups for the percent change from baseline in BMD with missing imputation based on last observation carried forward (LOCF). The Mixed-Effect Model Repeated Measure (MMRM) model was used for a sensitivity analysis.

The statistical analysis plan (SAP) was finalized on 08 December 2014 prior to study completion and database lock on 10 December 2014. All statistical analyses were performed in accordance with the methods specified in the SAP with minor modifications contained in an amendment to the SAP dated 24 March 2015. These included a modification to the definition of nonvertebral fractures (now excluding the breast bone and knee cap) and the primary endpoint (from new and/or worsening to new vertebral fractures alone). Further, ANOVA (LOCF) was to be used instead of MMRM with MMRM for sensitivity purposes.

Overall, statistical methods were acceptable. Changes were however made to the statistical analysis plan whereof a few seemingly post-hoc. While not that easy to follow exactly when they were made, they are overall per se acceptable.

The primary analysis was based on a modified ITT population. At the planning stage it was expected that approximately 20% of randomised patients were to be excluded from the analysis of the primary endpoint. The exclusion of subjects (in the primary analysis) with missing post-baseline data is generally only acceptable if this concerns a negligible amount of subjects. Only one sensitivity analysis was planned using the method of multiple imputations (MI). Considering that this sensitivity analysis is based on the assumption of missing at random (MAR) additional sensitivity analyses to examine the sensitivity of inferences to

departures from the MAR assumption should have been planned. A supportive analysis was based on PP but is not considered to add any valuable information in support of the primary comparison (vs. placebo). Although the proportion of patients excluded in the primary analysis was less than expected, additional sensitivity analyses have been requested.

Multiplicity was handled through the use of a sequential testing procedure which is acceptable. The key secondary endpoint, time to NVF, was number 5 in the hierarchical testing sequence.

Comparisons between the Abaloparatide-SC and the teriparatide groups were considered for descriptive purposes with the active control group to serve mere as an internal validity control.

Regarding the analyses of the additional key secondary efficacy endpoints based on Bone Mineral Density (BMD), BMD was measured at 3 post-baseline visits (6, 12 and 18 month). The primary population for the analysis of BMD data was the ITT population for those patients who had baseline and at least one post-baseline BMD data. Analogous the discussion above on the mITT population, this is neither according to the intention-to-treat principle. The primary analysis was based on an ANCOVA using last-observation carried-forward (LOCF). Sensitivity analyses were planned using MMRM and the analyses were repeated based on the PP population, neither which is considered sufficiently conservative. BMD responder analyses were planned for exploratory purposes. While responder analyses may be useful in support of the primary analyses of BMD endpoints, subjects with missing data were however to be excluded in the responder analyses. Additional analysis with patients with any missing data imputed as non-responder were therefore asked for.

Study BA058-05-005

The primary and secondary efficacy endpoints for BA058-05-005 occurred at Month 25 from the BA058-05-003 baseline and were analysed and reported in the 6-month interim study report. The analyses at Month 25 used a hierarchical approach to control the overall type-I error rate at the 2-sided significance level of 5% for multiple comparisons as described below. Additional subsequent analyses for Months 31, 37 and 43 were performed with no statistical adjustment for multiple comparisons.

The efficacy and safety data were analysed as a follow-up to the 18 month fracture endpoint for Study BA058-05-003. Subjects were analysed based on the randomisation assignment in the BA058-05-003 study. The pre-specified endpoints were assessed using the cumulative (integrated) data with Day 1 of Study BA058-05-003 as baseline. Additionally, the endpoints were also assessed using the BA058-05-005 study baseline (Visit 9 of BA058-05-003).

The primary efficacy endpoint comparison was performed using the mITT and PP populations. The mITT Population comprised all patients from the BA058-05-003 mITT population who had a post-baseline Month 25 (Visit 3 in Study BA058-05-005) evaluable radiologic assessment (spinal X-rays). The Per-Protocol (PP) Population included all patients in the mITT population who complied with treatment and did not have any protocol violations and was to be used as a supportive population for efficacy analyses including the primary.

The percentage of patients who had one or more new vertebral fractures and 95% CI were provided for each BA058-05-003 double blind treatment group (abaloparatide-SC and placebo) and overall using the Wilson's score method. The Fisher's exact test was used to compare the treatment groups. Analyses were further performed within a number of pre-defined subgroups with relative risk ratios and 95% CIs for treatment differences presented using a Forest plot. A hierarchical approach was planned to control the overall type-I error rate at a 2-sided significance level of 5% for testing the multiple hypotheses on the primary and secondary efficacy endpoints at 25 months. The 10 fixed-sequence tests were to be performed in a sequential

order. P-values and 95% confidence intervals (CIs) for treatment comparisons of all other efficacy endpoints were generated for exploratory purposes without any further multiplicity adjustment.

Subsequent analyses of the same efficacy endpoints were performed at Months 31, 37 and 43 using the BA058-05-003 baseline.

The SAP was finalized on 30 May 2015, prior to the 6-month database lock on 2 June 2015.

Overall, based on that the endpoints were similar, the same analysis approach as used for the analysis of study BA058-05-003 was planned also for the analysis of study BA058-05-005.

- **Participant flow**

Figure 5. Participant flow study BA058-05-003
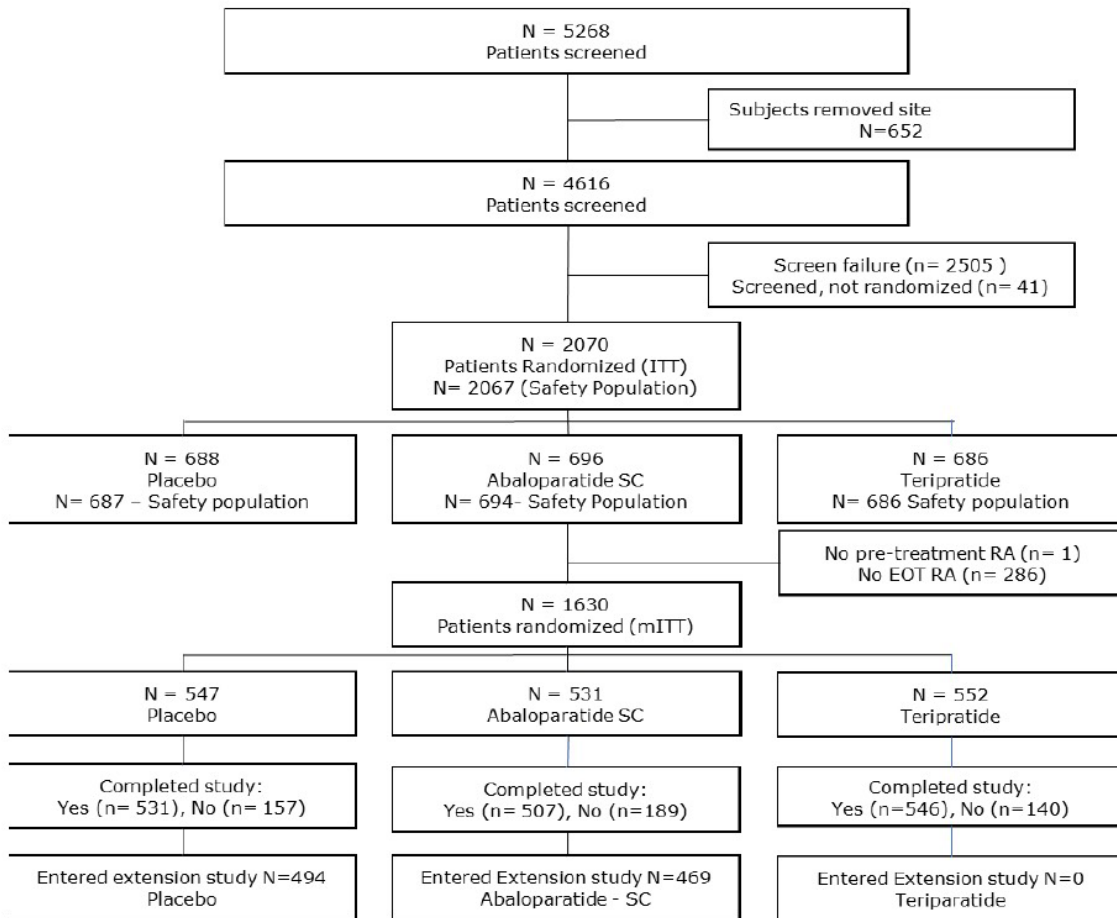
Table 10. The reasons for treatment discontinuation (selection from Table 1, BA058-05-003)

Parameter	Placebo n (%)	Abaloparatide-SC n (%)	Teriparatide n (%)	Overall n (%)
Completed study [3, 6]				
Yes	531 (77.2)	507 (72.8)	546 (79.6)	1584 (76.5)
No	157 (22.8)	189 (27.2)	140 (20.4)	486 (23.5)
Primary reasons for non-completion [7, 8]				
Adverse Event	41 (26.1)	72 (38.1)	44 (31.4)	157 (32.3)
Withdrew Consent	46 (29.3)	45 (23.8)	43 (30.7)	134 (27.6)
Refusal of Treatment	26 (16.6)	26 (13.8)	17 (12.1)	69 (14.2)
Patient Died During Study	3 (1.9)	3 (1.6)	2 (1.4)	8 (1.6)
Lost to follow up	5 (3.2)	14 (7.4)	9 (6.4)	28 (5.8)
Inability to Complete Study Procedures	7 (4.5)	10 (5.3)	4 (2.9)	21 (4.3)
Non-compliance	9 (5.7)	4 (2.1)	9 (6.4)	22 (4.5)
Serious Intercurrent Illness	0	3 (1.6)	3 (2.1)	6 (1.2)
Protocol Violation	2 (1.3)	4 (2.1)	5 (3.6)	11 (2.3)
Continuing significant deterioration from baseline (>7%) of BMD at lumbar spine or hip (after confirmation of the findings)	11 (7.0)	1 (0.5)	0	12 (2.5)
Administrative Reasons	0	1 (0.5)	0	1 (0.2)
Hypercalcemia or Hypercalciuria	0	1 (0.5)	1 (0.7)	2 (0.4)
Treatment related SAE	0	0	2 (1.4)	2 (0.4)
Severe hypersensitivity to abaloparatide/placebo/teriparatide	1 (0.6)	0	0	1 (0.2)
Other	6 (3.8)	5 (2.6)	1 (0.7)	12 (2.5)

[3] Percentages based on number randomized.
[6] Study completion as indicated by the investigator on the End of Study CRF.
[7] Percentages based on the number of patients who did not complete the study.
[8] Primary reasons were exclusive; i.e., each patient had only one primary reason

A total of 5268 patients were screened. Primary reasons for screen failure were withdrawal of participation, x-ray did not provide evidence of lumbar or vertebral fracture according to inclusion criteria and laboratory tests did not meet inclusion criteria.

The discontinuation rates of 20-27% are within the expected range for a daily subcutaneous injection in the treatment of osteoporosis. However, discontinuations were most frequent in the abaloparatide arm. The teriparatide treatment was not blinded which might have influenced the discontinuation rate.

Of those who discontinued, more abaloparatide-SC patients discontinued due to AEs (38.1%) compared to placebo (26.1%) and teriparatide (31.4%). More patients in the placebo group (7.0%) discontinued due to significant BMD deterioration compared to active treatment arms (0.5% abaloparatide-SC and none in the teriparatide arm).

Teriparatide patients were not eligible for the extension study BA058-05-005.

A total of 75 eligible patients who completed Study BA058-05-003 did not enter BA058-05-005. The primary reason patients did not enter into BA058-05-005 was because the patient was unwilling to continue in the study (41/75; 55%).

However, compared to the number of patients initially randomised to abaloparatide and placebo in study BA058-05-003, it was approximately 30% that did not enter study BA058-05-005. Further, it was a slightly higher proportion of former placebo than abaloparatide patients that entered study BA058-05-005; 71% (494/688) in the placebo arm compared to 67% (469/696) in the abaloparatide arm.

- **Baseline data**

The treatment groups were well balanced regarding baseline demographics and BMD, as expected.

Study BA058-05-003

Table 2. Patient Demographics and Baseline Characteristics (ITT Population)

Category	Placebo (N = 688)	Abaloparatide-SC (N = 696)	Teriparatide (N = 686)
Female gender, n (%)	688 (100)	696 (100)	686 (100)
Age (years) [1]			
Mean (SD)	69.3 (6.13)	69.5 (6.32)	69.4 (6.14)
Median	69.0	69.0	69.0
Q1, Q3	65.0, 73.0	66.0, 74.0	66.0, 73.0
Min, Max	51, 86	50, 85	50, 84
Age groups n (%)			
<65 years	102 (14.8)	102 (14.7)	99 (14.4)
65 to <75	453 (65.8)	455 (65.4)	443 (64.6)
75 to <85	130 (18.9)	138 (19.8)	144 (21.0)
≥85	3 (0.4)	1 (0.1)	0
Years since menopause (years)	n = 687	n = 696	n = 686
Mean (SD)	20.6 (7.91)	21.2 (8.13)	20.9 (8.10)
Median	20.0	21.0	20.0
Q1, Q3	15.0, 25.0	15.0, 26.0	15.0, 26.0
Min, Max	5, 55	5, 55	5, 56
BMI (kg/m²)			
Mean (SD)	24.89 (3.496)	24.80 (3.486)	24.95 (3.488)
Median	24.60	24.70	24.60
Q1, Q3	22.20, 27.50	22.10, 27.00	22.20, 27.50
Min, Max	18.4, 33.0	18.5, 32.9	18.5, 33.2
Race, n (%)			
White	522 (75.9)	535 (76.9)	513 (74.8)
Asian	131 (19.0)	128 (18.4)	137 (20.0)
Black or African America	23 (3.3)	26 (3.7)	24 (3.5)
Other	12 (1.7)	7 (1.0)	12 (1.7)
Region n (%)			
North America	13 (1.9)	17 (2.4)	9 (1.3)
South America	217 (31.5)	222 (31.9)	222 (32.4)
Europe	328 (47.7)	332 (47.7)	323 (47.1)
Asia	130 (18.9)	125 (18.0)	132 (19.2)

BMD T-Scores and Baseline Vertebral Fractures

Based on investigator assessments of BMD inclusion criterion, the study was conducted in accordance with the protocol, with only 0.6% of patients failing to meet this criterion.

Based on laboratory central assessments, results suggest a much broader patient population than was specified in the original BA058-05-003 study design, with 18% of patients not meeting this inclusion criterion. The largest percentage (6.7%) of patients not meeting criterion #3 occurred among patients ≥65 years of age with no prior osteoporotic fracture across both treatment groups.

Table 3Patient Baseline Fracture and BMD T-Scores (ITT Population)

Category	Placebo (N = 688)	Abaloparatide-SC (N = 696)	Teriparatide (N = 686)
Prevalent Vertebral Fracture at Baseline, n (%) [1]			
Yes	149/687 (21.7)	145/696 (20.8)	182/686 (26.5)
Prior Osteoporotic fracture [6]			
Yes	370/688 (53.8)	388/696 (55.7)	378/686 (55.1)
Prior Major Osteoporotic Fracture [2,6]			
Yes	226/688 (32.8)	238/696 (34.2)	208/686 (30.3)
BMD T-score [7]			
Lumbar Spine BMD T-score	N= 688	N = 695	N = 686
Mean (SD)	-3.01 (0.796)	-2.94 (0.880)	-2.91 (0.885)
Median	-3.10	-3.00	-3.00
Q1, Q3	-3.50, -2.60	-3.50, -2.50	-3.50, -2.40
Femoral Neck BMD T- score	n = 687	n = 694	n = 686
Mean (SD)	-2.202 (0.6691)	-2.195 (0.6293)	-2.164 (0.6719)
Median	-2.233	-2.187	-2.186
Q1, Q3	-2.671, -1.786	-2.630, -1.818	-2.614, -1.730
Total Hip BMD T-score	n = 687	n = 694	N = 686
Mean (SD)	-1.94 (0.786)	-1.93 (0.723)	-1.89 (0.760)
Median	-2.00	-1.90	-1.90
Q1, Q3 Mean (SD)	-2.50, -1.40	-2.40, -1.40	-2.40, -1.40
Severe Disease n (%) [8]			
Yes	127/687 (18.5)	113/695 (16.3)	142/686 (20.7)

[1] Evaluated by laboratory.
[2] Based on fractures that occurred prior to Visit 3 recorded on the "Clinical Fractures" CRF page.
[6] Includes those of upper arm, forearm, wrist, hip, shoulder, and/or spine.
[7] Based on centralized reading from Laboratory.
[8] Severe disease is defined as having at least one BMD T-score <= -2.5 measured at spine, femoral neck or total hip and prevalent vertebral fracture at baseline.

- **Numbers analysed**

Table 13. Patient enrollment and disposition

Parameter	Placebo n (%)	Abaloparatide-SC n (%)	Teriparatide n (%)	Overall n (%)
Screened				4616
Screen Failure				2505
Screened, Not Randomized				41
Reason not randomized				
Randomization stopped				39
SAE				1
Missing				1
Randomized (ITT) [1]	688 (100.0)	696 (100.0)	686 (100.0)	2070 (100.0)
Safety Population [2, 3]	687 (99.9)	694 (99.7)	686 (100.0)	2067 (99.9)
Modified ITT (mITT) [3, 4]	600 (87.2)	583 (83.8)	600 (87.5)	1783 (86.1)
Reasons excluded from mITT population				
Did not have pre-treatment radiologic assessment	1 (0.1)	0	0	1 (<0.048)
Did not have post-baseline radiologic assessment	87 (12.6)	113 (16.2)	86 (12.5)	286 (13.8)
Per Protocol (PP) population [3, 5]	547 (79.5)	531 (76.3)	552 (80.5)	1630 (78.7)
Completed study [3, 6]				
Yes	531 (77.2)	507 (72.8)	546 (79.6)	1584 (76.5)
No	157 (22.8)	189 (27.2)	140 (20.4)	486 (23.5)

Approximately 14% of the ITT population were excluded from the mITT population due to lack of radiologic assessments. In addition, approximately 10% patients were not included in the PP population. The reasons have been summarized by the applicant and included: treatment duration <3 months; did not meet BMD inclusion criteria; prior treatment with bisphosphonates, fluoride or strontium and abnormal serum calcium (albumin-corrected), PTH (1-84), serum phosphorus or alkaline phosphatase values during the Screening Period. The criteria of these exclusions is acceptable. The discontinuations due to adverse events are discussed in detail in the safety section.

All patients withdrawn prior to completing the study were to be encouraged to complete study procedures scheduled for the End of Treatment and End of Study Visits. The analysis of the primary endpoint was to be based on both scheduled (at Visit 1 and Visit 9) and unscheduled (e.g. at early termination) X-rays. More patients in the abaloparatide-SC arm, 27.2% (189/696) than in the placebo 22.8% (157/688) and teriparatide 20.4% (140/696) treatment arms respectively did not complete the study (003). It was more abaloparatide than placebo and teriparatide patients that also were excluded from the mITT due to the lack of a post-baseline radiologic assessment. The details of why a post-base line assessment was not performed in a large number of patients was discussed in the previous procedure. According to the applicant, the two primary reasons were that the patient discontinued less than 3 months from the time of baseline (32%), that the patients refused the procedure (35%), that the patients did not return for the early termination visit (15%), and that the clinical site inadvertently did not conduct the procedure (5%). The most common reason

in the abaloparatide group was early termination (40% vs 28% in the placebo group). It should be noted that these numbers are calculated including excluded sites and thus are not correct for the current population.

- **Outcomes and estimation**

 Primary efficacy endpoint in study BA058-05-003: new vertebral fractures after 18 months abaloparatide versus placebo

Abaloparatide-SC met the primary endpoint with a statistically significant reduction in the incidence of new vertebral fracture versus placebo (0.51% versus 4.17%, respectively, p<0.0001) (*Table 4*). There was an 88% relative risk reduction (RRR) in new vertebral fractures in patients receiving abaloparatide-SC versus placebo.

Table 4 At least one incidence of New Vertebral Fracture (mITT Population)

Statistic	Placebo (N=600)	Abaloparatide-SC (N=583)	Teriparatide (N=600)
n/N (%)	25/600 (4.17)	3/583 (0.51)	4/600 (0.67)
95% CI [1]	2.84, 6.08	0.18, 1.50	0.26, 1.70
Risk Reduction vs Placebo (95% CI) [3]		-3.65 (-5.59, -2.00)	-3.50 (-5.45, -1.82)
Relative Risk Reduction vs Placebo (95% CI) [4]		-0.88(-0.96, -0.59)	-0.84 (-0.94, -0.54)
p-value [2]		<0.0001	<0.0001

Only New vertebral fractures were included in the analysis.
[1] 95% CI for Percent was based on the Wilson's Score method.
[2] P-value was from Fisher's exact test with Abaloparatide-SC compared to Placebo.
[3] The risk reduction was calculated as (Abaloparatide-SC - Placebo) and (Teriparatide – Placebo). 95% CI was based on the Newcombe's method.
[4] The relative risk reduction was calculated as (Abaloparatide-SC - Placebo) / Placebo and (Teriparatide - Placebo) / Placebo. 95% CI was based on the Wald's method

A sensitivity analysis was performed using the ITT population to assess the impact of missing data and to confirm the findings. Based on the multiple imputation method, missing data were imputed to create a total of five augmented datasets. Results from these five imputed datasets were combined to produce the final inferential results.

Table 15. Incidence of New Vertebral Fracture Sensitivity Analysis (ITT Population). Statistical Estimation based on multiple imputations

Statistic	Placebo N = 688	Abaloparatide-SC N = 696	Teriparatide N = 686
Incidence rate	3.98	0.86	0.87
95 % CI	2.39, 5.58	0.10, 1.62	-0.01, 1.76
Risk Reduction vs Placebo (95% CI)		-3.12 (-4.82, -1.42)	-3.11 (-4.77, -1.45)
P-value		0.0003	0.0002
RRR vs Placebo (95% CI)		-0.79 (-0.92, -0.45)	-0.79 (-0.92, -0.40)

CI = confidence interval, ITT = intend-to-treat, RRR = relative risk reduction.
[1] 95% CI for Percent was based on the Wilson's Score method.
[2] The risk reduction was calculated as (Abaloparatide-SC - Placebo) and (Teriparatide - Placebo). 95% CI was based on the Newcombe's method.
[3] The relative risk reduction was calculated as (Abaloparatide-SC - Placebo) / Placebo and (Teriparatide - Placebo) / Placebo. 95% CI was based on the Wald's method.
[4] P-value from Fisher's exact test comparing Abaloparatide-SC with Placebo and Teriparatide with Placebo.

The analysis of the primary endpoint showed a highly statistically significant difference in favour of abaloparatide-SC versus placebo. The event rate was however smaller than the vertebral fracture rates expected at the planning stage of the study, i.e. 3% (abaloparatide) and 7% (placebo).

In the primary analysis, 16.2% (113/696) and 12.8% (88/688) of patients randomised to the abaloparatide-SC and placebo group respectively were excluded. The corresponding proportion for the teriparatide arm was 12.5% (86/686). The only sensitivity analysis planned and performed (based on ITT using the method of Multiple Imputation (MI); table above) showed slightly smaller point estimates for the difference between abaloparatide-SC and placebo compared with the primary analysis. Considering that this sensitivity analysis is based on the assumption of missing at random (MAR) several additional sensitivity analyses to examine the sensitivity of inferences to departures from the MAR assumption were requested to confirm data robustness; of particular importance given the single pivotal status of study BA058-05-003:

While a failure imputation is a widely used method, imputing missing as failures is in this case not meaningful (the number of patients with missing data were considerable higher (abaloparatide: 113, placebo 88) than the number of patients with ≥1 new vertebral fracture (abaloparatide:3, placebo: 25)). Further, taking into account reasons for non-completion (see table above on reasons for treatment discontinuation) and using a failure imputation if a patient discontinued due to safety or lack of efficacy seemingly results in very similar number of failures in the two groups. With 72 patients in the abaloparatide arm and 41 in the placebo arm discontinuing due to an AE and one patient in the abaloparatide and 11 patients in the placebo group discontinuing due to continuing significant BMD deterioration the "total" number of failures add up to 76/696 (10.9%) with abaloparatide-SC (3 fractures+72 AEs+1 BMD deterioration) compared to 77/688 (11.2%) with placebo (25 fractures+41 AEs+11 BMD deterioration).

In summary, considering that only one sensitivity analysis was planned, additional sensitivity analyses were requested based on different missing pattern assumptions (i.e. MNAR, e.g. using a pattern mixture model).

The sensitivity analysis using multiple imputation based on the ITT population provided by the applicant is acknowledged. Not including treatment as a factor in the imputation model implies the assumption that the risk of vertebral fracture for patients with missing data is the same in all treatment groups (conditional on covariates), and that this risk is approximately the average risk in patients with non-missing data over all treatment groups. This assumption leads to a more conservative analysis than the primary analysis, which is appreciated. However, the treatment effect which is targeted by this analysis is not clear. Therefore, a placebo multiple imputation (pMI) analysis was requested to be performed replacing missing values for patients without outcome data similarly as in the sensitivity analysis but using a logistic regression model based only on placebo completers; this analysis aims at the treatment effect assuming loss of benefit after treatment drop-out, conditional on covariates.

Furthermore, the sensitivity analysis performed by the applicant did not replace values for patients in the mITT population who discontinued the study. Therefore, an ITT-based analysis replacing values of all drop-outs without vertebral fracture, including those with post-baseline evaluable radiologic assessment before month 18, using pMI was requested to be performed, and an analysis where values for drop-outs without vertebral fracture are replaced based on pMI but considering the risk of vertebral fracture as proportional to the time after drop-out.

The sensitivity analyses that were requested were performed and generally support the primary outcome showing clinically relevant and statistically significant superiority to placebo although treatment effects are reduced as expected for analyses addressing the treatment effect assuming loss of benefit after discontinuation from treatment. The sensitivity analyses were also repeated excluding data from the two excluded EU sites.

Additionally, ITT-based tipping point analyses were requested to be performed, i.e. the number of vertebral fractures in the abaloparatide group in patients without outcome data and all dropouts should be determined that would have changed the conclusion with regard to statistical significance, which confirmed that conclusions would have changed only under extreme assumptions.

Primary efficacy endpoint in study BA058-05-005: new vertebral fractures after 18 months abaloparatide versus placebo

During the 24 months BA058-05-005 extension (from month 18 to 43), 2 new vertebral fractures occurred in the previously abaloparatide treated group compared to 10 new vertebral fractures in the previously placebo treated group.

The risk reduction in abaloparatide treated group compared to placebo remained significant also in the study BA058-05-005.

Table 16. New Vertebral Fracture through Month 43 (Visit 6 in BA058-05-005) from Study BA058-05-003 Baseline (mITT Population)

Parameter	Statistic	Placebo /Alendronate (N = 489)	Abaloparatide-SC /Alendronate (N = 457)
At Least One Incident New Vertebral Fracture at Month 43	n/N (%)	26/489 (5.32)	4/457 (0.88)
	95% CI [1]	3.65, 7.68	0.34, 2.23
	Risk Reduction vs Placebo (95% CI) [2]		-4.44 (-6.86, -2.30)
	Relative Risk Reduction vs Placebo (95% CI) [3]		-0.84 (-0.94, -0.53)
	p-value		< 0.0001
At Least One Incident New Vertebral Fracture at Month 25	n/N (%)	18/444 (4.05)	1/436 (0.23)
	95% CI [1]	2.58, 6.23	0.04, 1.29
	Risk Reduction vs Placebo (95% CI) [2]		-3.86 (-6.06, -2.00)
	Relative Risk Reduction vs Placebo (95% CI) [3]		-0.90 (-0.98, -0.57)
	p-value		< 0.0001
At Least One Incident New Vertebral Fracture at Month 18	n/N (%)	16/489 (3.27)	2/457 (0.44)
	95% CI [1]	2.02, 5.25	0.12, 1.58
	Risk Reduction vs Placebo (95% CI) [2]		-2.83 (-4.84, -1.14)
	Relative Risk Reduction vs Placebo (95% CI) [3]		-0.87 (-0.97, -0.42)
	p-value		0.0013

Alendronate monotherapy started at 19 Months.
[1] 95% CI for Percent was based on the Wilson's Score method.
[2] The risk reduction was calculated as (Abaloparatide-SC/Alendronate - Placebo/Alendronate). 95% CI was based on the Newcombe's method.
[3] The relative risk reduction was calculated as (Abaloparatide-SC/Alendronate - Placebo/Alendronate) / Placebo/Alendronate. 95% CI was based on the Wald's method.

Some reassurance of the efficacy of abaloparatide can be found in that a number of events were observed (in the extension study) in the former placebo treated group compared to only two new events in the former abaloparatide treated group. There was however approximately 30% of those initially randomised to abaloparatide and placebo respectively in study BA058-05-003 that were not included in study BA058-05-005, hence the above cannot be considered as based on a truly randomised comparison.

Secondary Efficacy Endpoints

1. **Key secondary efficacy endpoint:** nonvertebral fractures in study BA058-05-003

Abaloparatide-SC prolonged the time to the first incidence of nonvertebral fracture versus placebo but the difference was not statistically significant (log-rank p = 0.37) for the ITT population. The K-M estimated event rates at 19 months were lower in the abaloparatide-SC group versus placebo (2.7% versus 3.6%, respectively), with a 26% reduction in the hazard of nonvertebral fracture (hazard ratio 0.74, 95% CI [0.38, 1.43]). The K-M event curve was lower in the abaloparatide-SC group versus the placebo group at any time-point during the overall 19 months of the study period (Figure).

For the teriparatide group, the K-M estimated event rates at 19 months were lower than placebo (2.0% versus 3.6%, respectively, HR 0.56, 95% CI [0.28, 1.15], p = 0.11).

Table 17. Time-to-event analyses of Non-vertebral fractures (ITT population)

Parameter	Statistic	Placebo (N = 688)	Abaloparatide-SC (N = 696)	Teriparatide (N = 686)
K-M Estimated Event Rate at 19 Months	%	3.6	2.7	2.0
	Standard error	0.7670	0.6891	0.5618
	95% CI [1]	2.33, 5.42	1.63, 4.44	1.11, 3.43
Absolute Risk Reduction(ARR) vs placebo [2]	ARR (95% CI)		-0.87 (-2.89, 1.15)	-1.61 (-3.47, 0.26)
Absolute Risk Reduction(ARR) vs teriparatide [2]	ARR (95% CI)		0.73 (-1.01, 2.48)	
Number of Patients with Event	n (%)	21 (3.1)	15 (2.2)	12 (1.7)
Number of Patients Censored	n (%)	667 (96.9)	681(97.8)	674 (98.3)
Hazard ratio vs placebo [3]	Hazard ratio (95% CI)		0.74 (0.38, 1.43)	0.56 (0.28, 1.15)
Hazard ratio vs teriparatide [3]			1.30 (0.61, 2.79)	
p-value vs Placebo [4]			0.3675	0.1095
p-value vs teriparatide [4]			0.4919	

Figure 6. Kaplan Meier Curve of Time to first incidence of nonvertebral fractures by treatment group (ITT population)
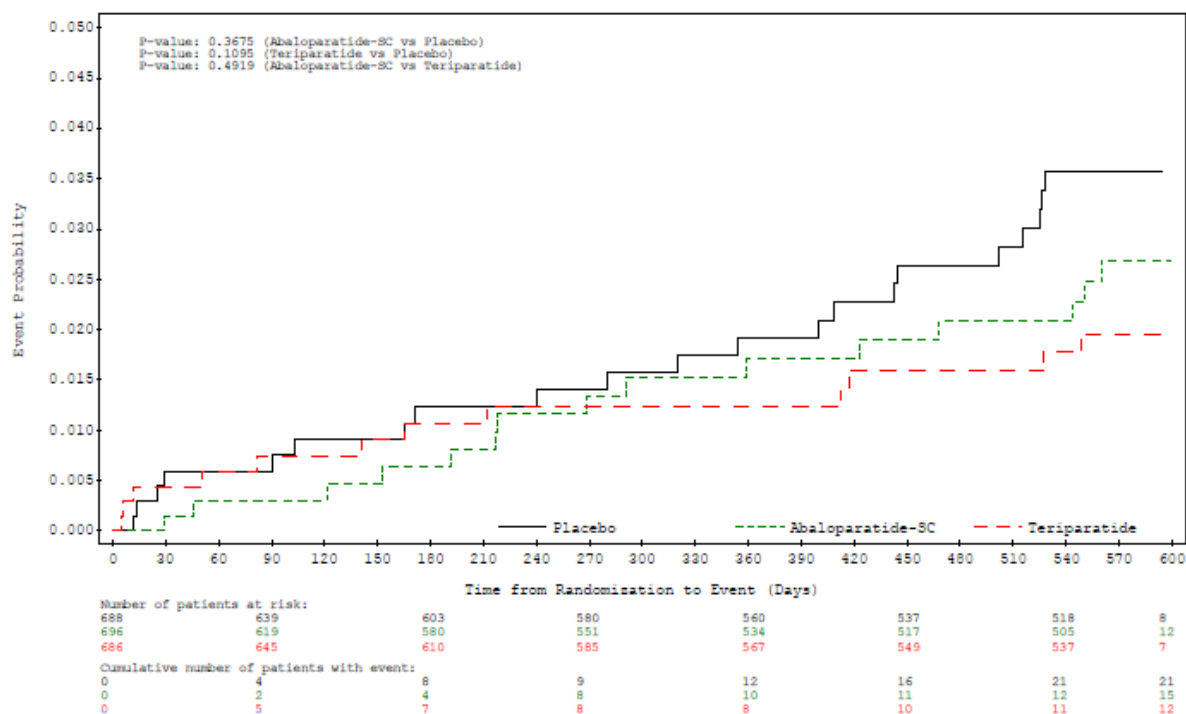
P-value was from the logrank test.

The analysis of the effect of abaloparatide versus placebo on the time to first incidence non-vertebral fracture was not statistically significant, however the available data indicate a trend in favour of abaloparatide. The total number of events was 21 in placebo, 12 in abaloparatide and 11 in teriparatide groups at 18 months. The result for the comparison between placebo and abaloparatide was not significant (HR 0.74, 95% CI [0.38, 1.43]).

With overall few events there was a high level of censored data with seemingly earlier censoring in the abaloparatide-SC arm than in the placebo and teriparatide arm; the discontinuations were more frequent in the abaloparatide group resulting in fewer abaloparatide treated patients at risk: at 18 months the number of patients at risk was 13 patients more in the placebo group and 32 patients more in the teriparatide group.

Patient discontinuations were more frequent in the abaloparatide-SC arm, 27.2% (189/696) than in the placebo 22.8% (157/688) and teriparatide 20.4% (140/696) treatment arms respectively. In the previous procedure the applicant presented descriptive statistics for the follow-up time of all ITT patients and time to study withdrawal for patients who terminated early. Time to study withdrawal among those patients who terminated early indicates discontinuations occurred earlier in the abaloparatide-SC treatment group (125 median days versus 185 median days for placebo group and 184 for teriparatide treatment group). The corresponding presentation for the ITT population excluding the two excluded sites could not be found.

The comparison of non-vertebral fractures for abaloparatide versus teriparatide was not statistically significant (p=0.49) and the reduction in the hazard ratio was accompanied by wide confidence intervals.

The scale of the y-axis leads to the visual impression of relatively large differences while the absolute differences are relatively small and attributable to a small number of events. Therefore, although visually different, differences between the curves may well be attributable to chance.

Key secondary efficacy endpoint; non-vertebral fracture in Extension Study BA058-05-005

Based on the ITT population, the incidence of patients with at least one incident nonvertebral fracture (NVF) from the BA058-05-003 baseline through Month 25 (Visit 3 in BA058-05-005), favoured abaloparatide-SC/alendronate versus placebo/alendronate (2.4% versus 4.5%; RRR [95% CI] -0.47 (-0.74, 0.07), p = 0.0723.

There were no statistically significant reductions in the risk of nonvertebral fractures in the former abaloparatide-SC group versus former placebo group at 18 months (during study BA058-05-003), at 25 months or at 43 months.

During the alendronate treatment period in the BA058-05-005 extension from month 25 through 43, 8 new nonvertebral fractures occurred in the previously abaloparatide treated group compared to 10 new non vertebral fractures in the previously placebo treated group.

The Kaplan-Meier estimated event rates for nonvertebral fractures were lower in the abaloparatide-SC/alendronate group than in the placebo/alendronate group at Month 25 (K-M estimates 2.4% vs 4.5%; HR[95% CI] 0.52 [0.25, 1.08], p=0.073) and at Month 43 (K-M estimates 4.2% versus 6.7%; HR [95% CI] 0.61 [0.35, 1.08)], p = 0.088).

Of note, considering that approximately 30% of those initially randomised to abaloparatide and placebo respectively in study BA058-05-003 were not included in study BA058-05-005 and hence that the above is not based on a truly randomised comparison.

Nonvertebral fracture from BA058-05-003 baseline:

Table 18. Time-to-event analyses of Non-vertebral fractures from baseline (visit 3 in BA058-05-003) at month 25 (visit 3 in BA058-05-005) and month 43 (visit 6 in BA058-05-005) (ITT population)

Time-to-Event Variable	Parameter	Statistic	Placebo /alendronate (N = 494)	Abaloparatide-SC /alendronate (N = 469)
Nonvertebral Fractures	K-M Estimated Event Rate **at 25 Months**	%	4.5	2.4
		Standard error	0.9429	0.7116
		95% CI [1]	3.00, 6.79	1.33, 4.27
	Absolute Risk Reduction(ARR) vs placebo [2]	ARR (95% CI)		-2.13 (-4.45, 0.18)
	Number of Patients with Event	n (%)	22 (4.5)	11 (2.3)
	Number of Patients Censored	n (%)	472 (95.5)	458 (97.7)
	Hazard ratio vs placebo [3]	Hazard ratio (95% CI)		0.52 (0.25, 1.08)
	P-value vs Placebo [4]			0.0734
Nonvertebral Fractures	K-M Estimated Event Rate **at 43 Months**	%	6.7	4.2
		Standard error	1.1423	0.9329
		95% CI [1]	4.77, 9.32	2.67, 6.43
	Absolute Risk Reduction(ARR) vs placebo [2]	ARR (95% CI)		-2.53 (-5.42, 0.36)
	Number of Patients with Event	n (%)	32 (6.5)	19 (4.1)
	Number of Patients Censored	n (%)	462 (93.5)	450 (95.9)
	Hazard ratio vs placebo [3]	Hazard ratio (95% CI)		0.61 (0.35, 1.08)
	P-value vs Placebo [4]			0.0877

Figure 7. Kaplan Meier curve of time to first incident nonvertebral fractures from baseline (visit 3 in BA058-05-003) through month 43 (visit 6 in BA058-05-005) for abaloparatide-SC/alendronate vs Placebo/alendronate (ITT population)
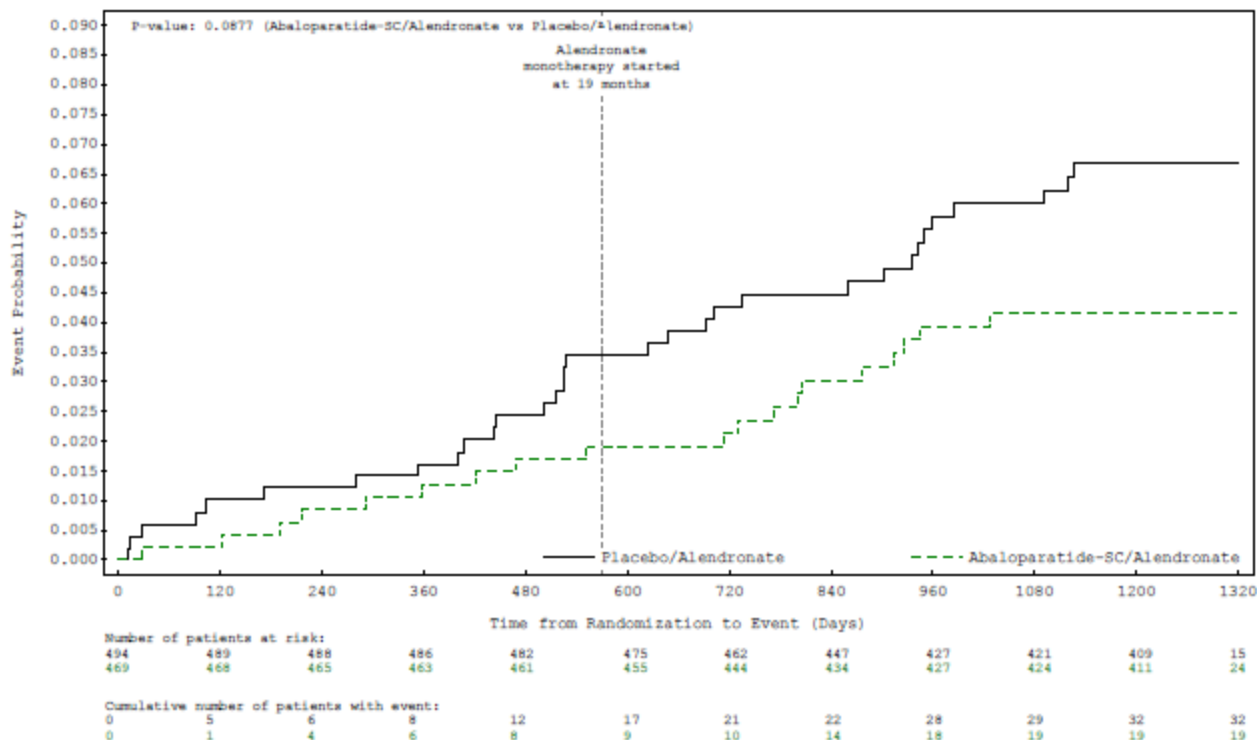
P-value was from the logrank test

Nonvertebral fracture from BA058-05-005 baseline:

The K-M estimated event rates for nonvertebral fractures from study BA058-05-005 baseline were lower, but the difference not statistically significant, in the abaloparatide-SC/alendronate group versus the placebo/alendronate group at Month 6 (K-M estimates 0.4% versus 1.0%; HR [95% CI] 00.42 [0.08, 2.17)], p = 0.2871) and through Month 24 (K-M estimates 2.2% versus 3.2%; HR [95% CI] 0.69 [0.31, 1.54], p = 0.3639).

Additional key secondary efficacy endpoints bone mineral density at total hip, femoral neck, and lumbar spine at 18 months (Study BA058-05-003)

While BMD was lost or unchanged over time in the placebo group, gains in BMD at the total hip, femoral neck and lumbar spine were observed in both the abaloparatide-SC and teriparatide groups at all time-points.

- *The % change from baseline in **lumbar spine** BMD through end of 18-month treatment.*

Figure 8. Mean (+/- SE) percent change in lumbar spine BMD over time by treatment group using LOCF (ITT population)
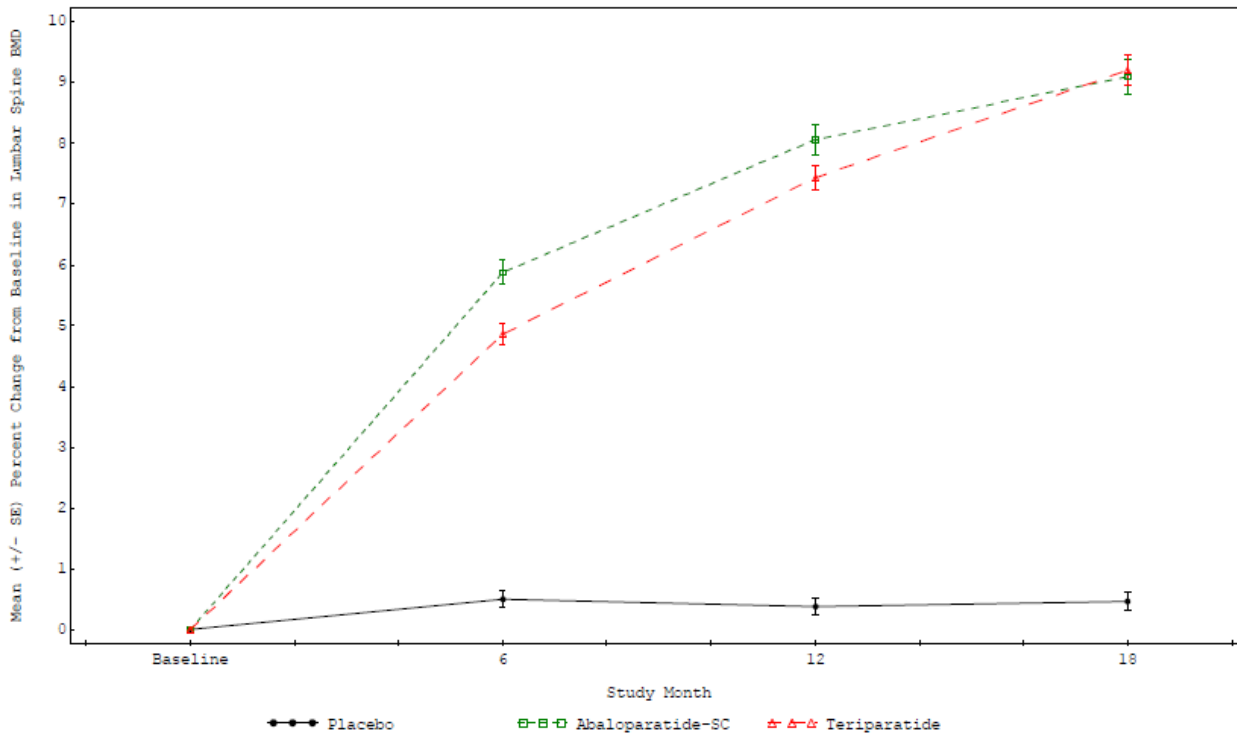
Table 19. Percent change in Lumbar Spine BMD from baseline by visit using LOCF (ITT population). Visit Month 18

Statistic	Placebo (N=688) Value (g/cm²)	Placebo (N=688) % Change from Baseline	Abaloparatide-SC (N=696) Value (g/cm²)	Abaloparatide-SC (N=696) % Change from Baseline	Teriparatide (N=686) Value (g/cm²)	Teriparatide (N=686) % Change from Baseline
n	688	688	695	695	686	686
Mean (SD)	0.8210 (0.0997)	0.470 (3.8468)	0.8990 (0.1243)	9.092 (7.5904)	0.9041 (0.1207)	9.202 (6.2799)
Median	0.8160	0.000	0.8930	8.718	0.8925	8.728
Q1, Q3	0.7530, 0.8705	-1.747, 2.858	0.8160, 0.9640	3.360, 13.710	0.8280, 0.9670	4.909, 13.239
Min, Max	0.570, 1.238	-13.34, 10.86	0.593, 1.374	-9.16, 43.64	0.577, 1.765	-5.78, 34.62
SE	0.0038	0.1467	0.0047	0.2879	0.0046	0.2398
95% CI	0.8135, 0.8284	0.182, 0.758	0.8897, 0.9082	8.527, 9.657	0.8950, 0.9131	8.731, 9.673
P-value vs Placebo [1]				<.0001		<.0001
P-value vs Teriparatide [1]				0.7861		

Missing BMD data were imputed using the method of last observation carried forward (LOCF).
[1] P-values were derived from contrast tests based on the ANCOVA model fitted using only the data of the two treatment groups to be compared.

• *The % change from baseline in **total hip BMD** through end of 18-month treatment.*

Table 20. Percent change in total hip BMD from baseline by visit using LOCF (ITT population). Visit Month 18

Statistic	Placebo (N=688)		Abaloparatide-SC (N=696)		Teriparatide (N=686)	
	Value (g/cm²)	% Change from Baseline	Value (g/cm²)	% Change from Baseline	Value (g/cm²)	% Change from Baseline
n	687	687	694	694	686	686
Mean (SD)	0.7623 (0.0995)	-0.029 (2.8125)	0.7887 (0.0942)	3.328 (3.4061)	0.7918 (0.0965)	2.961 (3.3284)
Median	0.7590	0.000	0.7900	2.921	0.7880	2.625
Q1, Q3	0.6940, 0.8290	-1.603, 1.585	0.7220, 0.8530	0.590, 5.509	0.7270, 0.8510	0.394, 5.038
Min, Max	0.506, 1.041	-14.08, 10.46	0.452, 1.065	-6.52, 18.73	0.502, 1.165	-5.91, 28.28
SE	0.0038	0.1073	0.0036	0.1293	0.0037	0.1271
95% CI	0.7549, 0.7698	-0.239, 0.182	0.7817, 0.7957	3.074, 3.581	0.7845, 0.7990	2.712, 3.211
P-value vs Placebo [1]				<.0001		<.0001
P-value vs Teriparatide [1]				0.0211		

Missing BMD data were imputed using the method of last observation carried forward (LOCF).
[1] P-values were derived from contrast tests based on the ANCOVA model fitted using only the data of the two treatment groups to be compared.

• *The % change from baseline in **femoral neck BMD** through end of 18-month treatment.*

Table 21. Percent change in femoral neck BMD from baseline by visit using LOCF (ITT population). Visit Month 18

Statistic	Placebo (N=688)		Abaloparatide-SC (N=696)		Teriparatide (N=686)	
	Value (g/cm²)	% Change from Baseline	Value (g/cm²)	% Change from Baseline	Value (g/cm²)	% Change from Baseline
n	687	687	694	694	686	686
Mean (SD)	0.7269 (0.0964)	-0.417 (3.5462)	0.7496 (0.0947)	2.676 (3.9737)	0.7523 (0.0946)	2.304 (3.4582)
Median	0.7240	-0.272	0.7480	1.987	0.7490	2.174
Q1, Q3	0.6610, 0.7830	-2.497, 1.437	0.6890, 0.8060	0.000, 4.953	0.6890, 0.8120	0.000, 4.209
Min, Max	0.437, 1.289	-10.70, 36.69	0.453, 1.150	-6.53, 27.49	0.463, 1.072	-7.61, 16.51
SE	0.0037	0.1353	0.0036	0.1508	0.0036	0.1320
95% CI	0.7197, 0.7341	-0.682, -0.151	0.7426, 0.7567	2.380, 2.972	0.7452, 0.7594	2.044, 2.563
P-value vs Placebo [1]				<.0001		<.0001
P-value vs Teriparatide [1]				0.0389		

Missing BMD data were imputed using the method of last observation carried forward (LOCF).
[1] P-values were derived from contrast tests based on the ANCOVA model fitted using only the data of the two treatment groups to be compared.

Both abaloparatide and teriparatide significantly increased the BMD at lumbar spine, total hip and femoral neck. The change was most rapid and greatest in lumbar spine, approximately 9% in the active treatment groups compared to 0.5% in placebo.

There was a smaller but statistically significant difference between abaloparatide and teriparatide for BMD in total hip (3.3 % vs 3.0%) and femoral neck (2.7% vs 2.3%).

The primary population for the analysis of BMD data was the ITT population for those patients who had baseline and at least one post-baseline BMD data. LOCF was used to handle missing data. Seemingly, according to the sensitivity analyses using MMRM, it was approximately 10% of the patients that had missing data at month 6 and 20-25% of the patients that had missing BMD data at month 18. With MMRM offered as the only sensitivity analysis, additional sensitivity analyses (based on other assumptions) for the BMD endpoints should have been useful and were therefore requested. When using placebo multiple imputation in the active treatment group after treatment drop-out, the results of mean percentage change in BMD supported the results of the original ANCOVA (LOCF) analysis.

Considering the expected BMD progression over time, it may be difficult to define a sensitivity approach that can be considered sufficiently conservative. In the exploratory BMD responder analyses, patients who lacked data were excluded. Additional responder analysis treating patients with missing data as non-responders was performed on request, which showed statistically significant superiority of abaloparatide over placebo; however, the difference was smaller than for observed cases due to higher drop-out in the abaloparatide group.

Additional key secondary efficacy endpoints bone mineral density at total hip, femoral neck, and lumbar spine up to month 43 (Study BA058-05-005)

There were continued increases in BMD when abaloparatide or placebo subjects were transitioned to subsequent treatment with alendronate. Differences in BMD response from the BA058-05-003 baseline were statistically significant (p<0.0001) favouring the abaloparatide/alendronate vs. placebo/alendronate at the total hip, femoral neck and lumbar spine (figure below) for all timepoints.

At month 43, greater number of subjects in the abaloparatide/alendronate group (59%) achieved clinically meaningful gains in BMD >3% from baseline at all three anatomic sites (lumbar spine, total hip and femoral neck) than in the placebo/alendronate group (23%), p<0.0001. Similarly, a greater number of subjects in the abaloparatide/alendronate group achieved BMD increase > 6% at all three anatomic sites vs. placebo/alendronate (31% vs. 4%, p<0.0001).

Increases in BMD were apparent in both treatment groups from the BA058-05-005 study baseline, but mean percent BMD increases were generally greater in the placebo/alendronate group for total hip, femoral neck and lumbar spine than in the abaloparatide/alendronate group, but not statistically significant except at Month 24 for total hip (p=0.0025) and the lumbar spine at all timepoints (p<0.0001).

Figure 9. Mean (+/- SE) Percent change in lumbar spine BMD from baseline (visit 1 in BA058-05-003) through month 43 (visit 6 in BA058-05-005) over time by treatment group using LOCF (ITT population)
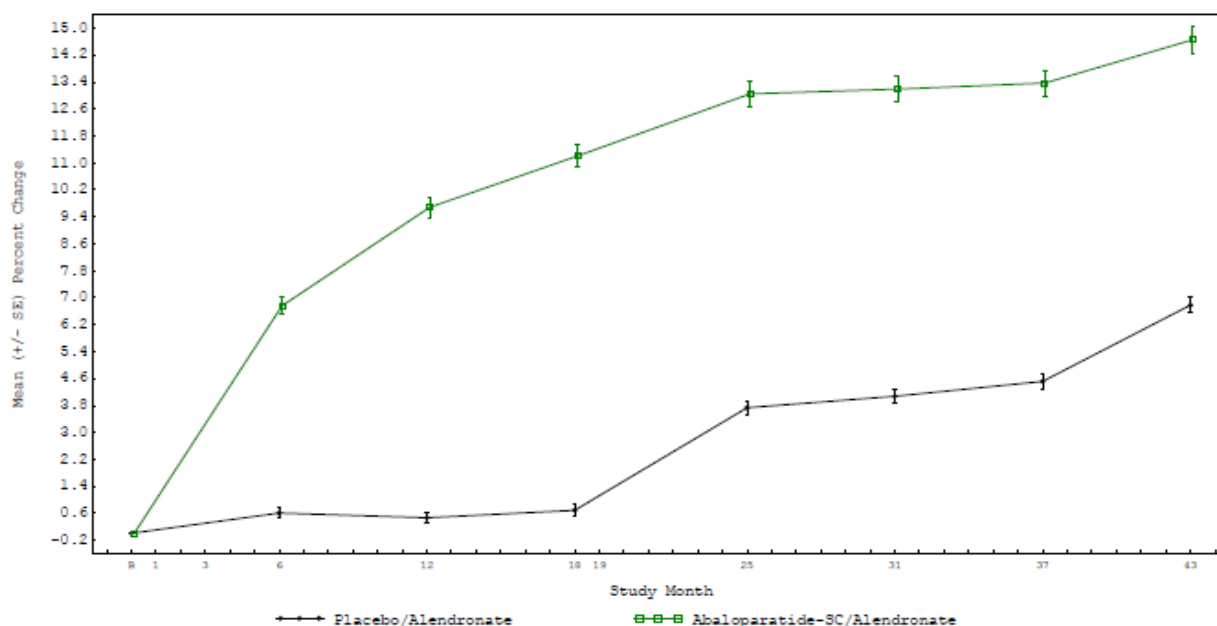
The BMD increased in all patients who started alendronate treatment in study BA058-05-005.

From the 18 month/study BA058-05-005 base line, the mean percent increases were generally greater in the placebo/alendronate group than in the abaloparatide/alendronate group. This is also reflected in the slope in the curve from study month 18 to 25 in the graph presented above.

The effects of sequential anabolic and anti-resorptive therapies are not clear. This was discussed by the applicant in the previous procedure upon request. It was concluded that no definitive published information on the effects on fracture exist at this time.

Other Predefined Efficacy Endpoints

- There were no significant differences in vertical height from baseline to end of 18-months of treatment in study BA058-05-003 or its extension BA058-05-005.

- The number of vertebral fractures in the studies was too low for meaningful severity analyses (incident new and/or worsening vertebral fractures over the study treatment period up to 18 months in abaloparatide-SC-treated patients when compared to placebo)

- The percent change in BMD at the distal 1/3 radius, ultra-distal radius, and total radius from baseline up to 18 months was heterogeneous. In all cases BMD decreased. At the distal 1/3 radius the decrease in bone mineral density was lowest in participants receiving placebo and highest in those receiving teriparatide. At the ultra-distal radius BMD increased from baseline to 6 months in all groups and declined thereafter at 12 and 18 months and BMD was lowest in subjects on placebo. At the total radius the percent change in BMD from baseline was higher for abaloparatide versus placebo at 6 months, but the difference became smaller at 12 and 18 months. Distal 1/3 radius BMD values remained below BA058-05-003 baseline values for the BA058-05-005 distal radius population, at all timepoints through Month 43 in both treatment groups with no statistically significant differences between groups.

- The % change in serum P1NP, BSAP osteocalcin and CTX in a subset of patients: The Biochemical Markers of Bone Turnover results are presented and discussed in the clinical pharmacology section.

- The incidence of one or more incident new vertebral fractures over 18 months of treatment in teriparatide-treated patients when compared to placebo. These results from this comparison vs teriparatide in study BA058-05-003 are presented together with the primary endpoint.

Ancillary analyses

No exploratory analyses were performed for trabecular bone score or for biochemical markers of cartilage formation and degradation as described in the protocol.

Subgroup Analyses

The primary efficacy endpoint (vertebral fractures) and the key secondary endpoint (NVF) were analyzed by patient subgroups as defined below. Additionally, all other secondary efficacy endpoints were tabulated descriptively by patient subgroups. The following subgroups were created for use in selected data analyses: Age (< 65, 65 to < 75, ≥75 years old), Years since menopause (< 15, 15-25, ≥25), Race, Region, Any prior fracture (yes, no), Any prior vertebral fracture (yes, no), Any prior nonvertebral fracture (yes, no), Any prior major osteoporotic fracture (yes, no) Prevalence of vertebral fracture at baseline (0, 1, ≥2), Severity of vertebral fracture (SQ score) at baseline (0, 1, ≥2), Severe disease (least BMD T-score ≤-2.5 and prevalent

vertebral fracture) at baseline (yes, no), Lumbar Spine BMD T-score at baseline, Total hip BMD T-score at baseline, Femoral neck BMD T-score at baseline. In general, the results were in line with those seen in the whole population and favoured abaloparatide-SC versus placebo for all subgroups analysed with a few exceptions. The exceptions are not presented here since they consisted of low number of subjects and no definitive conclusions could be drawn.

FRAX analysis

FRAX analysis was performed as a pre-specified exploratory analysis. The primary aims of the analysis were to (1) assess the baseline levels of disease severity and their consistency across treatment groups as well as (2) explore the efficacy of abaloparatide and teriparatide in relation to baseline fracture probability estimates and seek possible treatment interactions across baseline levels of disease severity. This analysis showed a broad osteoporosis population that included the disease severity range described in the EU guidance on osteoporosis trials and that the treatment groups were well balanced. This analysis also showed efficacy results consistent with those described in this BA058-005-003 clinical study report and no significant interaction of fracture probability between efficacy and disease severity.

3D-DXA modelling (analysis not presented during the previous procedure)

This study was a retrospective analysis of DXA scans in a randomly selected subset of subjects from Study BA058-05-003. Hip DXA images were subjected to 3D modelling to better understand and compare the effects of abaloparatide and teriparatide compared to placebo on the cortical and trabecular compartments of the proximal femur over 18 months.

A total of 624 subjects of Study BA058-05-003 were randomly selected for inclusion across the three different treatment groups (placebo [n= 208], abaloparatide [n= 207], teriparatide [n= 209]). The 3D-DXA analysis was performed on the hip scans which had been collected at baseline, month 6, and month 18.

Further correlations were performed to explore potential relationships between the treatment-related changes in serum biomarkers and the observed changes in 3D-DXA parameters at 18 months. Blood samples were analysed where available for the respective subjects to measure biomarkers of bone turnover, (procollagen type I N-terminal propeptide [s-PINP], and carboxy-terminal cross-linking telopeptide of type I collagen [s-CTX]).

The 3D-DXA modelling at the proximal femur demonstrated significant increases in trabecular volumetric BMD (vBMD) and cortical thickness and significantly increased cortical vBMD compared to baseline after 18 months of abaloparatide treatment. Additionally, HSA-indices (CSMI and section modulus) at the femoral neck, intertrochanteric region and the shaft significantly improved as early as 6 months after the initiation of abaloparatide treatment and support the clinical data suggesting fracture risk reduction at nonvertebral sites.

In the teriparatide group, changes in cortical volumetric BMD were inversely correlated with changes in serum CTX and PINP.

Figure 10. 3D-DXA endpoints in study 3D DXA
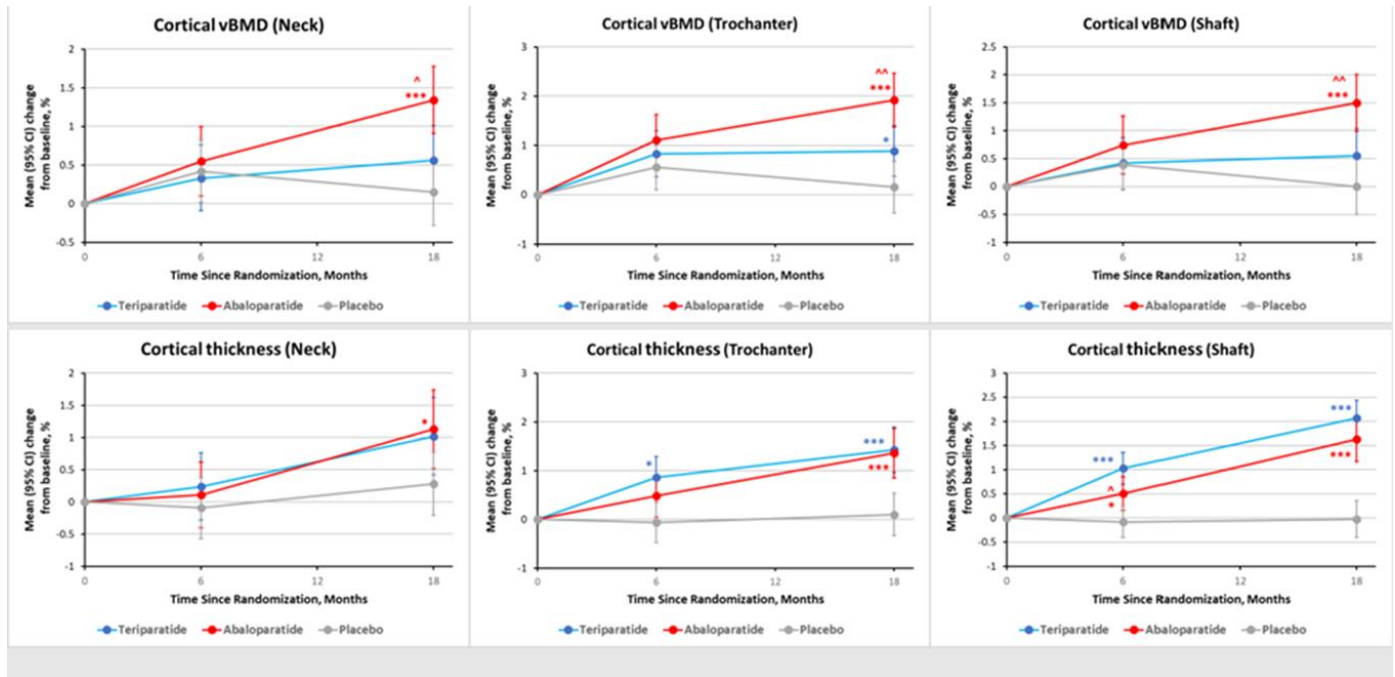
*: P<0.05 vs placebo; ***: P<0.01 vs placebo; ^: P<0.05 vs teriparatide; ^^: P<0.01 vs teriparatide

vBMD: volumetric bone mineral density; CI: Confidence interval.

Analysis of Time to First Incidence of other fracture endpoints

The applicant has presented results for several fracture endpoint combinations that were not pre-defined endpoints in study BA058-05-003. These included clinical fractures, major osteoporotic fractures, wrist fractures, nonvertebral fractures including any level of trauma and clinical spine fractures. There were fewer fractures in the abaloparatide group in all these categories and the difference was statistically significant except for wrist fractures, see table below.

Hip fractures are not presented in the table below. However, in the BA058-05-003 study there were no hip fractures in the abaloparatide-SC or teriparatide groups and 1 hip fracture in the placebo group and in the BA058-05-005 study there were no hip fractures in the abaloparatide/alendronate group, and 2 hip fractures in the placebo/alendronate group.

Table 22. Other Fracture efficacy results from studies BA058-05-003 and BA058-05-005

	Study BA058-05-003			Study BA058-05-005			
	18/19 Months			25 Months		43 Months	
Parameters	Placebo (N=688)	ABL (N=696)	Teriparatide (N=686)	Placebo/ ALN (N=494)	ABL/ ALN (N=469)	Placebo/ ALN (N=494)	ABL/ ALN (N=469)
Secondary and Exploratory Fracture Endpoints							
Incidence and Time to First Incident of Clinical Fracture[8] (ITT)							

| | Study BA058-05-003 | | | Study BA058-05-005 | | | |
| | 18/19 Months | | | 25 Months | | 43 Months | |
Parameters	Placebo (N=688)	ABL (N=696)	Teriparatide (N=686)	Placebo/ ALN (N=494)	ABL/ ALN (N=469)	Placebo/ ALN (N=494)	ABL/ ALN (N=469)
K-M estimated event rate (%)	7.4	3.8	3.4	6.1	3.4	8.7	6.1
Number of subjects with event, n (%)	35 (5.1)	21 (3.0)	21 (3.1)	30 (6.1)	16 (3.4)	42 (8.5)	28 (6.0)
Number of subjects censored, n (%)	653 (94.9)	675 (97.0)	665 (96.9)	464 (93.9)	453 (96.6)	452 (91.5)	441 (94.0)
HR vs. Placebo[5],(95% CI)		0.61 (0.36, 1.06)	0.59 (0.35, 1.02)		0.55 (0.30, 1.02)		0.68 0.42, 1.10)
HR vs Teriparatide[5],(95% CI)		1.04 (0.57, 1.90)					
p-value vs. Placebo[6]		0.0753	0.0555		0.0529		0.1185
p-value vs. Teriparatide[6]		0.9037					
Incidence and Time to First Incident of Major Osteoporotic Fracture[9](ITT)							
K-M estimated event rate (%)	5.4	1.2	2.2	4.1	1.5	5.8	2.8
Number of subjects with event, n (%)	23 (3.3)	7 (1.0)	14 (2.0)	20 (4.0)	7 (1.5)	28 (5.7)	13 (2.8)
Number of subjects censored, n (%)	665 (96.7)	689 (99.0)	672 (98.0)	474 (96.0)	462 (98.5)	466 (94.3)	456 (97.2)
HR vs. Placebo[5], HR(95% CI)		0.31 (0.13, 0.72)	0.60 (0.31, 1.17)		0.37 (0.15, 0.86)		0.48 (0.25, 0.92)
HR vs. Teriparatide[5], HR (95% CI)		0.51 (0.21, 1.27)					
p-value vs. Placebo[6]		0.0041	0.1330		0.0168		0.0244
p-value vs. Teriparatide[6]		0.1396					
Incidence and Time to First Incident of Wrist Fracture (ITT)							
K-M estimated event rate (%)	1.7	0.9	1.6	2.3	1.1	3.3	2.0
Number of subjects with event, n (%)	10 (1.5)	5 (0.7)	10 (1.5)	11 (2.2)	5 (1.1)	16 (3.2)	9 (1.9)
Number of subjects censored, n (%)	678(98.5)	691(99.3)	676(98.5)	483(97.8)	464 (98.9)	478 (96.8)	460 (98.1)

| Parameters | Study BA058-05-003 | | | Study BA058-05-005 | | | |
| | **18/19 Months** | | | **25 Months** | | **43 Months** | |
	Placebo (N=688)	**ABL** (N=696)	**Teriparatide** (N=686)	**Placebo/ ALN** (N=494)	**ABL/ ALN** (N=469)	**Placebo/ ALN** (N=494)	**ABL/ ALN** (N=469)
HR vs. Placebo[5], HR(95% CI)		0.52 (0.18, 1.51)	1.00 (0.41, 2.39)		0.48 (0.17, 1.37)		0.58 (0.26, 1.32)
HR vs. Teriparatide[5], HR (95% CI)		0.51 (0.18, 1.50)					
p-value vs. Placebo[6]		0.2198	0.9926		0.1605		0.1925
p-value vs. Teriparatide[6]		0.2159					
Incidence and Time to First Incident of Nonvertebral Fracture including all trauma level (ITT)							
K-M estimated event rate (%)	3.9	2.9	2.1	4.9	2.4	7.5	4.8
Number of subjects with event, n (%)	23 (3.3)	16 (2.3)	13 (1.9)	24 (4.9)	11 (2.3)	36 (7.3)	22 (4.7)
Number of subjects censored, n (%)	665 (96.7)	680 (97.7)	673 (98.1)	470 (95.1)	458 (97.7)	458 (92.7)	447 (95.3)
HR vs. Placebo[5], HR(95% CI)		0.72 (0.38, 1.36)	0.56 (0.28, 1.10)		0.48 (0.23, 0.97)		0.63 (0.37, 1.07)
HR vs. Teriparatide[5], HR (95% CI)		1.28 (0.62, 2.66)					
p-value vs. Placebo[6]		0.3046	0.0886		0.0376		0.0816
p-value vs. Teriparatide[6]		0.5072			NA		NA
Incidence and Time to First Incident of Major Nonvertebral Fracture (ITT)							
K-M estimated event rate (%)	3.2	1.8	1.8	4.1	1.7	6.5	3.1
Number of subjects with event, n (%)	19 (2.8)	10 (1.4)	11 (1.6)	20 (4.0)	8 (1.7)	31 (6.3)	14 (3.0)
Number of subjects censored, n (%)	669 (97.2)	686 (98.6)	675 (98.4)	474 (96.0)	461 (98.3)	463 (93.7)	455 (97.0)
HR vs. Placebo[5], HR (95% CI)		0.54 (0.25, 1.16)	0.57 (0.27, 1.20)		0.42 (0.18, 0.95)		0.46 (0.25, 0.87)
HR vs Teriparatide[5], HR (95% CI)		0.94 (0.40, 2.21)					
p-value vs. Placebo[6]		0.1100	0.1370		0.0309		0.0144
p-value vs. Teriparatide[6]		0.8849					

Incidence and Time to First Incident of Clinical Spine Fracture (ITT)							
K-M estimated event rate (%)	3.0	0	0.5	1.0	0.0	1.2	0.4
Number of subjects with event, n (%)	9 (1.3)	0	3 (0.4)	5 (1.0)	0(0.0)	6 (1.2)	2 (0.4)
Number of subjects censored, n (%)	679 (98.7)	696 (100.0)	683 (99.6)	489 (99.0)	469 (100.0)	488 (98.8)	467 (99.6)
HR vs. Placebo[5], HR (95% CI)		0.00 (0.000)	0.33 (0.09, 1.22)		0.00 (NE)		0.35 (0.07, 1.72)
HR vs. Teriparatide[5], HR (95% CI)		0.00 (0.00)					
p-value vs. Placebo[6]		0.0027	0.0793		0.0291		0.1735
p-value vs. Teriparatide[6]		0.0854					

Abbreviations: ABL=abaloparatide; ALN=alendronate; CI=confidence interval; EMA=European Medicines Agency; HR=hazard ratio; ITT=intent-to-treat; K-M=Kaplan-Meier.

[1] 95% CI for percentage was based on the Wilson's score method

[2] The risk reduction was calculated as (abaloparatide -SC – Placebo) and (Teriparatide-Placebo). 95% CI was based on Newcombe's method.

[3] The RRR was calculated as (abaloparatide -SC – Placebo)/Placebo and (Teriparatide-Placebo)/Placebo. 95% CI was based on Wald's method.

[4] p-value from Fisher's exact test comparing abaloparatide -SC with placebo and teriparatide with placebo.

[5] Cox proportional hazard model was used to calculate the HR with placebo or teriparatide as reference.

[6] p-values were from the log rank test

[7] Nonvertebral fractures include those of the hip, wrist, forearm, shoulder, collar bone, upper arm, ribs, upper leg, knee, lower leg, foot, ankle, hand, pelvis, tailbone and other, and excluded fingers, toes, sternum, patella, skull, and facial bone

[8] Includes clinical fracture at any site

[9] Major osteoporotic fractures include those of the wrist, hip, shoulder, and clinical spine

[10] Severe disease is defined for the purposes of this protocol as having at least one BMD T-score ≤ -2.5 at anyanatomical sites and prevalent vertebral fracture at baseline.

The results from the post-hoc analyses on other fracture endpoints and combinations are, in general, considered to be in line with the results for primary and key secondary endpoints.

It is noted that the EMA osteoporosis guideline does not specify fracture combinations "clinical fractures and major osteoporotic fractures" to be studied. In contrast, the guideline states that in addition to vertebral fractures, hip or major non-vertebral fractures are to be studied. The applicant has presented the number of hip fractures.

Study ITM-058-301

This was a Phase 3, 2-arm, multi-centre, randomised, placebo-controlled, double blind, parallel group study in Japanese subjects with osteoporosis who were at high risk of fracture. This study was conducted to support a marketing authorization for abaloparatide in Japan.

Methods (ITM-058-301)

The study consisted of 2 periods; a run-in period (up to an 8-week time frame) and a treatment period.

- **Study participants**

The study enrolled male or postmenopausal female osteoporosis subjects aged 55-85 years who were at high risk of fracture having any of the following:

- Lumbar spine BMD < 80% of young adult mean (YAM), and at the same time, 1 or more fragility vertebral fracture; or

- Lumbar spine BMD ≤ 70% or −2.5 standard deviation (SD) of YAM, and at the same time, aged 65 years or older; or

- Lumbar spine BMD < 65% of YAM

All subjects needed to have measurable lumbar spine bone mineral density (BMD) on DXA which was required for assessment of primary and secondary efficacy endpoints.

Women were required to have had menopause at the age of 43 years or older and to be postmenopausal for at least 3 years at the time of informed consent.

Subjects with secondary osteoporosis due to endocrine, nutritional, drug-induced or other reasons, subjects with current or past history of specific diseases affecting the bone and subjects treated with drugs affecting calcium or bone metabolism were excluded.

- **Outcomes/endpoints**

Primary endpoint

The primary efficacy endpoint is percent change in lumbar spine (L1-L4) bone mineral density (BMD) at the last visit.

Secondary efficacy endpoints included:

- % change from baseline in lumbar spine (L1 L4) BMD at Week 12, 24, 48 and 78

- % change from baseline in lumbar spine (L2 L4) BMD and % change from baseline in Hip (total, neck[1]) BMD at Week 12, 24, 48, and 78 and the last visit

- Incidence of new vertebral fractures and new nonvertebral fractures (X ray assessment) at Week 24, 48 and 78 and the last visit

- Changes in bone metabolism markers at Week 1, 2, 6, 12, 24, 36, 48, 60, 72, and 78 and the last visit (procollagen type I N terminal propeptide [PINP], procollagen type I C terminal propeptide [PICP], BAP, osteocalcin [OC], type I collagen C telopeptides [CTX], and tartaric acid resistant acid phosphatase 5b [TRACP 5b])

- Evaluation of QOL at Week 3, 12, 24, 48, and 78 and the last visit (MOS 36 item Short Form Health Survey version 2 [SF 36v2TM], QOL questionnaire specific to low back pain [Roland Morris Disability Questionnaire: RDQ])

Exploratory efficacy endpoints included

- Hip structure analysis (HSA) (assessment sites: narrow neck [NN], intertrochanter [IT], and femoral shaft [FS]) at Week 12, 24, 48, and 78 and the last visit (at selected sites)

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[1] In the CSR ITM 058 301 the term hip neck is used for the femoral neck.

- Analysis of computed tomography (CT) images by quantitative computed tomography (QCT) at Week 78 (assessment sites: neck, intertrochanter, and shaft) (at selected sites)

- % changes in bone quality markers (pentosidine and homocysteine) at Week 6, 12, 24, 36, 48, 60, 72 and 78 and the last visit

- % changes in 1,25-$(OH)_2$ vitamin D, 25-(OH) vitamin D, sclerostin at Week 24, 48 and 78 and the last visit

- % change in PTH (1 84) at Week 6, 12, 18, 24, 36, 48, 60, 72 and 78 and the last visit

- Analysis of CT images by high resolution peripheral quantitative computed tomography (HR pQCT) at Week 78 and the last visit (assessment sites: forearm bone and lower leg bone) (at selected sites)

Sample size

Sample size of 195 patients was planned: 130 patients in the ITM-058 80 µg group and 65 patients in placebo group.

Based on data from Japanese Phase II study (Study No.: ITM-058-004) and Phase III study BA058-05-003, it was estimated that percent change (standard deviation) in lumbar spine (L1-L4) BMD at 18 months of administration in this study is approximately 12% (7%) in the ITM-058 group and approximately 1% (4%) in the placebo group. Using these assumptions, and assuming a statistical significance level of 0.025 (one-sided) and a statistical power of 90%, a sample size of 10 subjects in the ITM-058 group and 5 subjects in the placebo group would be required.

Meanwhile, this study is a bridging study based on percent changes in lumbar spine BMD. With the treatment period of 18 months, the study is also designed to collect not only efficacy data but safety data after 18-month administration. According to "Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (Notification No. 592 of the Evaluation and Licensing Division, PAB dated May 24, 1995)," it is acceptable to adopt the results of drug administration for at least 1 year in 100 patients as part of the safety database. Assuming that safety data of ITM-058 are collected after 18-month administration, it is considered necessary to include the number of patients specified in the above guideline (i.e. 100 patients).

Based on these and assumed withdrawal/dropout rate of approximately 20%, the target sample size was determined to be 130 subjects in the ITM-058 group and 65 subjects in the placebo group.

Randomisation

Subjects were randomized in a 2:1 double-blinded fashion for daily treatment by self-administration with the electrically operated injector of either abaloparatide or placebo.

Dynamic allocation was performed by the registration center, using allocation (stratification) factors:
1) Lumbar spine (L1-L4) BMD (at the pre-screening test), categories:
   Lumbar spine (L1-L4) BMD≥ 0.709 g/cm2
   Lumbar spine (L1-L4) BMD < 0.709 g/cm2 and ≥ 0.643 g/cm2
   Lumbar spine (L1-L4) BMD< 0.643 g/cm2
2) Sex (Women/Men)

Blinding (masking)

This clinical study was performed in a double-blind manner. The blinding of the study was secured with the use of a control drug which is indistinguishable from the study drug.

Statistical methods

The primary analysis population for efficacy evaluation was Full Analysis Set (FAS), defined as a group of the enrolled subjects who received at least one dose of the investigational drug (study drug or control drug) and had efficacy assessment data after administration. Per Protocol Set (PPS), defined as a group of the subjects in the FAS who had no major protocol violation, was used for secondary (sensitivity) analysis. Safety population was defined as a group of the enrolled subjects who received at least one dose of the investigational drug (study drug or control drug) and had safety assessment data after administration.

In the primary efficacy analysis of percent change in lumbar spine (L1-L4) BMD at the last visit, superiority of the ITM-058 group over the placebo group was tested in:
1. the entire population including patients with postmenopausal osteoporosis and patients with male osteoporosis
2. subset of patients with postmenopausal osteoporosis.

The closed testing procedure was used for multiplicity adjustment, in such way that the primary endpoint was tested first in the entire population and, if a statistically significant result was found, then statistical test was performed in the subset of patients with postmenopausal osteoporosis. Two-sided significance level of 0.05 (or one-sided significance level of 0.025) was used for testing. No multiplicity adjustment was performed for the other analyses.

For the first comparison between the ITM-058 group and the placebo group in the entire population including patients with postmenopausal osteoporosis and patients with male osteoporosis, analysis of covariance (ANCOVA) was applied to percent changes in the lumbar spine (L1-L4) BMD at the last visit from the baseline test values, with treatment group and sex (allocation factor) as factors and lumbar spine (L1-L4) BMD at the pre-screening test (allocation factor) as a covariate. For the second test, i.e., comparison between the ITM-058 group and the placebo group in the subset of patients with postmenopausal osteoporosis, ANCOVA was applied to percent changes in the lumbar spine (L1-L4) BMD at the last visit from the baseline test values, with treatment group as a factor and lumbar spine (L1-L4) BMD at the pre-screening test (allocation factor) as a covariate. The ANCOVA model was used to calculate the adjusted mean (least squares mean) lumbar spine (L1-L4) BMD at the last visit and its standard error for each treatment group, and the adjusted mean (least squares mean) of the between-group difference displayed along with its 95% CI and p-value.

Secondary analyses were performed for the entire population and the subset of patients with postmenopausal osteoporosis, on the FAS and PPS, respectively. For lumbar spine (L1-L4) BMD, lumbar spine (L2-L4) BMD, Hip (total) BMD, and Hip (neck) BMD, the percent change in each endpoint from baseline to the last visit was analyzed on the entire population by ANCOVA using a model similar to the primary analysis model. The analyses were performed in two ways, without imputation of missing data and with imputation by last observation carried forward (LOCF). Longitudinal data was also analysed using MMRM.

For the secondary endpoints Incidence of new vertebral fractures and Incidence of new nonvertebral fractures, any new fractures occurring after pre-screening test and before start of treatment were excluded from the analysis. The cumulative number of fractures and the cumulative proportion of subjects who have fracture during the period from the pre-screening test to Weeks 24, 48 and 78 and the last visit were

calculated for each treatment group, and the 95% CIs were calculated using Wilson method. The treatment groups were compared using Fisher's exact test, and the 95% CI was calculated by Newcombe's method. The relative risk reduction (RRR) was determined, with the 95% CI calculated by Wald's method.

Missing data were in some cases imputed by LOCF, so that the last value obtained before each evaluation time point was used for imputation.

The SAP was finalized on October 10, 2019. The database locked on October 11, 2019, and the key was opened on October 16, 2019.

Definition of FAS is not following the ICH E9 principle that all randomized subjects should be included in the analysis. Analyses based on all randomized subjects may be requested if deemed necessary. The stepwise testing procedure for the entire population and the subset of patients with postmenopausal osteoporosis was used to control the Type 1 error rate at 5% two-sided which is endorsed. Analysis based on PPS is not considered to add value as a sensitivity analysis, and LOCF applied in ANCOVA is likely not sufficient to demonstrate robustness of the results. Amount of missing data is not summarised, but it can be derived from the available tables that approximately 20-23 % of patients with postmenopausal osteoporosis (in FAS) did not have observed values on the primary endpoint at Week 78 in the placebo and ITM-058 group, respectively. The primary ANCOVA analysis was based on the observed values and no corresponding analysis with LOCF could be found. Descriptive analysis using LOCF shows that 95% CI for the between treatment difference is in line with the results of the primary and the MMRM analysis. Considering that the efficacy estimates from this study are not intended for presentation in the SmPC, no further sensitivity analysis will be requested.

Results (Study ITM-058-301)

Participant flow

Of 213 randomized subjects (141 in the abaloparatide group and 72 in the placebo group), 206 were included in the FAS of which were 136 in the abaloparatide group and 70 in the placebo group). The PPS consisted of 188 subjects (123 and 65).

Table 23. Disposition of subjects in treatment period (randomized subjects)

	ITM-058 (N = 141) n (%)	Placebo (N = 72) n (%)	Total (N = 213) n (%)
Treatment Period			
Number of subjects treated	140 (99.3)	72 (100.0)	212 (99.5)
Number of subjects but not treated	1 (0.7)	0 (0.0)	1 (0.5)
Reason for discontinuation [a]			
Adverse event	0 (0.0)	0 (-)	0 (0.0)
Death	0 (0.0)	0 (-)	0 (0.0)
Physician decision	1 (100.0)	0 (-)	1 (100.0)
Physician decision (adjusted serum calcium)	0 (0.0)	0 (-)	0 (0.0)
Withdrawal by subject	0 (0.0)	0 (-)	0 (0.0)
Lack of efficacy	0 (0.0)	0 (-)	0 (0.0)
Other	0 (0.0)	0 (-)	0 (0.0)
Emergency code break	0 (0.0)	0 (-)	0 (0.0)
Number of subjects discontinued in treatment period	39 (27.7)	15 (20.8)	54 (25.4)
Reason for discontinuation [b]			
Adverse event	2 (5.1)	3 (20.0)	5 (9.3)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	7 (17.9)	1 (6.7)	8 (14.8)
Physician decision (adjusted serum calcium)	2 (5.1)	1 (6.7)	3 (5.6)
Withdrawal by subject	19 (48.7)	5 (33.3)	24 (44.4)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Other	9 (23.1)	5 (33.3)	14 (25.9)
Emergency code break	0 (0.0)	0 (0.0)	0 (0.0)
Number of subjects completed in treatment period	101 (71.6)	57 (79.2)	158 (74.2)

a) Denominator is the number of subjects but not treated.
b) Denominator is the number of subjects discontinued in treatment period.

Baseline data

Table 24.5 Patient demographics and baseline characteristics

	ITM-058 (N = 136)	Placebo (N = 70)	Total (N = 206)
Age (years)			
n	136	70	206
Mean (SD)	68.6 (6.0)	68.8 (5.6)	68.7 (5.8)
Median	68.0	68.0	68.0
Min, Max	56, 85	58, 84	56, 85
Age (n[%])			
< 65	31 (22.8)	14 (20.0)	45 (21.8)
65 <= < 75	84 (61.8)	46 (65.7)	130 (63.1)
75 <=	21 (15.4)	10 (14.3)	31 (15.0)
Sex (n[%])			
Male	14 (10.3)	6 (8.6)	20 (9.7)
Female	122 (89.7)	64 (91.4)	186 (90.3)
Race (n[%])			
Asian	136 (100.0)	70 (100.0)	206 (100.0)
American Indian or Alaska native	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other pacific islander	0 (0.0)	0 (0.0)	0 (0.0)
White	0 (0.0)	0 (0.0)	0 (0.0)
BMI (kg/m^2)			
n	136	70	206
Mean (SD)	21.54 (3.02)	21.47 (2.46)	21.52 (2.84)
Median	21.30	21.40	21.35
Min, Max	15.0, 32.7	15.8, 28.1	15.0, 32.7
Menopause or total hysterectomy (n[%]) [a]			
Menopause	116 (95.1)	63 (98.4)	179 (96.2)
Total hysterectomy	6 (4.9)	1 (1.6)	7 (3.8)
Time since menopause or total hysterectomy (years) [a]			
n	122	64	186
Mean (SD)	17.3 (7.3)	17.4 (6.8)	17.3 (7.1)
Median	16.5	17.5	17.0
Min, Max	4, 37	5, 37	4, 37

Demographic and other baseline characteristics were comparable for both groups. The proportion of the subjects with insufficiency fracture was higher in the abaloparatide group than in the placebo group: 46.3% versus 28.6%, respectively. The PINP concentration (mean ± SD) was slightly lower in the abaloparatide group than in the placebo group: 48.54 ± 14.47 ng/mL versus 56.91 ± 20.01 ng/mL, respectively.

The submitted Phase 3 study ITM-058-301 was conducted in Japanese subjects (213 participants) with approximately 10% male patients. The patient population was slightly younger in the 301 study compared with the BA058-05-003 study (mean age 69 vs 70 years in the abaloparatide group) with a larger proportion of patients being <65 years (20% vs 15%). The population in 301 study had a lower BMI than in the BA058-05-003 study (21.5 kg/m2 vs 24.8 kg/m2 in the abaloparatide group).

Table 65. Patient baseline fracture and BMD scores

	ITM-058 (N = 136)	Placebo (N = 70)	Total (N = 206)
Parents history of hip fracture(n[%])			
Yes	13 (9.6)	7 (10.0)	20 (9.7)
No	123 (90.4)	63 (90.0)	186 (90.3)
Fragility fracture (n[%])			
Yes	63 (46.3)	20 (28.6)	83 (40.3)
No	73 (53.7)	49 (70.0)	122 (59.2)
Unknown	0 (0.0)	1 (1.4)	1 (0.5)
Number of vertebral fracture (n[%])			
0	75 (55.1)	51 (72.9)	126 (61.2)
1	46 (33.8)	13 (18.6)	59 (28.6)
2 <=	15 (11.0)	6 (8.6)	21 (10.2)
Lumbar Spine (L1-L4) BMD (g/cm^2)			
n	136	70	206
Mean (SD)	0.6469 (0.0719)	0.6502 (0.0661)	0.6480 (0.0698)
Median	0.6470	0.6480	0.6470
Min, Max	0.465, 0.792	0.454, 0.824	0.454, 0.824
Lumbar Spine (L1-L4) BMD (g/cm^2) (n[%])			
0.709 <=	24 (17.6)	10 (14.3)	34 (16.5)
0.643 <= < 0.709	50 (36.8)	27 (38.6)	77 (37.4)
< 0.643	62 (45.6)	33 (47.1)	95 (46.1)
Hip (Total) BMD (g/cm^2)			
n	136	70	206
Mean (SD)	0.6635 (0.0860)	0.6568 (0.0748)	0.6612 (0.0823)
Median	0.6545	0.6570	0.6555
Min, Max	0.440, 0.894	0.370, 0.793	0.370, 0.894
Hip (Neck) BMD (g/cm^2)			
n	136	70	206
Mean (SD)	0.5346 (0.0774)	0.5294 (0.0569)	0.5328 (0.0710)
Median	0.5340	0.5355	0.5340
Min, Max	0.359, 0.765	0.303, 0.666	0.303, 0.765
Lumbar Spine (L1-L4) T-score			
n	136	70	206
Mean (SD)	-3.68 (0.65)	-3.64 (0.59)	-3.67 (0.63)
Median	-3.70	-3.70	-3.70
Min, Max	-5.3, -2.3	-5.4, -2.0	-5.4, -2.0

Numbers analysed

The subjects who never received the investigational drug were excluded from all analysis sets of FAS, PPS, and safety population. The subjects for whom no evaluable data of lumbar spine BMD after administration of the investigational drug are available were excluded from the FAS. Subjects were excluded from the PPS if they violated the inclusion criteria or the exclusion criteria, violated the dose and administration method of the investigational drug, or violated the concomitant medication or therapy. The analysis sets are shown in table below.

Table 76. Analysis Populations (Randomized Subjects)

	ITM-058 (N = 141) n (%)	Placebo (N = 72) n (%)	Total (N = 213) n (%)
Full analysis set	136 (96.5)	70 (97.2)	206 (96.7)
Per protocol set	123 (87.2)	65 (90.3)	188 (88.3)
Safety analysis set	140 (99.3)	72 (100.0)	212 (99.5)

There were 7 (3.3%) subjects excluded from the FAS due to not receiving the investigational drug or for whom no evaluable data of lumbar spine BMD after administration of the investigational drug were available. This is not according to the ICH E9 principle that all randomized subjects should be included in the analysis. A re-run of the primary analysis based on all randomized subjects may be required; however, considering the strong statistical significance and the observed treatment difference, it is likely that the result would not impact the efficacy conclusion. Safety analysis set excluded one untreated subject in the abaloparatide group.

Outcomes and estimation

Primary endpoint

The least squares mean of the percent change in lumbar spine (L1-L4) BMD at the last visit from the baseline test was 16.33% in the abaloparatide group and 3.78% in the placebo group in the entire population. The lumbar spine (L1-L4) BMD increased at the last visit from the baseline test in both groups.

The least squares mean of the percent change in lumbar spine (L1-L4) BMD at the last visit from the baseline test was 14.15% in the ITM-058 group and 1.93% in the placebo group in patients with postmenopausal osteoporosis (122 in the ITM-058 group and 64 in the placebo group). The lumbar spine (L1-L4) BMD increased at the last visit compared to the baseline test in both groups.

Table 27. Analysis of covariance or percent change in lumbar spine (L1 L4) BMD at the last visit from the baseline test

Parameter (Unit)/ Analysis Population	Treatment group	n	Least Square Mean (LSM)	Standard error	Difference in LSM	95% CI for Difference in LSM[3]	P Value of Test for Comparing[4]
Entire Population (FAS)[1, A]							
Percent change in Lumbar Spine (L1 L4) BMD at the last visit (%)	ABL	136	16.33	0.99	12.55	10.30 – 14.80	p<0.001
	Placebo	70	3.78	1.21	-	-	-
Subjects with Postmenopausal Osteoporosis (FAS)[2, B]							
Percent change in Lumbar Spine (L1 L4) BMD at the last visit (%)	ABL	122	14.15	0.64	12.22	10.07 – 14.36	p<0.001
	Placebo	64	1.93	0.88	-	-	-

FAS: full analysis set. BMD: bone mineral density, ABL: Abaloparatide, CI: confidence interval, LSM: Least Square Mean
1: The FAS included all subjects who received the investigational drug and for whom evaluable data of lumbar spine BMD were available.
2: this subset of the entire FAS consisted only of postmenopausal women, while male subjects were excluded.

3: ITM 058 Placebo
4: ITM 058 vs Placebo
A: The model of analysis of covariance includes treatment group and sex as factor and lumbar spine (L1 L4) BMD (continuous variable) at the pre-screening test as covariate.
B: The model of analysis of covariance includes treatment group as factor and lumbar spine (L1 L4) BMD (continuous variable) at the pre-screening test as covariate.

The primary endpoint; least squares mean of the percent change in lumbar spine (L1-L4) BMD was 16 % in the abaloparatide group and 4 % in the placebo group. In the BA058-05-003 study the BMD increase in lumbar spine was 9% in the abaloparatide group and 0.5 % in the placebo group. Also, for total hip and femoral neck the changes in BMD were numerically greater in study 301 than in study BA058-05-003.

The primary endpoint in the pivotal BA058-05-003 study, new vertebral fractures, was also analysed in the 301 study. In the 301 study, with its limited number of participants, no new vertebral fractures were identified in the abaloparatide group versus 3/70 (4.3%) in the vehicle group. This is in the same range as in the BA058-05-003 study.

Secondary endpoints

- **% change from baseline in lumbar spine (L1 L4) BMD at Week 12, 24, 48 and 78**

- **% change from baseline in lumbar spine (L2 L4) BMD and % change from baseline in Hip (total, neck[2]) BMD at Week 12, 24, 48, and 78 and the last visit**

The percent change in lumbar spine (L2-L4) BMD showed almost no changes before and after the start of treatment in the placebo group but increased over time in the ITM-058 group

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[2] In the CSR ITM 058 301 the term hip neck is used for the femoral neck.

Figure 2 Mean Change from Baseline in Lumbar Spine, Total Hip and Femoral Neck BMD in Male (yellow) and Female (green) subjects - ITT
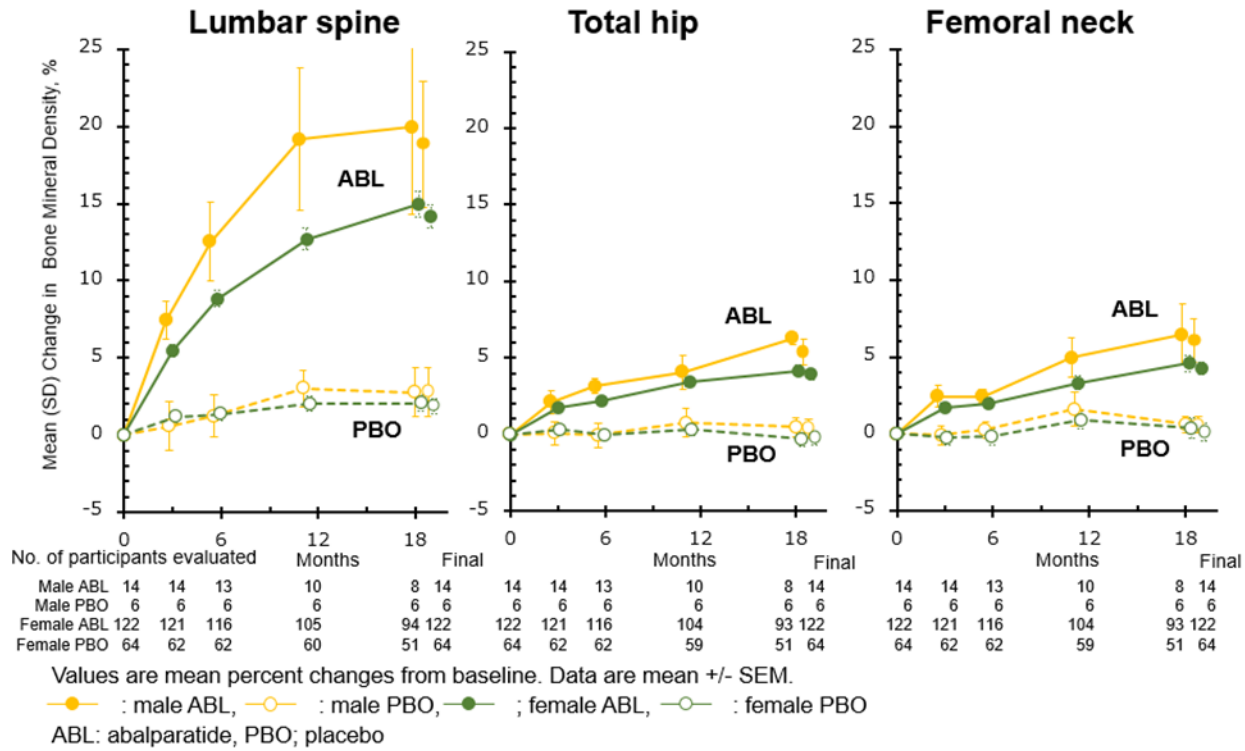
ABL = abaloparatide; BMD = bone mineral density; PBO = placebo; SEM = standard error of the mean
Abaloparatide: plain line; placebo: dotted line

No new vertebral fracture occurred in the ITM-058 group from the pre-screening test to the last visit. In the placebo group, the cumulative number of new vertebral fractures up to the last visit was 4, and the cumulative incidence was 4.3% (3/70).

The between-group difference (ITM-058 group − placebo group) in the cumulative incidence of new vertebral fractures at the last visit (95% CI) was −4.3% (−11.86 to −0.35). The relative risk reduction rate for new vertebral fractures was not calculated because no new vertebral fractures occurred in the ITM-058 group from the pre-screening test to the last visit

The cumulative number of new nonvertebral fractures up to the last visit was 3 in the ITM-058 group and 2 in the placebo group, and the cumulative incidence of new nonvertebral fractures was 2.2% (3/136 subjects) in the ITM-058 group and 2.9% (2/70 subjects) in the placebo group. The between-group difference (ITM-058 group − placebo group) in the cumulative incidence of new nonvertebral fractures at the last visit (95% CI) was−0.7% (−7.78 to 3.92). The relative risk reduction rate (95% CI) for new nonvertebral fractures at the last visit was 0.228 (−3.514 to 0.868).

In summary, the results in the study are in line with the results from the pivotal BA058-05-003 study. The number of fractures was too low to draw any conclusions on efficacy in fracture reduction.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28. Summary of efficacy for study BA058-05-003

Title: A Randomized, Double-blind, Placebo-controlled, Comparative Phase 3 Multicenter Study to Evaluate the Safety and Efficacy of BA058 for Injection for Prevention of Fracture in Ambulatory Postmenopausal Women with Severe Osteoporosis and at Risk of Fracture			
Study identifier	Protocol BA058-05-003 (ACTIVE Study)		
Design	Comparative Phase 3, randomized, double-blind, placebo-controlled, multi-center, international study to assess the efficacy and safety of abaloparatide-SC vs placebo or teriparatide in the prevention of fracture in otherwise healthy ambulatory postmenopausal women with osteoporosis.		
	Duration of main phase:	19 months	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	24 months (Extension Study BA058-05-005)	
Hypothesis	• Abaloparatide-SC for 18 months is superior to placebo in postmenopausal women with osteoporosis for reduction in new vertebral fracture, non-vertebral fracture, major osteoporotic fracture, wrist and clinical fracture. • Abaloparatide-SC for 18 months is superior to teriparatide in postmenopausal women with osteoporosis for reduction in non-vertebral fracture, major osteoporotic fracture, wrist and clinical fracture. • Abaloparatide-SC for 18 months is superior to placebo in postmenopausal women with osteoporosis for increase in BMD at lumbar spine, femoral neck and total hip. • Abaloparatide-SC for 18 months is superior to teriparatide in postmenopausal women with osteoporosis for increase in BMD at lumbar spine, femoral neck and total hip.		
Treatment groups	Abaloparatide-SC		Double-blind abaloparatide-SC: 18 Months, 696 randomized
	Placebo		Double-blind placebo: 18 months, 688 randomized
	Teriparatide		Open-label teriparatide: 18 months, 686 randomized
Endpoints and definitions	Key endpoint	Incidence of new vertebral fracture at 18 months	Percentage of patients with one or more incidents of new vertebral fracture according to Genant's method (Genant et al, 1993) from the baseline lumbar and thoracic spine radiographs until post-baseline lumbar and thoracic spine radiographs (over the study treatment period up to 18 months.
	Key endpoint	Time to the first incident non-vertebral fracture (NVF) over 19 months	Time to the first incident non-vertebral fracture (NVF) over 19 months.
Database lock	10 December 2014		

Results and Analysis

Analysis description	Key Analysis: Incidence of new vertebral fracture at 18 months		
Analysis population and time point description	Modified Intent-to-Treat (mITT) Population included all randomized patients who had both the pre-treatment and the post-baseline evaluable radiologic assessment (lumbar and thoracic spine X-rays). Analysis at 18 months.		

Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=600	N=583	N=600
	Number (%) of patients with new vertebral fracture	25 (4.17)	3 (0.51)	4 (0.67)
	95% CI	(2.84, 6.08)	(0.18, 1.50)	(0.26, 1.70)

Effect estimate per comparison	Percent of patients with new vertebral fracture	Comparison groups	Abaloparatide-SC vs. Placebo
		Risk Reduction	-3.65
		95% CI	(-5.59, -2.00)
		Relative Risk Reduction	-0.88
		95% CI	(-0.96, -0.59)
		P-value (Fisher's exact test)	<0.0001

Effect estimate per comparison	Percent of patients with new vertebral fracture	Comparison groups	Teriparatide vs. Placebo
		Risk Reduction	-3.50
		95% CI	(-5.45, -1.82)
		Relative Risk Reduction	-0.84
		95% CI	(-0.94, -0.54)
		P-value (Fisher's exact test)	<0.0001

Analysis description	Key analysis: Time to the first incident non-vertebral fracture (NVF) over 19 months		
Analysis population and time point description	Intent-to-Treat (ITT) Population included all patients who were randomized into the study. Analysis at 19 months.		

Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=688	N=696	N=686
	K-M estimated event rate (%)	3.6	2.7	2.0
	Number of subjects with event	21	15	12

Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs. Placebo
		Hazard Ratio	0.74
		95% CI	(0.38, 1.43)
		P-value (Log-rank test)	0.3675
		Comparison groups	Teriparatide vs. Placebo

Effect estimate per comparison		Hazard Ratio	0.56
		95% CI	(0.28, 1.15)
		P-value (Log-rank test)	0.1095
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs. Teriparatide
		Hazard Ratio	1.30
		95% CI	(0.61, 2.79)
		P-value (Log-rank test)	0.4919

2.5.5.3. Clinical studies in special populations

With the exception of phase 2 study BA058-05-011 in male and female volunteers with renal impairment no data from clinical studies in special populations have been submitted. For the pivotal trial BA058-05-003 subgroups analyses including the effect of age on abaloparatide efficacy have been provided; age groups investigated were <65 years, 65 to <75 years, and ≥75 years.

Table 8 Number (percent) of patients per age group study BA058-05-003

	Age <65 years (Older subjects number / total number; %)	Age 65 to <75 years (Older subjects number / total number; %)	Age ≥75 years (Older subjects number / total number; %)
Controlled Trials BA058-05-003			
Abaloparatide	102 / 696 (14.7%)	455 / 696 (65.4%)	139 / 696 (20.0%)
Teriparatide	99 / 686 (14.4%)	443 / 686 (64.6%)	144 / 686 (21.0%)
Placebo	102 / 688 (14.8%)	453 / 688 (65.8%)	133 / 688 (19.3%)

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The applicant has only provided data from one pivotal trial and its extension. Thus, no relevant pooled analyses or meta-analysis have been submitted

2.5.5.6. Supportive study(ies)

Study BA058-05-028

A Retrospective, Observational Cohort Study Evaluating the Effectiveness and Cardiovascular Safety of Abaloparatide in Postmenopausal Women New to Anabolic Therapies

This was a retrospective observational cohort study using administrative claims data for the period from 01 May 2012 to 31 January 2021. This study used anonymized patient claims data from PRA's Symphony Health Patient Source Integrated Dataverse (IDV) database with the inclusion of enhanced hospital data, which are claims and remittance from the inpatient hospital setting and proprietary Patient Transactional Dataset (PTD)

claims and prescription data, to apply the inclusion/exclusion criteria for patient selection to form the data set for this study.

The database cross-sectionally covers over 80% of the population in the USA (approximately 300 million lives) annually. It includes claims submitted to all payer types, including commercial plans, Medicare, and Medicaid. Medical claims are open unadjudicated claims.

Mortality data recorded on the hospital (medical facility) discharge status covers about one-third of the total death records. According to National Center for Health Statistics data published on Centers for Disease Control and Prevention (CDC) Wide- ranging Online Data for Epidemiologic Research (WONDER) [Centers for Disease Control and Prevention], in 2019 35% of total deaths and 37% of cardiovascular (CV) deaths occurred at a medical facility which includes hospital inpatient, outpatient, or emergency room, death on arrival, or unknown status. For women 50 to 65 years of age, more than 50% of CV deaths occurred in medical facilities. The data are de-identified, in compliance with HIPAA guidelines, with stable unique identifiers to allow for longitudinal tracking over time. The terms of the Research Exception provisions of the Privacy Rule, 45 CFR Part 164.514(e), exempts IRB approval for this nonexperimental study, which is fully HIPAA compliant.

Figure 3 Study design schematic
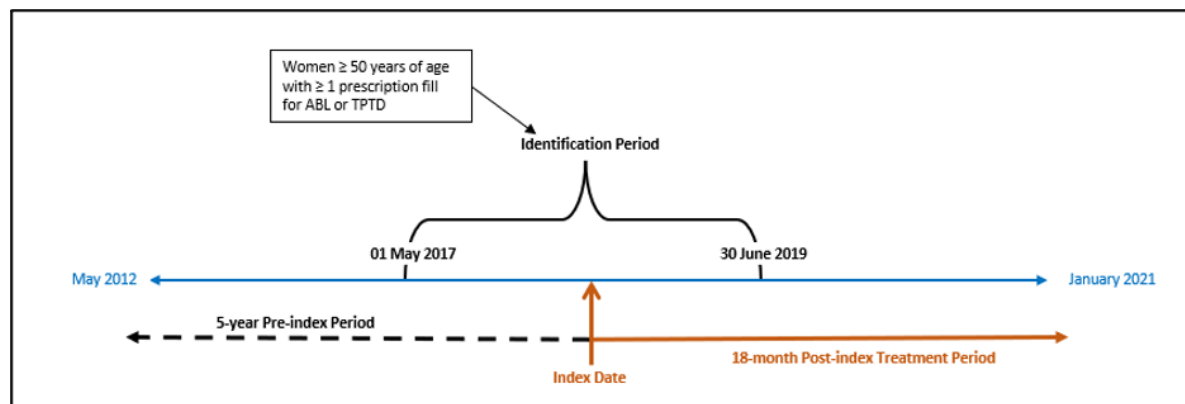
ABL = abaloparatide; TPTD = teriparatide
The index date is the date on which the patient filled their first claim for a prescription for either abaloparatide or teriparatide during the identification period.
The pre-index period consists of the 5 years before the index date during which medical history was available for the patient.
The post-index treatment period consists of the 18 months after the index treatment initiation of an anabolic drug (abaloparatide or teriparatide) since the index date.
The maximum evaluation period is 18 months plus 30 days follow-up (19 months).

Treatments

Treatments were not assigned. Instead, cohorts were defined as follows:

· Abaloparatide Cohort: Female patients who filled ≥1 prescription for abaloparatide as their index medication during the identification period

· Teriparatide Cohort: Female patients who filled ≥1 prescription for teriparatide as their index medication during the identification period

Number of Patients (Planned): It was estimated that approximately 16,000 patients were to be included in the analyses; 8,000 patients in each cohort.

Diagnosis and Main Criteria for Inclusion and Exclusion:

The study eligibility criteria are in alignment with the prescribing information in the FDA-approved product labels for both abaloparatide and teriparatide and include women with postmenopausal osteoporosis. Men were not included in this study since abaloparatide is not approved for use in men. Patients with secondary osteoporosis, or Paget's disease, as well as those who would not be candidates for the anabolic therapy due to high morbidity burden or high risk of mortality (eg, malignancies), were excluded. Patients with prior alendronate therapy were included because almost half of the population of patients new to anabolic therapies have previously used bisphosphonates (BP).

Study objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the effectiveness 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.	Time to the first incidence of nonvertebral fracture (hip, pelvis, shoulder, radius or ulna, wrist, femur, tibia or fibula, ankle) within the 18 months plus 30 days follow-up after treatment initiation.
Secondary	
To evaluate the CV 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.	• Time to the first incidence of the composite endpoint of nonfatal myocardial infarction (MI), nonfatal stroke, or hospital CV death within the 18 months after treatment initiation while on therapy plus 30 days follow-up. • Time to the first incidence of the composite endpoint of nonfatal MI, nonfatal stroke, heart failure, or hospital CV death within the 18 months after treatment initiation while on therapy plus 30 days follow-up.
Exploratory	
To further evaluate the effectiveness and CV 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.	Effectiveness • Time to the first incidence of hip fracture within 18 months plus 30 days follow-up after treatment initiation. Safety The following exploratory safety endpoints were assessed within the 18 months after treatment initiation while on therapy plus 30 days follow-up. • Time to the first incidence of MI • Time to the first incidence of stroke • Time to the first incidence of hospital CV death • Time to the first incidence of heart failure

Estimated Sample Size

Between May 2017 and June 2019, a total of 16,482 unique female patients ≥ 50 years of age treated with ABL and 45,350 unique patients ≥ 50 years of age treated with TPTD have been identified in the Symphony database. After applying inclusion/exclusion criteria, the final number of patients was determined through propensity score (PS) matching. Based on previous studies, it was estimated that approximately 8,000 matched patients would be included in each cohort.

The power calculation was based on comparison of abaloparatide versus teriparatide with a noninferiority margin of 30%, assuming a nonvertebral fracture rate of 3.5% for teriparatide at the end of 18 months, 8000 matched subjects in each group, and 95% power for HR up to 1.3.

Although this was not a randomized study, propensity score (PS)-matching was used to define study cohorts and provide confidence that the 2 cohorts were comparable in their probability to receive and benefit from treatment.

Statistical Methods

The analysis population is all patients meeting the study inclusion/exclusion criteria and selected after PS-matching. The same matched population was used for both effectiveness and safety analyses.

The effectiveness evaluation was conducted using an intent-to-treat (ITT) analysis, meaning that the first fracture event during the 18 months plus 30 days follow-up after the index date was summarized regardless of when treatment ended.

CV safety outcomes were evaluated using an as-treated (AT) analysis based only on events occurring while on therapy (until end of treatment) for up to 18 months plus 30 days follow-up, regardless of the anabolic drug possession gap between any 2 prescription fills.

Note that the protocol did not describe the observation period consistently, why periods for ITT and AT analysis (as described above) were corrected in the CSR.

Propensity score matching
In the absence of randomization, logistic regression-based PS-matching was used to create the analytic cohorts from all patients meeting the study inclusion/exclusion criteria. A greedy matching algorithm with no replacement was adopted. Cohorts were prospectively specified to match on age, prior fracture history, chronic comorbidities, and concomitant medications during the pre-index period that are associated with an increased fall risk.

Prematch and postmatch cohorts were evaluated using prespecified criteria for standardized mean difference to ensure that PS-matching was successful. After matching, the standardized mean difference on each covariate between abaloparatide and teriparatide was expected to be <0.10.

Effectiveness analyses
The primary analyses of effectiveness was noninferiority analyses for ABL versus TPTD on time to the first incidence of nonvertebral fractures with a margin of 30%. Noninferiority of ABL to TPTD was to be concluded if the upper bound of 2-sided 95% CI of HR between ABL versus TPTD was < 1.3.

In a recently published historical control observational study evaluating the real-world effectiveness of osteoporosis therapies using Medicare claim data between 2008 and 2011, the fracture incidence rates for the 12-month pretreatment period were compared with the 12-month on-treatment period [Yusuf A.A. et al., 2018]. For patients treated with teriparatide, the incidence rate ratio (IRR [95% CI]) was 0.36 (0.31 to 0.41) for hip fracture and 0.34 (0.32 to 0.36) for any fracture. Based on the FDA noninferiority margin guidelines [FDA] if the upper boundary of abaloparatide versus teriparatide is HR <1.3, then abaloparatide will preserve approximately 70% of the teriparatide benefit, which is higher than the minimum required threshold of 50%.

Comparisons of the time to the first incidence of fracture between the PS-matched ABL and TPTD groups were based on a Cox proportional hazards model. The Kaplan-Meier method was used to estimate event rates. Log rank test was performed to obtain p-values.

For the fracture outcomes, and the corresponding sensitivity and subgroup analyses, patients were followed for up to 18 months or until their first fracture event (for the fracture site of interest under evaluation), whichever comes first. All analyses were based on index medication cohort.

For the fracture outcomes, an ITT analysis was applied. Patients were followed for up to 18 months + 30-day follow-up, or until their first fracture event (for the fracture site of interest under evaluation) or in-hospital death, whichever came first. Duration, in days, from the index date to the last follow-up date was calculated. For calculation purposes, 1 month is equivalent to 30 days. All analyses were based on the patient's index medication cohort.

The time to the first incidence of hip fracture and the other 7 individual fracture sites was analyzed using similar methods. The K-M curves were generated to graphically display the fracture event or 18 months plus 30 days follow-up.

Safety analyses

A Cox proportional hazards model was used for the time to first cardiovascular event. HR and 95% CIs were presented.

The As-Treated (AT) analysis was conducted for the safety evaluation. The first incidence of a cardiovascular event after the index date and before the 30 days after the end of treatment was analyzed. A cardiovascular event was defined as the first incidence of the composite endpoint of nonfatal MI, nonfatal stroke, or in-hospital cardiovascular death; the first incidence of the composite incidence of nonfatal MI, nonfatal stroke, heart failure or in-hospital cardiovascular death; or the first incidence of MI, stroke, heart failure, or in-hospital cardiovascular death separately.

Sensitivity analyses

To evaluate the stability of the PS matched cohorts, 2 different calipers (0.15, 0.3) were carried out to the PS matching. The sensitivity analyses on effectiveness and safety endpoints were performed on these matching populations, and also on sub-population with each of additional exclusion criteria:
- Exclude patients without a minimum of 12 months of anabolic drug exposure:
  (1) 12-consecutive months of anabolic drug exposure as assessed by medication dispensed; and
  (2) 12-month cumulative anabolic drug exposure during the 18-month follow-up
- Exclude patients with prescriptions dispensed for ≤ 1 month, 3 months, 6 months, and 9 months
- Exclude patients with previous use of denosumab or zoledronic acid.

Major change in the Planned Analyses

The protocol-specified identification period was inadvertently extended by 1 month (from 30 June 2019 to 31 July 2019) while keeping the same protocol-specified evaluation period of 01 May 2012 to 31 January 2021. This was not detected by the Sponsor until after the effectiveness and CV safety results were made available. Considering the impact to the overall population was minimal (i.e., +5% patients), and in order to prevent any data driven decision making, it was decided to keep the July 2019 index date for patients in the main analysis and add a sensitivity analysis using the planned index period (1 May 2017 to 30 June 2019) for this report.

Protocol stated that "Osteoporosis-related hospitalization" would be used as a factor in propensity score matching. This factor was not listed in the protocol as a risk factor and was therefore not used in the matching.

Statistical analysis plan was specified in the protocol. No separate document was provided.

Results

An accounting of each cohort of the number of patients who were included in this study is summarized in Table below. 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. Since teriparatide has been on the market (2002) longer than abaloparatide (2017), a larger number of patients were identified in the teriparatide cohort.

Figure 4 Disposition of patients

Parameter	Abaloparatide-SC n (%)	Teriparatide n (%)
Women age ≥50 years with ≥1 prescription claim between May 1, 2017 to June 30, 2019	17071	61015
Of above, patients without Paget's disease	17067 (99.9)	61011 (99.9)
Of above, patients without malignancies [1]	16361 (95.9)	59668 (97.8)
Of above, patients with ≥12 months pre-index [2]	12519 (76.5)	45100 (75.6)
Of above, patients had no anabolic treatment before index date [3]	11449 (91.5)	22958 (50.9)
Of above, patients did not treat with anabolics other than cohort medication during 18 months plus 30 days follow-up after index date	11029 (96.3)	22237 (96.9)
Of above, patients with Charles Comorbidity Index ≤10	11028 (99.9)	22227 (99.9)
Patients who met all inclusion/exclusion criteria	11028	22227
Of above, patients with propensity score-matching [4]	11027 (99.9)	11027 (49.6)

[1] Except for nonmelanoma skin cancers, carcinoma in situ of the cervix, ductal carcinoma in situ of breast
[2] ≥1 claim for medical or hospital visit and a pharmacy claim any time within 12 months prior index date
[3] Anabolic includes abaloparatide (Tymlos®), teriparatide (Forteo®), romosozumab (Evenity®)
[4] To protect patient privacy, IDV data only listed month and year of the death date. Database default death date is the 1st day of the month. One teriparatide patient had death date before index date and both this patient and the matched abaloparatide patient were excluded from analysis.

Figure 5 Distribution of the propensity score before and after PS matching
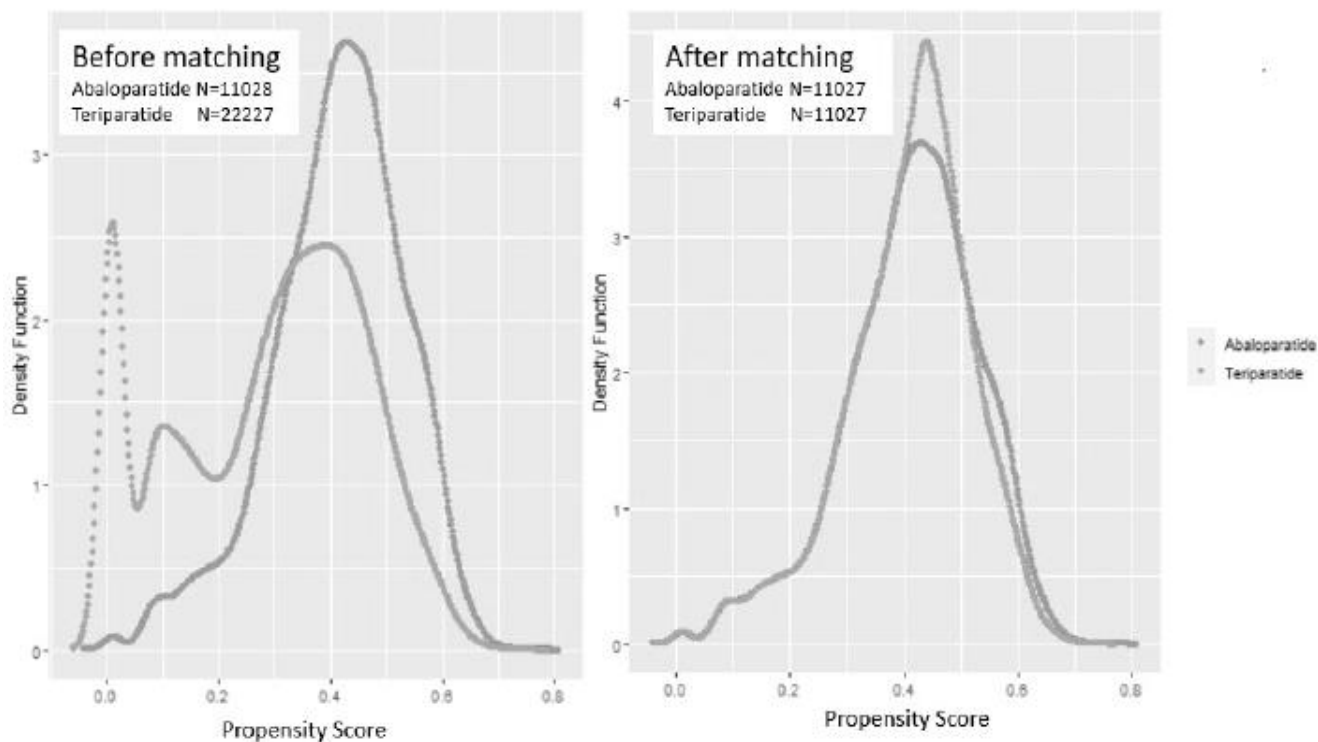
The distribution of the propensity score before PS matching showed limited/unbalanced overlap in the lower end of the PS-distributions. The applicant was asked to repeat the main effectiveness analysis by trimming the observations with propensity score <0.1. The results of the fracture and cardiovascular event in all eligible patients with propensity score ≥ 0.1 were in line with the original analyses.

Table 30. Demographics and Baseline Characteristics (All Population PS-Matched)

Parameters	Abaloparatide-SC (N=11027)	Teriparatide (N=11027)	Standardized Difference
Age (years) [1] [2]			
N	11027	11027	0.013
Mean (SD)	67.3 (8.35)	67.4 (8.39)	
Median	67.0	67.0	
Q1, Q3	61.0, 74.0	61.0, 75.0	
Min, Max	50, 80	50, 80	
Age Group (years) n (%)			
50 - 64	4543 (41.2)	4438 (40.2)	0.019
65 - 74	3769 (34.2)	3781 (34.3)	0.002
≥75	2715 (24.6)	2808 (25.5)	0.019
Race/ethnicity n (%) [2]			
African American	144 (1.3)	150 (1.4)	0.005
Asian	100 (0.9)	104 (0.9)	0.004
White	4137 (37.5)	4262 (38.7)	0.023
Hispanic	646 (5.9)	531 (4.8)	0.046
Other	127 (1.2)	107 (1.0)	0.018
Unknown	5873 (53.3)	5873 (53.3)	0.000
Census Region n (%)			
Northeast	1963 (17.8)	1912 (17.3)	0.012
South	4883 (44.3)	4905 (44.5)	0.004
Midwest	1916 (17.4)	1944 (17.6)	0.007
West	2246 (20.4)	2243 (20.3)	0.001
Unknown	19 (0.2)	23 (0.2)	0.008
Index Date Year Quarter n (%)			
2017-Q2	34 (0.3)	34 (0.3)	0.000
2017-Q3	331 (3.0)	346 (3.1)	0.008
2017-Q4	730 (6.6)	716 (6.5)	0.005
2018-Q1	(13.6)	1518 (13.8)	0.004
2018-Q2	1530 (13.9)	1572 (14.3)	0.011
2018-Q3	1539 (14.0)	1657 (15.0)	0.030
2018-Q4	1577 (14.3)	1615 (14.6)	0.010
2019-Q1	1888 (17.1)	1834 (16.6)	0.013
2019-Q2	1897 (17.2)	1735 (15.7)	0.040
Insurance n (%)			
Medicare	4864 (44.1)	5052 (45.8)	0.034
Medicaid	325 (2.9)	333 (3.0)	0.004
Third party	5802 (52.6)	5604 (50.8)	0.036
Cash	36 (0.3)	38 (0.3)	0.003
Prescribe Physician Specialty n (%)			
Endocrinology	2599 (23.6)	2593 (23.5)	0.001
Rheumatology	2738 (24.8)	2696 (24.4)	0.009
Parameters	**Abaloparatide-SC (N=11027)**	**Teriparatide (N=11027)**	**Standardized Difference**
Family medicine	1609 (14.6)	1633 (14.8)	0.006
Internal medicine	1314 (11.9)	1386 (12.6)	0.020
Surgery	1036 (9.4)	1041 (9.4)	0.002
Nurse Practitioner	144 (1.3)	144 (1.3)	0.000
Obstetrics & Gynecology	236 (2.1)	217 (2.0)	0.012
Others	1236 (11.2)	1204 (10.9)	0.009
Missing	115 (1.0)	113 (1.0)	0.002

Table 31. History of Patient Baseline Fracture and Type of Fracture (All Population PS-Matched)

Parameters	Abaloparatide-SC (N=11027)	Teriparatide (N=11027)	Standardized Difference
Fracture at any time pre-index, n (%)	2812 (25.5)	2785 (25.3)	0.006
Ankle	162 (1.5)	151 (1.4)	0.008
Hip	692 (6.3)	678 (6.1)	0.005
Other Femur	310 (2.8)	314 (2.8)	0.002
Pelvis	154 (1.4)	157 (1.4)	0.002
Radius or ulna	458 (4.2)	433 (3.9)	0.012
Shoulder	275 (2.5)	289 (2.6)	0.008
Spine	1296 (11.8)	1280 (11.6)	0.005
Tibia or fibula	213 (1.9)	216 (2.0)	0.002
Wrist	48 (0.4)	47 (0.4)	0.001
Fracture in the year prior to index date, n (%)	1784 (16.2)	1789 (16.2)	0.001
Ankle	69 (0.6)	65 (0.6)	0.005
Hip	392 (3.6)	393 (3.6)	0.000
Other Femur	209 (1.9)	218 (2.0)	0.006
Pelvis	80 (0.7)	88 (0.8)	0.008
Radius or ulna	194 (1.8)	185 (1.7)	0.006
Shoulder	126 (1.1)	127 (1.2)	0.001
Spine	907 (8.2)	907 (8.2)	0.000
Tibia or fibula	110 (1.0)	112 (1.0)	0.002
Wrist	18 (0.2)	14 (0.1)	0.010

Table 32. History of Cardiovascular Risk Factors and Events (All Population PS-Matched)

Parameters	Abaloparatide-SC (N=11027)	Teriparatide (N=11027)	Standardized Difference
Cardiovascular n (%)			
Any Cardiovascular Risk Factor [1] [2]	8453 (76.7)	8465 (76.8)	0.003
Cardiovascular Disease [3]	8260 (74.9)	8264 (74.9)	0.001
Hypertension	5574 (50.5)	626 (51.0)	0.009
Hyperlipidemia	4291 (38.9)	4175 (37.9)	0.022
Hypercholesterolemia	3458 (31.4)	3308 (30.0)	0.030
Hypertriglyceridemia	201 (1.8)	183 (1.7)	0.012
Cardiovascular Event Prior Index Date n (%)			
Prior MI	277 (2.5)	270 (2.4)	0.004
Prior Stroke	513 (4.7)	519 (4.7)	0.003
Prior Heart Failure	535 (4.9)	534 (4.8)	0.000
Prior MI or Stroke [1]	743 (6.7)	748 (6.8)	0.002
Prior MI or Stroke or Heart Failure [1]	1121 (10.2)	1156 (10.5)	0.010

Source: Section 14.1, Table 14.1.3

MI = myocardial infarction; PS = propensity score

[1] Variables are not included in the propensity score matching covariates.
[2] Including CV disease, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, hypertension.
[3] Includes cardiac, coronary, pulmonary, cerebrovascular, peripheral arterial, vasculitis, venous, and hypertension.

Demographic characteristics, osteoporosis disease and treatment history number of prior fractures, number of comorbidities, fall risk conditions, CV event history remained well balanced after the population in the 2 treatment cohorts were PS-matched. However, all these baseline characteristics were also well-balanced for the before PS-matching population.

The mean age was approximately 67.5 years. In the pivotal clinical study, the mean age was 2 years higher, 69.5 years.

Primary endpoint- Analysis of Effectiveness

Table 9 Time to First Incidence of Nonvertebral Fracture During 18 Months after Treatment Initiation by Fracture Sites (Overall PS-Matched)

Time-to-Event Variable	Parameter	Statistic	Abaloparatide-SC (N=11027)	Teriparatide (N=11027)
Nonvertebral Fracture	K-M Estimated Event Rate at 18 Months [1]	%	2.84	3.02
	Number of Patients with Event	n (%)	313 (2.8)	333 (3.0)
	Number of Patients Censored [2]	n (%)	10714 (97.2)	10694 (97.0)
	HR vs Teriparatide [3]	HR (95% CI)	0.94 (0.81, 1.10)	
	P-value vs Teriparatide [4]		0.4295	

Source: Section 14.2, Table 14.2.1
CI = confidence interval; HR = hazard ratio; K-M = Kaplan-Meier; PS = propensity score
  [1] The observation period was 18 months (540 days) plus 30 days follow-up after the index date.
  [2] Patients were censored at 570 days after index date or death, if no fracture event before that.
  [3] Cox proportional hazard model was used to calculate the hazard ratio with teriparatide as reference.
  [4] P-values were from the log rank test.
Note: A nonvertebral fracture was any fragility fracture at the hip, pelvis, femur, ankle, shoulder, radius/ulna, wrist, or tibia/fibula.

In the primary effectiveness analysis presented by the applicant, the number of patients with new non-vertebral fractures was comparable between abaloparatide 313 (2.8%) and teriparatide 333 (3.0%) treated patients.

Approximately 3% of the patients had a nonvertebral placebo group in clinical study BA058-05-003. The incidence was somewhat lower in the abaloparatide treated patients (2.2%) and teriparatide treated patients (1.7%) in the clinical study.

Table 34. Time to First Incidence of Hip Fracture During 18 Months after Treatment Initiation by Fracture Sites (Overall PS-Matched)

Time-to-Event Variable	Parameter	Statistic	Abaloparatide-SC (N=11027)	Teriparatide (N=11027)
Hip	K-M Estimated Event Rate at 18 Months [1]	%	1.02	1.14
	Number of Patients with Event	n (%)	112 (1.0)	125 (1.1)
	Number of Patients Censored [2]	n (%)	10915 (99.0)	10902 (98.9)
	HR vs Teriparatide [3]	HR (95% CI)	0.90 (0.69, 1.16)	
	P-value vs Teriparatide [4]		0.3951	

Source: Section 14.2, Table 14.2.1
CI = confidence interval; HR = hazard ratio; K-M = Kaplan-Meier; PS = propensity score
  [1] The observation period was 18 months (540 days) plus 30 days follow-up after the index date.
  [2] Patients are censored at 570 days after index date or death, if no fracture event before that.
  [3] Cox proportional hazard model was used to calculate the hazard ratio with teriparatide as reference.
  [4] P-values were from the log rank test.

Subgroup Analyses for Effectiveness

The following subgroup analyses were performed:

- Age group: <75 years versus ≥75 years
- Race/ethnicity: White, Hispanic, African American, Asian, Other, Unknown (includes 'Missing' race/ethnicity category)
- Prior use of BPs within 5 years before the index date: with versus without
- Prior fracture within 1 year before the index date: with versus without

Each subgroup was PS-matched separately to ensure the comparability between the patients in the abaloparatide and teriparatide groups.

Figure 15. Forest Plot of Hazard Ratios of Nonvertebral Fractures for Abaloparatide vs Teriparatide by Subgroup

	Abaloparatide n(%)	Teriparatide n(%)		Hazard ratio (95% CI)
Overall PSM (N=11027)	313 (2.84)	333 (3.02)		0.94 (0.81, 1.10)
Age group				
50 - 74 (N=8313)	220 (2.65)	220 (2.65)		1.00 (0.83, 1.21)
75+ (N=2708)	93 (3.44)	123 (4.55)		0.75 (0.58, 0.99)
Prior 1 year fracture				
Yes (N=1783)	114 (6.40)	107 (6.02)		1.07 (0.82, 1.39)
No (N=9242)	199 (2.16)	226 (2.45)		0.88 (0.73, 1.07)
Prior antiresorptive use				
Yes (N=5050)	158 (3.13)	169 (3.35)		0.93 (0.75, 1.16)
No (N=5976)	155 (2.60)	189 (3.17)		0.82 (0.66, 1.01)
Race/ethnicity				
African American (N=115)*	3 (2.61)	1 (0.87)		3.03 (0.32, 29.10)
Asian (N=66)*	1 (1.56)	1 (1.52)		1.02 (0.06, 16.24)
White (N=4137)	132 (3.19)	155 (3.75)		0.85 (0.67, 1.07)
Hispanic (N=602)	21 (3.49)	17 (2.83)		1.24 (0.66, 2.36)
Other (N=79)*	1 (1.27)	1 (1.27)		1.01 (0.06, 16.09)
Unknown (N=5873)	155 (2.64)	152 (2.59)		1.02 (0.82, 1.28)

HR 95% CI (scale: 0.01, 0.1, 1, 10)

Source: Section 14.2, Table 14.2.1, 14.2.1.1, 14.2.1.2, 14.2.1.3, 14.2.1.4, 14.2.1.5, 14.2.1.6, 14.2.1.7, 14.2.1.8, 14.2.1.9, 14.2.1.10, 14.2.1.11, 14.2.1.12
CI = confidence interval; HR = hazard ratio; PSM = propensity score matching
[1] N is number of matched pairs in each subgroup; n is number of events and % is K-M estimate at the end of 19 months since index date.
*Subgroup did not meet matching expectation (ie, standardized difference for some covariates >0.10).

In general, outcomes seem consistent among all subgroups when compared to the overall data for both nonvertebral and hip fractures.

Sensitivity Analyses

To evaluate the stability of the PS-matched cohorts, 2 additional caliper widths (0.15, 0.3) were used to perform the PS-matching. Since the overall abaloparatide and teriparatide patients are well matched, the PS-matched pairs were almost identical at different caliper widths.

Figure 16. Forest Plot of Hazard Ratios of Nonvertebral Fractures for Abaloparatide vs Teriparatide

	Abaloparatide n(%)	Teriparatide n(%)		Hazard ratio (95% CI)
Overall PSM Population				
Caliper = 0.20 (N=11027)	313 (2.84)	333 (3.02)		0.94 (0.81, 1.10)
Caliper = 0.15 (N=11026)	313 (2.84)	333 (3.02)		0.94 (0.81, 1.10)
Caliper = 0.30 (N=11027)	313 (2.84)	333 (3.02)		0.94 (0.81, 1.10)
Treatment Duration				
Consecutive > 12M (N=3792)	79 (2.08)	92 (2.43)		0.86 (0.64, 1.16)
Cumulative > 12M (N=3692)	80 (2.17)	96 (2.60)		0.83 (0.62, 1.12)
Cumulative > 9M (N=4828)	116 (2.40)	139 (2.88)		0.83 (0.65, 1.07)
Cumulative > 6M (N=5871)	150 (2.56)	161 (2.74)		0.93 (0.75, 1.17)
Cumulative > 3M (N=7183)	196 (2.73)	216 (3.01)		0.91 (0.75, 1.10)
Cumulative > 1M (N=9029)	249 (2.76)	261 (2.89)		0.95 (0.80, 1.13)
Without Prior Denosumab or Zolendronic Acid				
(N=9499)	250 (2.63)	281 (2.96)		0.89 (0.75, 1.06)
Index Date Started at Jan 1, 2018				
(N=9931)	273 (2.75)	309 (3.12)		0.88 (0.75, 1.04)

0.1   1   2
HR 95% CI

Source: Section 14.2, Table 14.2.1, 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4, 14.2.2.5, 14.2.2.6, 14.2.2.7, 14.2.3.1, 14.2.3.2, 14.2.3.3

CI = confidence interval; HR = hazard ratio; PSM = propensity score matching

[1] N is number of matched pairs in each subgroup; n is number of events and % is K-M estimate at the end of 19 months since index date.

Since the overall abaloparatide and teriparatide patients are well matched, the PS-matched pairs were almost identical at sensitivity analyses using different caliper widths.

Only a minority of the patients had a treatment duration of >12 months.

Strengths and limitations of the Study Design according to the applicant:

The methodology for the current study design has several strengths:

• The data are representative of a broad population of patients with a higher CV risk compared to the randomized controlled ACTIVE study in that there are no contraindications for cardiovascular disorders in the FDA approved product labels for abaloparatide and teriparatide.

• The effectiveness of abaloparatide was evaluated in a broad population of patients.

• Data were from multiple payers and geographically diverse settings across the USA, and the PRA IDV data captures over 90% of pharmacy claims in the USA [Symphony Health, 2020]. The prescription claims were for prescriptions filled, not just prescriptions written. As such, the findings from the study were expected to have a high generalizability.

• A claims-based algorithm, which has a high specificity and has been shown to have over 90% accuracy based on positive predictive value in previous studies, was used [Wright N.C. et al., 2019].

Limitations of the Study Design according to the applicant:

There are several limitations associated with the design of the current study:

• The data source is administrative claims data, which are not collected for research purposes. Administrative claims data have inherent limitations including coding errors, inconsistencies, underestimation, overestimation, or incomplete diagnoses data. The current study, however, used a claims-based algorithm to identify case qualifying (CQ) fragility fractures associated with osteoporosis. Furthermore, any misclassification of fractures is nondifferential between the treatment groups being compared and should not affect the results.

• Claims-based studies include potential inaccuracies related to the use of prescription medications. The prescription claim is for the date of first fill and not the date of first use of the medication, so the assumption is that these are the same date.

Detailed clinical data such as BMD T-scores or the presence of other risk factors (e.g., family history, smoking status, alcohol intake) associated with disease severity and increased future fracture risk were not available and, therefore, no adjustments have been made for these factors.

• Only deaths recorded on the hospital discharge status were available for the derivation of cardiovascular death in this study. The current study, however, used a claims-based algorithm to identify deaths that are likely to be caused by cardiovascular events. Furthermore, any misclassification of deaths is nondifferential between the treatment groups being compared and should not bias the results. The comparative evaluation of treatment options is ideally done within the controlled clinical study setting. The current study is observational, and treatments are not assigned.

As such, randomization is not possible. Although this was not a randomized study, PS matching was used to define the study cohorts and provide confidence that the 2 treatment groups are comparable in their probability to receive and benefit from treatment. Patients were matched on all indicators of disease severity and fracture risk including prior disease and treatment history. Furthermore, patients were also matched on history of falls as well as comorbid conditions and concomitant medications associated with increased fall risk or with bone quality and strength. While several comorbidities were initially considered, some measures were ultimately not included in the end due to lack of available data. This included duodenitis. Lastly, there could be residual confounding despite matching. The study was planned as an intention-to-treat (ITT) analysis for effectiveness evaluation and as-treated (AT) analysis for safety evaluation with additional consideration for duration of treatment exposure using sensitivity analyses on various length of observed treatment duration for the study cohorts. Interpretation was limited by the variable length of follow-up.

Overall discussion Study BA058-05-028 and discussion related to effectiveness

Data sources

Study BA058-05-028 was a retrospective observational cohort study using administrative claims data for the period from 01 May 2012 to 31 January 2021. This study used anonymized patient claims data from PRA's Symphony Health Patient Source Integrated Dataverse (IDV) database with the inclusion of enhanced hospital data, which are claims and remittance from the inpatient hospital setting and proprietary Patient

Transactional Dataset (PTD) claims and prescription data, to apply the inclusion/exclusion criteria for patient selection to form the data set for this study.

Data up to 31 January 2021 was used. Analysis using the database were presented during regulatory interactions with National Agencies during February-March 2021. It is noted that data final extraction from the PRA (Symphony Health's) Integrated Dataverse database was performed on 30 Jun 2021. No separate SAP is available but the study plan is described in detail in the only version of study protocol dated 09 July 2021. The applicant reassured that no study data were shared with the applicant prior to the finalization of the study protocol. The protocol was submitted to ClinicalTrials.gov on 18 June 2021, i.e., prior to the database extraction, but the sign-off (9 July 2021) was delayed due to valid administrative reasons that were out of the applicant's control. Integrity of data was therefore not at risk. However, it appears that the extract from the Symphony database used in the pilot study (Williams et al, 2019) did overlap with the data extract in study BA058-05-028 to a certain extent as "less than half patients reached 18 months after index date at the data cut" (as described in Table 1 in the response). Thus, it cannot be excluded that data from the pilot study had informed the choice of the non-inferiority margin in the BA058-05-028 study.

Furthermore, there was a major change in the planned analyses as the protocol-specified identification period was inadvertently extended by 1 month (from 30 June 2019 to 31 July 2019). The protocol-specified identification period as defined in the protocol has been analysed and presented as a sensitivity analysis only. This is not acceptable. The applicant's decision of having July 2019 as index date for patients in the main analysis may have been data driven.

The applicant has provided an updated Clinical study report using the original 30 June 2019 index date.

Analysis

The primary analysis of effectiveness was noninferiority analysis for ABL versus TPTD on time to the first incidence of nonvertebral fractures with a margin of 30%. Noninferiority of ABL to TPTD was concluded as the upper bound of 2-sided 95% CI of HR between ABL versus TPTD was < 1.3. The regulatory non-inferiority guidelines may not be fully applicable in an observational setting. The statistical derivation of the non-inferiority margin is based on just two studies (Fracture Prevention Trial (FPT) (Neer et al, 2001) and ACTIVE, both randomized clinical trials) and results in a margin of 1.102 compared to the pre-defined margin of 1.3 for the upper bound of the 95% CI for the HR. This should retain 50% of the effect of the reference product and the choice of how much effect should be retained is not further justified. As the meta-analysis of these two studies resulted in a hazard ratio and 95% CI of 0.51 (0.32, 0.82), the statistical derivation of the margin could be approximately followed ((1/0.83-1)*0.5=0.102 and therefore the upper bound of the non-inferiority margin should be 1.102). Of note, the upper bound of HR (95% CI) is 0.94 (0.805, 1.097) for time to first nonvertebral fracture for abaloparatide vs teriparatide, therefore the upper bound of the 95% CI is only marginally less than 1.102.

The applicant argues that any reduction in risk of NVF versus placebo that is greater than 25% is clinically important, since this would indicate an improvement in the effect for bisphosphonates, based on results from the HORIZON trial. Assuming 30% less effectiveness of abaloparatide compared to teriparatide, the point estimate of the relative risk of NVF for abaloparatide versus placebo would still be above that 25% threshold compared to placebo. Nevertheless, the non-inferiority margin should be justified with the upper bound of the confidence intervals and not the point estimates for also considering the uncertainty.

Of note, as this is an observational study, using formal criteria of non-inferiority is not fully endorsed. There are multiple factors that need to be considered in the interpretation of the results from a non-randomised experiment, not only random error.

The effectiveness evaluation was conducted using an "intent-to-treat (ITT) analysis", meaning that the first fracture event during the 18 months plus 30 days follow-up after the index date was summarized regardless of when treatment ended. The applicant uses terminology from RCT setting which is not fully endorsed. Referring to the analysis as an "ITT" analysis may be misleading. In the RCT setting the key feature of the ITT analysis is that it represents an instrumental variable analysis, with randomisation as a perfect instrument. This results in an unconfounded comparison. No similar effect can be achieved with an "ITT" analysis in a non-interventional study. The exposure definition may be more appropriately designated as an "ever exposed" approach.

Also, ITT tends towards underestimating differences between groups, which is non-conservative in the non-inferiority setting. Complementary analyses, such as "per protocol analysis" are therefore usually required.

The vast majority of patients did not complete 18 months of treatment, the mean exposure was 10 months. This is considerably less than in the clinical trial 003. To include 19 months data for all patients is not considered conservative in a "non-inferiority" setting and will likely dilute possible treatment differences between the groups.

In the Day 12 LoQ, the applicant was asked to perform several additional analyses:

Effectiveness evaluation using
1. "As-treated (AT) analysis" identical to the safety analysis based only on events occurring while on therapy (until end of treatment) for up to 18 months plus 30 days follow-up.

2. "Per protocol (PP) analysis" including only patients with at least 12 months exposure to the drug. (The first fracture event during the 18 months plus 30 days follow-up)

The results for the nonvertebral fracture outcome of the AT analysis were similar to those of the original ITT analyses in PS-matched subjects, i.e. the HR were again not significant, but the HR point estimate for the PP analysis was lower. Also, the point estimates of the HR for hip fracture are markedly lower for the AT analysis, but even more for the PP analyses. The lower HR estimates in the PP analyses can be explained by the higher exposure. Also using only events occurring while on therapy as in the AT analysis has a higher sensitivity for showing treatment differences. The upper bounds for the 95% CIs of the HR for non-vertebral fractures were below the pre-defined margin of 1.3, but above the statistically derived non-inferiority margin of 1.102. In the non-inferiority setting, methods that dilute differences between groups are non-conservative. In the propensity score analysis presented by the applicant, matching is performed based on adjustment for a large number of variables. Depending on the causal relationship between the factors, adjusting for a specific variable may, or may not, be appropriate. It is appropriate to use variables that causally affects both treatment choice and treatment outcome. However, adjustment for variables that are potential mediators (i.e., variables which carry forward the treatment effect) in the causal pathway between the treatment and the outcome, dilutes causal effects and is therefore non-conservative in the non-inferiority setting. Therefore, adjustment for variables related to the post-index period is not appropriate. The applicant has confirmed that all adjustment variables were related to treatment and disease history at baseline using data from pre-index period. One exception was current use of oral glucocorticoids which was defined within 30 days before or after index date, which is acceptable.

Few concerns are raised as regards to the choice of propensity score analysis to create the two cohorts. It is appreciated that selection of variables in the logistic regression-based PS-matching were predefined in the study protocol and based on clinical knowledge. The applicant has clarified that the variables in the logistic regression model were used as planned and as identified in the protocol; however, osteoporosis-related hospitalization was excluded and fragility fracture was used instead.

The applicant was asked to repeat the main effectiveness analysis by trimming the observations with propensity score <0.1. The results of the fracture and cardiovascular event in all eligible patients with propensity score ≥ 0.1 were in line with the original analyses.

Sensitivity analyses of effectiveness and safety endpoints are performed for the cohorts matched based on the same PS method using other calipers, and also on sub-populations with additional exclusion criteria. However, the same PS method was used, and the adjustment variables were same for both effectiveness and safety evaluation. Robustness of the primary and secondary results was further investigated using a Cox regression model fitted to the original data adjusting for all variables used for PS matching, stratification of propensity scores and inverse probability of treatment weighting (IPTW), as well as analysis using overlap weighting. Nonvertebral and hip fracture analysis results for all eligible patients (crude analysis) and for all eligible patients adjusted for age and prior fracture status show comparable results. In general, the results are similar across the various methods used. The additional analyses show that the efficacy and safety results are robust considering the matching algorithm.

Addressing the possibility that new drugs may be channelled to particular difficult patients at first, an analysis was performed excluding the first 8 months since the introduction of abaloparatide showing similar primary and secondary outcomes as the overall PSM population, but with lower point estimates for the HR.

Results

Effectiveness

Demographic characteristics, osteoporosis disease and treatment history number of prior fractures, number of comorbidities, fall risk conditions, CV event history remained well balanced after the population in the 2 treatment cohorts were PS-matched. Diagnostic plots confirm that most baseline characteristics were already on average well-balanced before PS-matching. In the original data, only the two non-clinical covariates, "index date year quarter" and "insurance type", had standardized differences > 0.1. After propensity score matching, the standardized differences for all covariates are < 0.05. Propensity score matching increased the average balance in the chosen covariates. The mean age was approximately 67.5 years. In the pivotal clinical study, the mean age was actually 2 years higher, 69.5 years.

In the primary effectiveness analysis presented by the applicant, the number of patients with new non-vertebral fractures was comparable between abaloparatide 313 (2.8%) and teriparatide 333(3.0%) treated patients. The number of patients with new hip fractures between abaloparatide 112 (1.0%) and teriparatide 125 (1.1%) treated patients was comparable as well.

Approximately 3% of the patients had a nonvertebral fracture in the placebo group in clinical study BA058-05-003. The incidence was somewhat lower in the abaloparatide treated patients (2.2%) and teriparatide treated patients (1.7%) in the clinical study.

Each subgroup was PS-matched separately. In general, outcomes seem consistent among all subgroups when compared to the overall data for both nonvertebral and hip fractures.

Since the overall abaloparatide and teriparatide patients are well matched, the PS-matched pairs were almost identical at sensitivity analyses using different caliper widths.

Only a minority of the patients had a treatment duration of >12 months.

Discussion:

Major concerns hampering the interpretability of the results of study BA058-05-028 are a) the lack of pre-specification, b) unclear assay sensitivity of the study and c) the inherent biases associated with the design and analysis that appear to be difficult to quantify.

The statistical analysis may be difficult to pre-specify. Thus, the possibility to – consciously or not – make data-driven decisions on numerous analysis options (PS derivation, selection of patients and matching, analysis model, …) cannot be excluded. This was roughly addressed by giving a clear rationale for each and every analysis option (and by justifying any difference to the methods used in the primary analysis of the pivotal trial) and by extensive sensitivity analyses.

The ability of the trial to detect differences between ABL and TPTD is vital as it should be demonstrated that there is no important loss in efficacy or increase in safety risk compared to TPTD. The use of teriparatide as a comparator in the study is endorsed. It is agreed that matching untreated patients would have been very challenging. Due to the non-inferiority setting of the study, "assay sensitivity" is challenging to demonstrate. For example, the claims data have inherent errors and inconsistencies, and while it is acknowledged that the claims-based algorithm leads to misclassification that is non-differential between treatment cohorts, this may well hamper the ability to detect differences. Also, considering a treatment effect regardless of any "post claim-of-drug-prescription" events that may impact fracture risk (which are in fact not recorded) will lead to an estimate that is biased towards equivalence. The applicant was invited to discuss and contextualize the observed effectiveness in relation to the clinical studies of teriparatide and/or any external data. A review of historical evidence of teriparatide effects on fractures was presented, referring to randomized clinical trials and observational data for time periods of different lengths, covering the treatment duration in the BA058-05-028 study. The referenced studies showed similar pattern for teriparatide effect in respect to incidence of non-vertebral and hip fractures for the relevant time period as observed in the BA058-05-028 study. Overall, external data provides assurance that teriparatide performed as could be expected, which is indicative of assay sensitivity.

Despite PS matching, the cohorts compared may be different with respect to disease state and prognostic characteristics, as well as other factors that may affect the outcomes of interest or the way an outcome is recorded. Furthermore, the mechanism to assign a patient to one or the other treatment (and the potential relationship with factors affecting efficacy and safety outcomes) was discussed. There is always a possibility of differential identification of outcomes in a study based on claims data. Due to the different price setting, the socioeconomic status of abaloparatide and teriparatide users may have been different which may have affected the possibility to capture fracture/MACE/death outcomes in the claim data. Geographic region, prescriber physician specialty, and insurance type as proxy for socioeconomic status is not optimal. Furthermore, there are unavailable important confounders that cannot be adjusted for in the analysis. As admitted by the applicant, detailed clinical data such as BMD T-scores or the presence of other risk factors (e.g. family history, smoking status, alcohol intake) associated with disease severity and increased future

fracture risk are not available. No access to income and education data in the study is also a limitation. It is difficult to estimate any potential bias caused by different price settings of abaloparatide/teriparatide. There are some differences in the use of anabolic therapies for osteoporosis between US and Europe and also within Europe. The US patient population may not be fully representative to the European patient population currently treated with teriparatide. For example, the average age of patients new to anabolic therapies may higher (73 years in Germany [Ziller V. et al., 2012] vs 67 years in study BA058-05-028). The applicant is proposing pharmacovigilance activities in European setting (a post-authorization safety study (PASS) to assess serious cardiovascular events of MI, stroke, all-cause and cardiovascular mortality, and arrhythmias for abaloparatide), see section 3.5.

Study BA058-05-007

Study BA058-05-007 was a randomised, double-blind, placebo-controlled, comparative Phase 2 study of abaloparatide-TD administered via a solid Microstructured Transdermal System in healthy postmenopausal **women** with osteoporosis. The primary objective of this study was to determine the clinical safety and efficacy of abaloparatide-TD (50, 100, and 150 µg) as assessed by changes in BMD when compared to a transdermal placebo and abaloparatide-SC (80 µg). Only patients who received the active control abaloparatide-SC and the placebo-TD will be presented and discussed in this submission.

Study No., Phase No., No. patient by region	Study Design Treatment Duration	Primary Efficacy Endpoint	Study population, Gender M/F Median Age (Range)	Dosage Form, Treatment: Dose, Route & Regimen	No. randomised
Study 007 Phase 2 13 in US, 52 in Denmark 15 in Estonia 21 in Poland	Randomised Double-blind (for ABL-TD/Placebo) Placebo-controlled Parallel Group Dose-finding 6 months of treatment	Change in BMD-spine, hip and forearm Change in serum bone markers (s-P1NP, P1CP, BALP, osteocalcin, s-CTX1)	PMW with osteoporosis 51 F (abaloparatide-SC) Median age: 66 yr (range: 56-84)	ABL-SC 80µg QD Placebo-TD	51 50

The mean changes from baseline in total analyzable BMD of the lumbar spine, femoral neck and total hip increased during the 6 months of treatment with abaloparatide-SC. The results at Week 12 and Week 24 are summarized below:

• Lumbar spine BMD: at Week 12: 3.0 ± 3.1 and at Week 24: 5.8 ± 4.2%. Mean BMD in the placebo group was significantly lower (0.04 ± 2.5% at Week 24). P<0.0001 vs placebo.

• Femoral neck BMD: at Week 12: 1.6 ± 3.4 and at Week 24: 2.6 ± 3.8%. Mean BMD in the placebo group was significantly lower at Week 24 (-0.5 ± 2.9%).

• Total hip BMD: at Week 12: 1.7 ± 2.9 and at Week 24: 2.7 ± 3.1%. Mean BMD in the placebo group was significantly lower Week 24 (-0.02 ± 2.4%). P<0.0001 vs placebo.

For the ultradistal radius BMD, there was a slight increase (0.9 ± 5%) in percent change from baseline seen at Week 24, compared to a reduction of BMD in the placebo group (% change of -0.4 ± 5 at Week 24).

The BMD results for abaloparatide-SC and placebo at 6 months from the study BA058-05-007 are consistent with the changes observed for the same dose of 80 µg and mode of administration SC in Study BA058-05-002 and Study BA058-05-003.

2.5.6. Discussion on clinical efficacy

Abaloparatide is intended for the treatment of osteoporosis in postmenopausal women at increased risk of fracture to reduce the risk of osteoporotic fractures. Abaloparatide has previously been submitted for market authorisation (2015) with a following negative opinion. The key reasons regarding <u>efficacy</u> in the grounds for refusal were:

- Only one pivotal study (BA058-05-003/005) was conducted. Due to serious GCP related findings, data from two sites were excluded, reducing the size of the study population, thus the study failed to demonstrate a statistically significant effect on nonvertebral fractures versus placebo

The applicant has now submitted a new application in which the following studies are new and were not included in the previous procedure:

- Study BA058-05-028: A prospectively planned, retrospective observational cohort study using US claims data from >11,000 patients

- Study ITM-058-301: placebo-controlled study, approximately 200 postmenopausal women and men with osteoporosis in Japan, BMD as primary endpoint

- Study BA058-05-020: 3 month open-label study, 23 US patients with bone biopsies

- In a sub-population of study BA058-05-003, an additional retrospective post-hoc analysis on hip dual-energy X-ray absorptiometry (DXA) images and bone mineral density (BMD) was conducted (3D-DXA study)

- Post-marketing safety reporting from United States since approval in 2017, approximately 47.618 patient-years of treatment.

Design and conduct of clinical studies

The basis for the original marketing authorisation application (MAA) of abaloparatide-SC was three Phase 3 studies; a pivotal Phase 3 study (ACTIVE, **Study BA058-05-003**) of postmenopausal women with osteoporosis for 18 months, tested the clinical efficacy and safety of daily 80 µg abaloparatide-SC, in comparison to a matched placebo and an open-label active control daily teriparatide-SC 20 µg. This was followed by extension **Study BA058-05-005**, where patients previously receiving abaloparatide-SC or placebo received 24 months of alendronate therapy. These data were supported by a 24-48 week dose-finding study (Study **BA058-05-002**) in the target population.

In study BA058-05-003, the duration of abaloparatide-SC treatment was determined to 18 months (due to potential long-term safety concerns of this anabolic treatment). The study design was modified according to several regulatory advices in order to provide 24 months of fracture assessment data as required in the current guidelines.

The inclusion criteria seem appropriate in relation to the targeted population. The exclusion criteria are relatively extensive which may impact the generalizability of the study, mainly regarding safety data, to the elderly osteoporosis population with concomitant chronic diseases. Several inclusion/exclusion criteria are considered of clinical importance regarding the known safety profile of the drug.

For study BA058-05-003, the primary comparison, abaloparatide-SC vs. placebo, was performed on data collected under double-blind conditions. Treatment with the active control was open-label. All fracture and BMD endpoint assessments were however performed by independent third-party blinded reviewers. A second reviewer was to confirm the assessment of the first reviewer only for all patient radiographs in which an incident fracture had been identified. This implies that the fracture event rate may have been underestimated compared to if instead two independent assessors had viewed and assessed all patient radiographs. Considering the primary objective being superiority versus placebo this can be considered conservative and therefore of no concern.

Overall, statistical methods were acceptable. The SAP was amended once before it was finalized but was further amended after database lock, on two occasions (on 24 March 2015 and, on 29 May 2015). These amendments concerned e.g. the definition of the primary endpoint that was changed (from new and/or worsening to new vertebral fractures alone); analyses using both definitions were performed and have been presented. Further, the non-vertebral fracture analysis was changed not only to take into account the occurrence but also time to first incidence of a non-vertebral fracture, implying a change with regard to the test to be used for the comparison between treatments (i.e. log tank instead of Fishers exact test). Although changes were made also post-hoc, they are per se acceptable and not considered to have introduced any bias. The primary analysis was based on a modified ITT population and at the planning stage it was expected that approximately 20% of randomised patients were to be excluded from the analysis of the primary endpoint. Only one sensitivity analysis was planned and although the proportion of patients excluded in the primary analysis was less than expected, additional sensitivity analyses were requested.

A total of 2070 patients were randomized into three treatment arms of approximately 680 patients in each group. The groups were well balanced regarding baseline demographics and BMD, as expected. There were at least numerically more patients with prevalent vertebral fractures at baseline in the teriparatide group and consequently more patients that were defined to have severe disease in this group (21% in teriparatide vs 16% in abaloparatide group). However, the fracture history did not reveal any difference in prior clinical fractures.

The discontinuation rate in study BA058-05-003 was highest in the abaloparatide group 189 (27.2%) compared to teriparatide 140 (20.4%) and placebo 157 (22.8%). Of those who discontinued, more abaloparatide-SC patients discontinued due to AEs (38.1%) compared to teriparatide (31.4%) and placebo (26.1%) and. More patients in the placebo group discontinuing due to significant BMD deterioration compared to the active treatment arms. Also, more abaloparatide than placebo and teriparatide patients were excluded from the mITT due to the lack of a post-baseline radiologic assessment. The details of why a post-base line assessment was not performed in a large number of patients was discussed in the previous procedure. According to the applicant, the two primary reasons were that the patient discontinued less than 3 months from the time of baseline (32%), that the patients refused the procedure (35%), that the patients did not return for the early termination visit (15%), and that the clinical site inadvertently did not conduct the procedure (5%). The most common reason in the abaloparatide group was early termination (40% vs 28% in the placebo group). It should be noted that these numbers are calculated including two EU sites which were excluded from the MAA and thus are not correct for the current population.

A total of 1038 patients who previously got placebo (n=531) and abaloparatide (n=507) entered the extension Study BA058-05-005 with alendronate treatment. Consequently, 24 months data is not available for the teriparatide treated patients for any comparisons.

In study BA058-05-005, all patients and investigators remained blinded to the previous BA058-05-003 double-blind treatment assignment through the first 6 months (Visit 3). Study BA058-05-005, was initially considered merely descriptive but was amended to include formal statistical analyses. Based on similar endpoints in study BA058-05-005 compared to BA058-05-003, the same analysis approach as used for the analysis of study BA058-05-003 was planned also for the analysis of study BA058-05-005. Overall, however, approximately 30% of those initially randomised to abaloparatide and placebo respectively in study BA058-05-003 were not included in study BA058-05-005 and, hence analyses cannot be considered as based on a truly randomised comparison.

Study ITM-058-301 was a Phase 3, 2-arm, multi-centre, randomised, placebo-controlled, double blind, parallel group study in Japanese subjects with osteoporosis who were at high risk of fracture. The primary endpoint in the study was percent change in lumbar spine (L1-L4) BMD. According to EMA osteoporosis guideline (CPMP/EWP/552/95 Rev), BMD may be the primary end point in exploratory studies but is not an appropriate surrogate for fracture reduction. 213 subjects were randomized in the study; 141 in the abaloparatide group and 72 in the placebo group. Approximately 10% of the subjects were men.

In the primary efficacy analysis of percent change in lumbar spine (L1-L4) BMD at the last visit, superiority of the ITM-058 group over placebo was tested sequentially in the entire population and in the subset of patients with postmenopausal osteoporosis, controlling the Type 1 error rate at 5% two-sided which is endorsed. The primary analysis population for efficacy evaluation was Full Analysis Set (FAS) that did not include all randomized subjects. Analysis based on PPS is not considered to add value as a sensitivity analysis, and LOCF applied in ANCOVA is likely not sufficient to demonstrate robustness of the results. Amount of missing data is not summarised, but it can be derived from the available tables that approximately 20-23 % of patients with postmenopausal osteoporosis (in FAS) did not have observed values on the primary endpoint at Week 78 in the placebo and ITM-058 group, respectively. The primary ANCOVA analysis was based on the observed values and no corresponding analysis with LOCF could be found. Descriptive analysis using LOCF shows that 95% CI for the between treatment difference is in line with the results of the primary and the MMRM analysis. Considering that the efficacy estimates from this study are not intended for presentation in the SmPC, no further sensitivity analysis will be requested.

Study **BA058-05-028**, a retrospective, observational cohort study, investigated the effectiveness on fracture prevention. It was noted that data extraction from the PRA (Symphony Health's) Integrated Dataverse database was performed prior to the date of the only version of study protocol. Any specifications or analysis described in the study protocol may have been impacted by the study data in hand. Furthermore, the index date used for the main analysis presented initially by the applicant was different from the one specified in the protocol (but updated in this report). The applicant reassured that no study data were shared with the applicant prior to the finalization of the study protocol. However, it appears that the extract from the Symphony database used in the pilot study (Williams et al, 2019) did overlap with the data extract in study BA058-05-028 to a certain extent as "less than half patients reached 18 months after index date at the data cut" (as described in Table 1 in the response). Thus, it cannot be excluded that data from the pilot study had informed the choice of the non-inferiority margin in the BA058-05-028 study.

The propensity score matching 1:1 for abaloparatide and teriparatide substantially reduced the number of analysed subjects. The baseline data was well balanced already before propensity score matching and

sensitivity analyses using data from all eligible patients showed similar results as the original PS-matched analysis.

Efficacy data and additional analyses

The study BA058-05-003 met its primary endpoint**. New vertebral fractures** occurred in 3 (0.5%) patients treated with abaloparatide and in 25 (4.2%) patients on placebo. During the 24 months extension, 2 new vertebral fractures occurred in the previously abaloparatide treated group compared to 10 new vertebral fractures in the previously placebo treated group.

The risk reduction in abaloparatide treated group compared to placebo in % (95% CI):

-3.65 (-5.59, -2.00) in study BA058-05-003 at month 18 (p<0.0001)

-2.83 (-4.84, -1.14) in study BA058-05-005 population at month 18 (p= 0.0013)

-4.44 (-6.86, -2.30) up to 43 months from baseline of study BA058-05-003 in the BA058-05-005 population (p<0.0001)

In the primary analysis, 16.2% (113/696) and 12.8% (88/688) of patients randomised to the abaloparatide-SC and placebo group respectively were excluded. The corresponding proportion for the teriparatide arm was 12.5% (86/686).

One sensitivity analysis was planned and performed using the method of multiple imputation (MI). Additional sensitivity analyses were requested in order to confirm data robustness; of particular importance given the single pivotal status of study BA058-05-003. A placebo multiple imputation (pMI) analysis was requested to be performed replacing missing values for patients without outcome data using a logistic regression model based only on placebo completers. Furthermore, the sensitivity analysis performed by the applicant did not replace values for patients in the mITT population who discontinued the study. Therefore, an ITT-based analysis replacing values of all drop-outs without vertebral fracture, including those with post-baseline evaluable radiologic assessment before month 18, using pMI was requested to be performed, and an analysis where values for drop-outs without vertebral fracture are replaced based on pMI but considering the risk of vertebral fracture as proportional to the time after drop-out. The requested sensitivity analyses were performed and generally support the primary outcome showing clinically relevant and statistically significant superiority to placebo although treatment effects are reduced as expected for analyses addressing the treatment effect assuming loss of benefit after discontinuation from treatment. The sensitivity analyses were also repeated excluding data from two EU sites excluded from the MAA. Additionally, ITT-based tipping point analyses were requested, i.e. the number of vertebral fractures in the abaloparatide group in patients without outcome data and all dropouts should be determined that would have changed the conclusion with regard to statistical significance, which confirmed that conclusions would have changed only under extreme assumptions.

Key secondary endpoints: Abaloparatide-SC did not prolong the time to the first incidence of **non-vertebral fracture** versus placebo. The total number of events was 21 in placebo, 15 in abaloparatide and 12 in teriparatide groups at 18 months. There were no statistically significant reductions in the risk of nonvertebral fractures in the former abaloparatide-SC group versus former placebo group at 18 months (during study BA058-05-003), at 25 months or at 43 months. During the alendronate treatment period in the BA058-05-005 extension from month 25 through 43, 8 new nonvertebral fractures occurred in the previously abaloparatide treated group compared to 10 new non vertebral fractures in the previously placebo treated group.

The Kaplan-Meier estimated event rates and time to first nonvertebral fracture vs placebo:

HR 0.74 (0.38, 1.43) during 18 months of study BA058-05-003 (p=0.37)

HR 0.52 (0.25, 1.08) in study BA058-05-005 population at month 18 (p= 0.073)

HR 0.61 (0.35, 1.08) up to 43 months from baseline of study BA058-05-003 in the BA058-05-005 population (p=0.088)

In the analysis of time to first nonvertebral fracture there were overall few events ; there was a high level of censored data with seemingly earlier censoring in the abaloparatide-SC arm than in the placebo and teriparatide arm. The discontinuations were more frequent in the abaloparatide group resulting in fewer abaloparatide treated patients at risk: at 18 months the number of patients at risk was 12 patients more in the placebo group and 35 patients more in the teriparatide group. The withdrawal pattern for each of the randomised treatment groups has been analysed and described in detail, confirming that discontinuations occurred earlier in the abaloparatide group compared to placebo or teriparatide groups.

Considering that approximately 30% of those initially randomised to abaloparatide and placebo respectively in study BA058-05-003 were not included in study BA058-05-005 and hence that the above is not based on a truly randomised comparison.

Both abaloparatide and teriparatide significantly increased the **bone mineral density BMD** at lumbar spine, total hip and femoral neck at 18 months. The BMD increase was greatest during the first 6 months of treatment. The change was most rapid and greatest in lumbar spine, approximately 9% in both abaloparatide and teriparatide groups compared to 0.5% in placebo.

There was a smaller but statistically significant difference between abaloparatide and teriparatide for BMD in total hip (3.3 % vs 3.0%) and femoral neck (2.7% vs 2.3%). BMD in the placebo group remained nearly unchanged.

The primary population for the analysis of BMD data was the ITT population for those patients who had baseline and at least one post-baseline BMD data. LOCF was used to handle missing data. Seemingly, according to the sensitivity analyses using MMRM, it was approximately 10% of the patients that had missing data at month 6 and 20-25% of the patients that had missing BMD data at month 18. With MMRM offered as the only sensitivity analysis additional sensitivity analyses (based on other assumptions) for the BMD endpoints should have been useful and were therefore requested. When using placebo multiple imputation in the active treatment group after treatment drop-out, the results of mean percentage change in BMD supported the results of the original ANCOVA (LOCF) analysis.

Considering the expected BMD progression over time, it may be difficult to define a sensitivity approach that can be considered sufficiently conservative. In the exploratory BMD responder analyses, patients who lacked data were excluded. Additional responder analysis treating patients with missing data as non-responders was performed on request, which showed statistically significant superiority of abaloparatide over placebo; however, the difference was smaller than for observed cases due to higher drop-out in the abaloparatide group.

The relationship of anti-drug antibodies (ADA) to efficacy is briefly summarised in the Integrated Summary of Immunogenicity. According to the data presented no differences in the incidence of fractures were seen in the ADA+, ADA+/NAb+, and ADA+/NAb- subgroups of Study BA058-05-003 compared with the ADA- subgroup. However, ADA had a certain impact on BMD, as consistent increases in total hip, femoral neck, lumbar spine, and radius ultra-distal BMD were seen in the ADA+, ADA+/NAb+, and ADA+/NAb- subgroups

compared with the ADA- subgroup. Differences increased over time and were statistically significant for some of the BMD parameters at Month 12 and/or Month 18. These findings are striking, since, in general, a loss of pharmacologic activity or loss of efficacy would be expected as a result of anti-drug antibodies rather than an increase. In the present case, however, the fact that the observed differences between patients with and without antibodies were significant – despite a large standard deviation – could be a chance finding based on the large sample size. Since pharmacologic activity or efficacy were not negatively impacted by ADA or NAb formation, there is no clinical concern related to this finding.

The BMD increased in all patients when transitioned from placebo or abaloparatide to alendronate treatment in study BA058-05-005. Considering the limited change in BMD during BA0058-005-003 in the placebo group compared to the abaloparatide, there was a large difference in baseline at month 18. The mean percent increases from the baseline at month 18 were generally greater in the placebo/alendronate group than in the abaloparatide/alendronate group. Statistically significant differences favouring the abaloparatide/alendronate group were observed at the total hip, femoral neck, and lumbar spine for all timepoints.

The effects of sequential anabolic and anti-resorptive therapies are not clear. This was discussed by the applicant in the previous procedure upon request. It was concluded that no definitive published information on the effects on fracture exist at this time.

A number of hip DXA images from study BA058-05-003 were retrospectively analysed using three-dimensional (3D) modelling methods (3D-SHAPER software) to evaluate changes in volumetric BMD and estimated bone strength indices from baseline to month 6 and month 18. After 18 months treatment of abaloparatide, the 3D-DXA scans modelling demonstrated increases in trabecular vBMD and cortical thickness and increased cortical vBMD compared to baseline. Both abaloparatide and teriparatide significantly increased the BMD at lumbar spine, total hip and femoral neck study BA058-05-003 compared to placebo. Additionally, the relationship between vBMD and biomarkers of bone turnover (s-PINP and s-CTX) was examined. In the teriparatide group, changes in cortical volumetric BMD were inversely correlated with changes in serum CTX and PINP, suggesting that higher bone turnover may have attenuated cortical gains. These retrospective modelling analyses are considered explorative in nature and the additional value and clinical relevance of differences seen in some variables is unclear. No SmPC amendments are proposed.

The results from the post-hoc analyses on **other fracture endpoints** and different combinations are, in general, considered to be in line with the results for primary and key secondary endpoints. The endpoints included clinical fractures, major osteoporotic fractures, wrist fractures, nonvertebral fractures including any level of trauma and clinical spine fractures. There were fewer fractures in the abaloparatide group compared to placebo in all these categories and the difference was statistically significant except for wrist fractures. Hip fractures are included in the "major osteoporotic fracture" combined endpoint. However, fractures falling into this category were nearly exclusively vertebral and wrist fractures, i.e. fractures that normally not need surgical treatment. In the BA058-05-003 study, there were no hip fractures in the abaloparatide-SC or teriparatide groups and 1 hip fracture in the placebo group and in the BA058-05-005 study there were no hip fractures in the abaloparatide/alendronate group, and 2 hip fractures in the placebo/alendronate group.

Compared to teriparatide, there was no difference in vertebral fractures in study BA058-05-003. The difference in nonvertebral fractures was not significant, either. The total number of vertebral and nonvertebral fractures in these groups were low (<30/ group). Regarding BMD, there was a trend of a faster BMD increase in abaloparatide treated patients compared to teriparatide and a significantly greater increase in BMD at month 18 in some locations. However, all comparisons with teriparatide were made at month 18 although the duration of randomised treatment of at least two years is recommended in the guideline.

Integrated analysis of the **bone turnover markers** from Study BA058-05-003/005 show consistent increases in both anabolic (s-P1NP, BSAP, Osteocalcin) and resorption marker (s-CTX) in both abaloparatide-SC and teriparatide groups compared to placebo. Increases in both formation and resorption seem somewhat more pronounced in the teriparatide group compared to abaloparatide. However, the CHMP does not agree with the conclusion of the applicant that this data would strongly support abaloparatide being more bone formation selective than teriparatide.

In **study ITM-058-301** in Japanese subjects, the primary endpoint; least squares mean of the percent change in lumbar spine (L1-L4) BMD was 16 % in the abaloparatide group and 4 % in the placebo group. In the BA058-05-003 study the BMD increase in lumbar spine was 9% in the abaloparatide group and 0.5 % in the placebo group. Also for total hip and femoral neck the relative changes in BMD were numerically greater in study 301 than in study BA058-05-003. The primary endpoint in the pivotal BA058-05-003 study, new vertebral fractures, was also analysed in the 301 study. In the 301 study, with its limited number of participants, no new vertebral fractures were identified in the abaloparatide group versus 3/70 (4.3%) in the vehicle group. New nonvertebral fractures was also analysed in the 301 study. In the abaloparatide group there were 3 (2.2 %) new non vertebral fractures up to the last visit and 2 (2.9%) in the placebo group. The number of fractures was thus too low to draw any conclusions on efficacy in fracture reduction.

The new histomorphometry (**Study BA058-05-020**) and 3D analysis (**Study BA058-05-003)** are supportive of an anabolic effect of abaloparatide on bone. However, it is unclear how this data can be translated into fracture risk reduction.

The analyses from study **BA058-05-02**8 including several sensitivity analyses support comparable effectiveness vs teriparatide in a US population. the number of patients with new non-vertebral fractures was comparable between abaloparatide 313 (2.8%) and teriparatide 333(3.0%) treated patients, HR 0.94 (0.81,1.10). The number of patients with new hip fractures between abaloparatide 112 (1.0%) and teriparatide 125 (1.1%) treated patients was comparable as well, HR 0.90 (0.69, 1.16). However, there are major concerns hampering the interpretability of the results of study BA058-05-028 concerning a) the lack of pre-specification, b) unclear assay sensitivity of the study and c) the inherent biases associated with the design and analysis that appear to be difficult to quantify. These limitations of the observational cohort study could only be partially addressed with corresponding sensitivity analyses.

2.5.7. Conclusions on the clinical efficacy

In summary, the applicant has demonstrated reduction of radiological vertebral fractures compared to placebo. The effect of abaloparatide versus placebo on non-vertebral fractures was not statistically significant but the data were indicative of a trend in favour of abaloparatide. The results regarding increasing BMD compared to placebo in lumbar spine, hip and femoral neck are convincing.

 Available data suggests reduction of radiological vertebral fractures comparable to teriparatide. There are no studies comparing abaloparatide with bisphosphonates, the current standard therapy for osteoporosis.

Regarding the grounds for refusal during the previous procedure; there is still only one randomised controlled trial conducted with fractures as the primary endpoint. (BA058-05-003/005). There were GCP-related findings during the procedure which led to a significantly reduced study population in the pivotal study with the consequence that the power to show a statistically significant effect on the non-vertebral fractures vs placebo was substantially reduced. However, additional supportive data has been submitted; a placebo-controlled Phase 3 study in Japan, a histomorphometric study in patients, an additional analysis of the hip

DXA images, and an observational cohort study using US claims data. There are important limitations in the design of this observational study but the main analyses as well as several sensitivity analyses support comparable effectiveness vs teriparatide in a US population to a degree that indicates superiority to a putative placebo.

From the totality of information, including both the data from the pivotal study and supportive studies as well as knowledge of the effects of teriparatide (same molecule class, same mode of action), the efficacy of abaloparatide could be considered sufficiently demonstrated in the applied indication. In this particular case, there seems not to be a scientific reason to presume efficacy only for vertebral but not for non-vertebral fractures, regardless of statistical significance being demonstrated for vertebral (but not for non-vertebral) fractures in the pivotal trial.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

The abaloparatide clinical programme consists of a total of 12 studies, including:

- 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)

- one Phase 3 study with primary fracture endpoints

- Study BA058-05-003 in postmenopausal women with osteoporosis followed by an open-label extension study (BA058-05-005).

- Study ITM-058-301 in postmenopausal women and men with osteoporosis in Japan

- One prospectively planned, retrospective observational cohort study (Study BA058-05-028).

Safety data are primarily derived from up to 18 months of treatment with abaloparatide compared to placebo and teriparatide in postmenopausal osteoporotic women in the pivotal phase 3 trial BA058-05-003. Data from extension study BA058-05-005 only derives safety data after abaloparatide discontinuation since all patients participating were switched to alendronate.

For Study BA058-05-003 and BA058-05-005, at the request of the Committee on Human Medicinal Products (CHMP), data from two sites in Europe were excluded from analysis due to GCP issues that were raised at the previous 2015 MAA. Therefore, all data from these two European investigative sites were excluded from all data analyses presented below.

Studies ITM-058-301 and BA058-05-028 are "new" i.e. they were not included or assessed in the previous procedure. Study BA058-05-028 is described in detail in the efficacy section including safety which was studied as secondary endpoint.

In study BA058-05-003, 694 patients received abaloparatide 80 µg SC daily and 507 (73%) completed 18 months of exposure, while on teriparatide 546 out of 686 (80%) and on placebo 531 out of 687 (77%) completed the trial. In prospective clinical studies together 1039 subjects received 80 µg abaloparatide daily.

The difference in patients completing trial BA058-05-003 was also reflected in the mean (±SD) exposure, 15.0 (±6.0) months on abaloparatide, 15.55 (±5.3) on teriparatide, and 15.8 (±5.1) on placebo. Patients on abaloparatide dropped out early, with drop-out ≤1 month and >1 month to ≤3 months being 7.9% and 3.8% on abaloparatide, respectively and 3.9% and 3.6% on teriparatide, respectively (data presented by the applicant in the previous procedure (EMA/CHMP/581111/2018).

Table 35. Subjects on Abaloparatide, Teriparatide, or Placebo by Study and Group of Studies (Safety Population)

Phase/type	Study	Abaloparatide	Teriparatide	Placebo	Total
Studies in postmenopausal women with osteoporosis					
Phase 3	Study BA058-05-003	694	686	687	2,067
Phase 3	Study ITM-058-301	140[a]	0	72[a]	212[a]
Phase 2	Study BA058-05-002	131	45	45	221
Phase 2	Study BA058-05-007	51[b]	0	50[c]	101
Phase 1 / PD study	Study BA058-05-020	23	0	0	23
<u>Subtotal for prospective clinical studies</u>		<u>1,039</u>	<u>731</u>	<u>854</u>	<u>2,624</u>
Retrospective observational study	Study BA058-05-028	11,027	11,027	0	22,054
Total		**12,066**	**11,758**	**854**	**24,678**
Phase 1 studies in healthy postmenopausal women, healthy volunteers and subjects with renal impairment					
Phase 1	Study 2-52-52127-001	75[d]	0	20	95
Phase 1	Study BA058-05-001	32	0	7	39
Phase 1	Study BA058-05-001B	24	0	6	30
Phase 1	Study BA058-05-010	51	0	8	59
Phase 1	Study BA058-05-011	32	0	0	32
Phase 1	Study BA058-05-012	52[g]	0	51[g]	55[e]

Phase/type	Study	Abaloparatide	Teriparatide	Placebo	Total
Total Phase 1 studies		**266**	**0**	**92**	**310**
TOTAL ALL STUDIES		**12,921**	**12,347**	**946**	**26,166**

[a] Study ITM-058-301 included postmenopausal women and men with osteoporosis: 14 men in the abaloparatide group and 6 men in the placebo group.

[b] For study BA058-05-007, subjects receiving abaloparatide 80 µg subcutaneously are considered, while subjects receiving abaloparatide transdermally as abaloparatide-solid microstructured transdermal system (sMTS) are described in the respective study report.

[c] Placebo administered transdermally (sMTS)

[d] Study 2-52-52127-001 comprised two parts: Part A with dose escalation 2-100 µg subcutaneously in a total of 60 subjects, and Part B with 15 subjects receiving 15 µg abaloparatide subcutaneously. Additionally, 16 subjects receiving abaloparatide via the intravenous route in Part B are not considered in this table.

[e] Study BA-058-05-012 was a 4-way-cross-over study. A total of 55 subjects were included in the safety population. Exposure to the different treatments in the cross-over study was as follows: received placebo (n=51), abaloparatide 80 µg (n=52), abaloparatide 240 µg (n=52), or moxifloxacin 400 mg (n=50). Therefore, subjects listed under abaloparatide may have a received abaloparatide only or abaloparatide and placebo. Likewise, subjects listed under placebo may have a received placebo only or placebo and abaloparatide.

Overall, the extent and duration of exposure is considered adequate to assess the safety of abaloparatide. Compared to the previous procedure, post-licensing safety data is now available from the observational study Study BA058-05-028 including 11,027 patients who have received recommended dose as by approved label, for assessment of e.g. rare events, as well as for the assessment of carcinogenicity.

2.5.8.2. Adverse events

Table 36. Treatment emergent adverse events (TEAEs) by System Organ Class in Subjects with Osteoporosis; number of subjects (%), Studies BA058-05-003, BA058-05-002, BA058-05-007, BA058-05-020 and ITM-058-301

Study	BA058-05-003			BA058-05-002					BA058-05-007		BA058-05-020	ITM-058-301	
	PBO 80 µg	ABL 80 µg	TPTD 20 µg	PBO	ABL 20 µg	ABL 40 µg	ABL 80 µg	TPTD 20 µg	PBO	ABL 80 µg	ABL 80 µg	PBO	ABL 80 µg
	0-18 mo	0-18 mo	0-18 mo	0-28 wks / *0-52 wks*	0-28 wks / *0-52 wks*	0-28 wks / *0-52 wks*	0-28 wks / *0-52 wks*	0-28 wks / *0-52 wks*	0-24 wks	0-24 wks	0-3 mo	0-18 mo	0-18 mo
System Organ Class	N=687 n (%)	N=694 n (%)	N=686 n (%)	N=45 / *N=11* n (%)	N=43 / *N=13* n (%)	N=43 / *N=10* n (%)	N=45 / *N=7* n (%)	N=45 / *N=14* n (%)	N=50 n (%)	N=51 n (%)	N=23 n (%)	N=72 n (%)	N=140 n (%)
Blood and lymphatic disorders	30 (4.4)	50 (7.2)	33 (4.8)	0 / *1 (9.1)*	2 (4.7) / *2 (15.4)*	0 / *0*	1 (2.2) / *0*	0 / *1 (7.1)*	1 (2.0)	2 (3.9)	0	0	0
Cardiac disorders	37 (5.4)	81 (11.7)	43 (6.3)	0 / *1 (9.1)*	1 (2.3) / *1 (7.7)*	0 / *1 (10.0)*	4 (8.9) / *1 (14.3)*	2 (4.4) / *3 (21.4)*	0	6 (11.8)	0	2 (2.8)	11 (7.9)
Congenital, familial and genetic disorders	1 (0.1)	1 (0.1)	0	1 (2.2) / *0*			0	0	0	0	0	0	0
Ear and labyrinth disorders	13 (1.9)	27 (3.9)	28 (4.1)	1 (2.2) / *1 (9.1)*	0	2 (4.7) / *1 (10.0)*	1 (2.2) / *1 (14.3)*	0	1 (2.0)	1 (2.0)	0	2 (2.8)	7 (5.0)
Endocrine disorders	10 (1.5)	11 (1.6)	10 (1.5)	1 (2.2) / *0*	0	0	0	0	1 (2.0)	0	0	0	0
Eye disorders	32 (4.7)	24 (3.5)	29 (4.2)	0	1 (2.3) / *1 (7.7)*	2 (4.7) / *1 (10.0)*	0	1 (2.2) / *0*	1 (2.0)	1 (2.0)	0	6 (8.3)	1 (0.7)
Gastrointestinal disorders	167 (24.3)	186 (26.8)	156 (22.7)	10 (22.2) / *4 (36.4)*	12 (27.9) / *4 (30.8)*	13 (30.2) / *2 (20.0)*	9 (20.0) / *2 (28.6)*	9 (20.0) / *3 (21.4)*	4 (8.0)	10 (19.6)	7 (30.4)	18 (25.0)	36 (25.7)
General disorders and administration site conditions	93 (13.5)	99 (14.3)	90 (13.1)	8 (17.8) / *3 (27.3)*	4 (9.3) / *1 (7.7)*	8 (18.6) / *2 (20.0)*	8 (17.8) / *0*	11 (24.4) / *2 (14.3)*	9 (18.0)	11 (21.6)	0	9 (12.5)	17 (12.1)
Hepatobiliary disorders	22 (3.2)	15 (2.2)	23 (3.4)	0	0	0	0 / *1 (14.3)*	0 / *1 (7.1)*	0	1 (2.0)	0	0	0
Immune system disorders	8 (1.2)	2 (0.3)	4 (0.6)	0	0	1 (2.3) / *1 (10)*	0	0	0	0	0	2 (2.8)	5 (3.6)
Infections and infestations	271 (39.4)	274 (39.5)	271 (39.5)	17 (37.8) / *5 (45.5)*	18 (41.9) / *7 (53.8)*	15 (34.9) / *6 (60.0)*	17 (37.8) / *3 (42.9)*	18 (40.0) / *8 (57.1)*	20 (40.0)	24 (47.1)	3 (13.0)	39 (54.2)	89 (63.6)
Injury, poisoning and procedural complications	74 (10.8)	56 (8.1)	64 (9.3)	3 (6.7) / *2 (18.2)*	3 (7.0) / *0*	3 (7.0) / *1 (10.0)*	7 (15.6) / *1 (14.3)*	3 (6.7) / *1 (7.1)*	5 (10.0)	3 (5.9)	4 (17.4)	6 (8.3)	20 (14.3)
Investigations	98 (14.3)	120 (17.3)	117 (17.1)	1 (2.2) / *1 (9.1)*	2 (4.7) / *2 (15.4)*	2 (4.7) / *1 (10.0)*	1 (2.2) / *0*	3 (6.7) / *2 (14.3)*	0	3 (5.9)	0	2 (2.8)	19 (13.6)
Metabolism and nutrition disorders	87 (12.7)	99 (14.3)	116 (16.9)	4 (8.9) / *2 (18.2)*	6 (14.0) / *3 (23.1)*	7 (16.3) / *2 (20.0)*	2 (4.4) / *1 (14.3)*	7 (15.6) / *2 (14.3)*	2 (4.0)	5 (9.8)	0	1 (1.4)	8 (5.7)
Musculoskeletal and connective tissue disorders	247 (36.0)	237 (34.1)	234 (34.1)	10 (22.2) / *6 (54.5)*	10 (23.3) / *3 (23.1)*	14 (32.6) / *5 (50.0)*	5 (11.1) / *1 (14.3)*	7 (15.6) / *4 (28.6)*	10 (20.0)	13 (25.5)	7 (30.4)	13 (18.1)	26 (18.6)

System Organ Class												
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	24 (3.5)	17 (2.4)	27 (3.9)	1 (2.2) / *0*	1 (2.3) / *0*	0	0	0	1 (2.0)	1 (2.0)	0	0	0
Nervous system disorders	135 (19.7)	175 (25.2)	136 (19.8)	7 (15.6) / *3 (27.3)*	3 (7.0) / *1 (7.7)*	11 (25.6) / *3 (30.0)*	11 (24.4) / *2 (28.6)*	9 (20.0) / *3 (21.4)*	5 (10.0)	13 (25.5)	5 (21.7)	11 (15.3)	26 (18.6)
Psychiatric disorders	32 (4.7)	34 (4.9)	21 (3.1)	1 (2.2) / *0*	0	4 (9.3) / *2 (20.0)*	4 (8.9) / *0*	1 (2.2) / *0*	0	1 (2.0)	0	0	0
Renal and urinary disorders	133 (19.4)	143 (20.6)	141 (20.6)	4 (8.9) / *1 (9.1)*	3 (7.0) / *1 (7.7)*	3 (7.0) / *1 (10.0)*	4 (8.9) / *1 (14.3)*	6 (13.3) / *1 (7.1)*	4 (8.0)	5 (9.8)	0	0	3 (2.1)
Reproductive system and breast disorders	18 (2.6)	24 (3.5)	12 (1.7)	0	0	1 (2.3) / *0*	0	0	2 (4.0)	1 (2.0)	0	0	0
Respiratory, thoracic and mediastinal disorders	43 (6.3)	49 (7.1)	43 (6.3)	5 (11.1) / *2 (18.2)*	2 (4.7) / *1 (7.7)*	5 (11.6) / *0*	3 (6.7) / *1 (14.3)*	1 (2.2) / *3 (21.4)*	1 (2.0)	4 (7.8)	3 (13.0)	4 (5.6)	2 (1.4)
Skin and subcutaneous tissue disorders	56 (8.2)	59 (8.5)	73 (10.6)	2 (4.4) / *1 (9.1)*	1 (2.3) / *0*	4 (9.3) / *0*	4 (8.9) / *0*	3 (6.7) / *1 (7.1)*	6 (12.0)	4 (7.8)	3 (13.0)	4 (5.6)	18 (12.9)
Surgical and medical procedures	11 (1.6)	9 (1.3)	5 (0.7)	0	2 (4.7) / *0*	1 (2.3) / *0*	0	0	2 (4.0)	0	0	0	0
Vascular disorders	56 (8.2)	81 (11.7)	69 (10.1)	2 (4.4) / *0*	0 / *1 (7.7)*	3 (7.0) / *1 (10.0)*	2 (4.4) / *1 (14.3)*	3 (6.7) / *0*	2 (4.0)	1 (2.0)	0	0	0

Source: Study BA058-05-002 CSR, Section 14.3.1 Tables 5.2.4 and 5.2.6; Study BA058-05-003-Add, Table 14.3.1.2; Study BA058-05-007 CSR, Table 14.3.1.2. Note that if there is no subject reporting TEAEs during the initial 6 months treatment period (0-28 weeks) and the extension period (0-52 weeks) in Study BA058-05-002, "0" is noted only once. Study BA058-05-020 CSR, Table 14.3.1.3; Study ITM-058-301 CSR, Table 14.3.1 2 3.
ABL=abaloparatide; PBO=placebo; TPTD=teriparatide

Table 37. Summary of Most Common TEAEs (≥ 5% of Subject in Any Treatment Group in Subjects with Osteoporosis, number of subjects (%), Studies BA058-05-003, BA058-05-002 [0-28 weeks], BA058-05-007, BA058-05-020 and ITM-058-301

Study	BA058-05-003			BA058-05-002					BA058-05-007		BA058-05-020	ITM-058-301	
	PBO 0-18 mo N=687	ABL 80 µg 0-18 mo N=694	TPTD 20 mg 0-18 mo N=686	PBO 0-28 wks 0-52 wks N=45 N=11	ABL 20 µg 0-28 wks 0-52 wks N=43 N=13	ABL 40 µg 0-28 wks 0-52 wks N=43 N=10	ABL 80 µg 0-28 wks 0-52 wks N=45 N=7	TPTD 0-28 wks 0-52 wks N=45 N=14	PBO 0-24 wks N=50	ABL 80 µg 0-24 wks N=51	ABL 80 µg 0-3 mo N=23	PBO 0-18 mo N=72	ABL 80 µg 0-18 mo N=23
AE Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiac disorders													
Palpitations	3 (0.4)	39 (5.6)	12 (1.7)	0	0	0	3 (6.7) *0*	1 (2.2) *0*	0	3 (5.9)	0	1 (1.4)	7 (5.0)
Ear and labyrinth disorders													
Vertigo	0	0	0	0	0	0	0	0	0	0	0	2 (2.8)	7 (5.0)
Eye disorders													
Cataract	0	0	0	0	0	0	0	0	0	0	0	5 (6.9)	0
Gastrointestinal disorders													
Abdominal discomfort	0	0	0	0	0	0	0	0	0	0	0	3 (4.2)	9 (6.4)
Abdominal pain	18 (2.6)	14 (2.0)	12 (1.7)	1 (2.2) *0*	3 (7.0) *0*	1 (2.3) *0*	0 *1 (14.3)*	0	1 (2.0)	1 (2.0)	0	1 (1.4)	6 (4.3)
Abdominal pain upper	16 (2.3)	17 (2.4)	18 (2.6)	0	0	1 (2.3) *0*	3 (6.7) *0*	2 (4.4) *1 (7.1)*	0	0	0	3 (4.2)	2 (1.4)
Constipation	37 (5.4)	28 (4.0)	28 (4.1)	1 (2.2) *0*	0	1 (2.3) *0*	1 (2.2) *1 (14.3)*	0	1 (2.0)	2 (3.9)	0	2 (2.8)	4 (2.9)
Diarrhoea	19 (2.8)	17 (2.4)	22 (3.2)	0	1 (2.3) *0*	5 (11.6) *0*	4 (8.9) *0*	3 (6.7) *1 (7.1)*	0	1 (2.0)	2 (8.7)	1 (1.4)	5 (3.6)
Nausea	21 (3.1)	59 (8.5)	37 (5.4)	0	0	5 (11.6) *1 (10.0)*	2 (4.4) *0*	2 (4.4) *1 (7.1)*	2 (4.0)	3 (5.9)	4 (17.4)	6 (8.3)	9 (6.4)
Vomiting	5 (0.7)	7 (1.0)	11 (1.6)	0 *0*	3 (7.0) *0*	2 (4.7) *1 (10.0)*	1 (2.2) *0*	1 (2.2) *1 (7.1)*	0	1 (2.0)	0	1 (1.4)	4 (2.9)
General disorders and administration site conditions													
Injection site haematoma	3 (0.4)	0	3 (0.4)	5 (11.1) *2 (18.2)*	2 (4.7) *0*	5 (11.6) *1 (10.0)*	1 (2.2) *0*	6 (13.3) *1 (7.1)*	0[a]	0	0	0	0
Injection site haemorrhage	0	4 (0.6)	0	0	0	0	1 (2.2) *0*	3 (6.7) *0*	0	0	0	0	0
Injection site bruising	0	0	0	0	0	0	0	0	0	0	0	7 (9.7)	11 (7.9)
Infections and infestations													
Bronchitis	14 (2.0)	12 (1.7)	24 (3.5)	3 (6.7) *0*	5 (11.6) *1 (7.7)*	2 (4.7) *0*	3 (6.7) *1 (14.3)*	2 (4.4) *3 (21.4)*	1 (2.0)	1 (2.0)	0	0	4 (2.9)
Gastroenteritis	14 (2.0)	12 (1.7)	12 (1.7)	0	1 (2.3)	3 (7.0)	3 (6.7)	0	0	0	0	2 (2.8)	3 (2.1)

					1 (7.7)	*2 (20.0)*	*0*						
Influenza	21 (3.1)	43 (6.2)	23 (3.4)	7 (15.6) *0*	2 (4.7) *0*	3 (7.0) *2 (20.0)*	5 (11.1) *1 (14.3)*	6 (13.3) *2 (14.3)*	4 (8.0)	5 (9.8)	0	3 (4.2)	5 (3.6)
Nasopharyngitis	56 (8.2)	43 (6.2)	43 (6.3)	2 (4.4) *0*	5 (11.6) *1 (7.7)*	2 (4.7) *1 (10.0)*	3 (6.7) *2 (28.6)*	6 (13.3) *1 (7.1)*	9 (18.0)	13 (25.5)		36 (50.0)	81 (57.9)
Upper respiratory tractinfection	61 (8.9)	65 (9.4)	65 (9.5)	1 (2.2) *0*	2 (4.7) *0*	1 (2.3) *0*	0	3 (6.7) *0*	1 (2.0)	3 (5.9)	2 (8.7)	0	0
Urinary tract infection	36 (5.2)	37 (5.3)	34 (5.0)	1 (2.2) *1 (9.1)*	4 (9.3) *3 (23.1)*	1 (2.3) *1 (10.0)*	2 (4.4) *0*	5 (11.1) *3 (21.4)*	1 (2.0)	0	0	0	0
Injury, poisoning and procedural complications													
Fall	0	0	0	0	0	0	0	0	0	0	2 (8.7)	0	0
Confusion	0	0	0	0	0	0	0	0	0	0	0	4 (5.6)	11 (7.9)
Investigations													
Blood calcium increased	2 (0.3)	4 (0.6)	5 (0.7)	0	0	0	0	0	0	0	0	1 (1.4)	7 (5.0)
Blood uric acid increased	0	0	0	0	0	0	0	0	0	0	0	0	8 (5.7)
Metabolism and nutrition disorders													
Hypercalcaemia	4 (0.6)[a]	15 (2.2)[a]	33 (4.1)[a]	1 (4.8) *1 (9.1)*	1 (2.3) *1 (7.7)*	3 (7.0) *0*	2 (4.4) *0*	4 (8.9) *0*	0	0	0	0	0
Hypertriglyceridaemia	21 (3.1)	20 (2.9)	24 (3.5)	0	4 (9.3) *0*	1 (2.3) *0*	0	1 (2.2) *0*	0	0	0	0	0
Musculoskeletal and connective tissue disorders													
Arthralgia	61 (8.9)	58 (8.4)	60 (8.7)	4 (8.9) *3 (27.3)*	2 (4.7) *1 (7.7)*	5 (11.6) *2 (20.0)*	1 (2.2) *0*	3 (6.7) *2 (14.3)*	3 (6.0)	3 (5.9)	0	3 (4.2)	6 (4.3)
Back pain	69 (10.0)	60 (8.6)	52 (7.6)	5 (11.1) *2 (18.2)*	3 (7.0) *1 (7.7)*	6 (14.0) *1 (10.0)*	1 (2.2) *0*	1 (2.2) *0*	5 (10.0)	3 (5.9)	0	6 (8.3)	7 (5.0)
Osteoarthritis	0	0	0	0	0	0	0	0	0	0	0	3 (4.2)	7 (5.0)
Pain in extremity	40 (5.8)	34 (4.9)	39 (5.7)	2 (4.4) *3 (27.3)*	1 (2.3) *0*	2 (4.7) *0*	0	0	2 (4.0)	1 (2.0)	0	2 (2.8)	2 (1.4)
Bursitis	0	0	0	0	0	0	0	0	0	0	3 (13.0)	0	0
Nervous system disorders													
Dizziness	49 (7.1)	77 (11.1)	56 (8.2)	2 (4.4) *1 (9.1)*	0 *1 (7.7)*	4 (9.3) *1 (10.0)*	5 (11.1) *0*	2 (4.4) *1 (7.1)*	1 (2.0)	8 (15.7)	4 (17.4)	3 (4.2)	7 (5.0)

Headache	40 (5.8)	59 (8.5)	49 (7.1)	3 (6.7) *1 (9.1)*	2 (4.7) *0*	6 (14.0) *1 (10.0)*	6 (13.3) *0*	6 (13.3) *1 (7.1)*	5 (10.0)	5 (9.8)	3 (13.0)	8 (11.1)	19 (13.6)
Sciatica	11 (1.6)	16 (2.3)	11 (1.6)	0	0	3 (7.0) *1 (10.0)*	1 (2.2) *0*	0	0	0	0	0	0
Renal and urinary disorders													
Hypercalciuria	86 (12.5)[b]	108 (15.6)[b]	124 (18.1)[b]	4 (8.9) *1 (9.1)*	3 (7.0) *1 (7.7)*	2 (4.7) *0*	4 (8.9) *1 (14.3)*	5 (11.1) *1 (7.1)*	3 (6.0)	3 (5.9)	0	0	0
Respiratory, thoracic and mediastinal disorders													
Cough	21 (3.1)	20 (2.9)	20 (2.9)	0	2 (4.7) *1 (7.7)*	3 (7.0) *0*	2 (4.4) *0*	0 *1 (7.1)*	0	2 (3.9)	0	0	0
Wheezing	0	0	0	0	0	0	0	0	0	0	2 (8.7)	0	0
Skin and subcutaneous tissue disorder													
Ecchymosis	0	0	0	0	0	0	0	0	0	0	2 (8.7)	0	0
Eczema	0	0	0	0	0	0	0	0	0	0	0	4 (5.6)	7 (5.0)
Vascular disorders													
Hypertension	37 (5.4)[c]	47 (6.8)[c]	36 (5.2)[c]	2 (4.4) *0*	0	2 (4.7) *1 (10.0)*	1 (2.2) *1 (14.3)*	2 (4.4) *0*	1 (2.0)	0	0	0	0
	41 (6.0%)[d]	53 (7.6%)[d]	43 (6.3%)[d]										

Source: Study BA058-05-002 CSR, Tables 12-5 and 12-6; Study BA058-05-003-Add, Table 14.3.1.2; Study BA058-05-007 CSR, Table 14.3.1.2. Note that if there is no subject reporting TEAEs during the initial 6 months treatment period (0-28 weeks) and the extension period (0-52 weeks) in Study BA058-05-002, "0" is noted only once. a - transdermal placebo was administered. Study BA058-05-020 CSR, Table 14.3.1.3; Study ITM-058-301 CSR, Table 14.3.1 2 3
[a] PTs: hypercalcaemia, blood calcium increased
[b] PTs: hypercalciuria, urine calcium increased, urine calcium/creatinine ratio increased
[c] PT of hypertension only
[d] PT terms hypertension but also PTs blood pressure increased, hypertensive crisis, and systolic hypertension
ABL=abaloparatide, PBO=placebo, TPTD=teriparatide

In study BA058-05-003, the incidence of adverse events was higher in patients on abaloparatide compared to teriparatide and placebo in the system organ classes 'cardiac disorders (12%, 6,3%, 5,4%)', 'gastrointestinal disorders (27%, 23%, 24%)' and 'nervous system disorders (25%, 20%, 20%)'.

In the system organ class 'cardiac disorders' the difference was primarily driven by palpitations (5.6%, 1.7%, 0.4%), in the system organ class 'gastrointestinal disorders' by nausea (8.5%, 5.4%, 3.1%), and in the system organ class 'nervous system disorders' by dizziness (11%, 8.2%, 7.1%) and headache (8.5%, 7.1%, 5.8%).

The adverse event dizziness appeared to show a dose-response effect with 0%, 9%, and 11% in patients treated with abaloparatide 20 µg, 40 µg, and 80 µg, respectively, and 4% on both teriparatide and placebo in study BA058-05-002. The higher frequency of abaloparatide in the system organ class (SOC) 'cardiac disorders' was mainly driven by the increased rate of palpitations.

Hypercalciuria occurred slightly less frequently in patients on abaloparatide than on teriparatide (16% vs 18%) but more often than on placebo (13%).

The highest incidence of TEAEs by SOC for the majority of SOCs occurred with an onset between 0 to < 2 months and the greatest differences among treatment groups were noted during this time period. For example, in the Cardiac disorders SOC, between 0 to < 2 months TEAEs were reported in 5.6%, 2. 8%, and 1.5% of abaloparatide, teriparatide and placebo subjects, respectively. Between 2 to < 6 months, the incidence of TEAEs declined within each treatment group for the Cardiac disorders SOC (2.2%, 1.2%, and 1.8%, respectively).

The diminishing differences in frequency of adverse events might partly be attributable to the differential drop-out between treatment groups; fewer patients on abaloparatide than on either teriparatide or placebo completed the 18 months trial BA058-05-003 and patients on abaloparatide dropped out earlier than on teriparatide or placebo.

Around 80% of adverse events were considered mild to moderate and the frequencies were comparable between treatment groups. Frequencies of severe adverse events were too low for a reliable comparison between groups.

The analyses of adverse events considered related to treatment by the investigators are in line with the analyses of adverse events independent of the relation to treatment.

In the analysis of the data from the follow-up study BA058-05-005 there were no relevant differences between patients previously treated with abaloparatide and those previously treated with placebo.

Adverse events of special interest

TEAEs were analysed to address key safety concerns potentially associated with the administration of abaloparatide. Adverse events of special interest (AESIs) include hypercalcaemia, hypercalciuria, hypersensitivity, orthostatic hypotension, renal impairment, palpitations, nausea and dizziness. These events represent the more frequent AEs for PTH analogues.

Hypercalcemia

Adverse events of hypercalcaemia occurred less frequently in patients treated with abaloparatide than those treated with teriparatide but more often than those treated with placebo. In study BA058-05-003 hypercalcaemia AEs occurred more often on teriparatide (4.8%) than abaloparatide (2.2%) or placebo (0.6%). Severe or serious hypercalcaemia AEs were reported for no patient on abaloparatide or placebo compared to 1 (0.1%) serious AE considered related to treatment on teriparatide. The percentage of patients who discontinued treatment due to hypercalcaemia AEs was numerically higher on teriparatide (0.6%) compared to abaloparatide (0.3%). There was no evidence of an increase in the incidence of hypercalcaemia with increasing doses of abaloparatide in study BA058-05-002. The incidences of hypercalcaemia related AEs and adverse reactions did not tend to increase with decreasing renal function.

Based on laboratory data, hypercalcemia [albumin-adjusted serum calcium value ≥ 10.7 mg/dL (or 2.67 mmol/L)] occurred in 41 (6%) patients in the teriparatide, 23 (3%) in the abaloparatide and 2 (0.4%) of the placebo treated patients.

Hypercalciuria

The incidence of hypercalciuria was lower in patients on abaloparatide than on teriparatide but higher than on placebo. In study BA058-05-003 the incidence of hypercalciuria AEs was slightly lower on abaloparatide (16%) than on teriparatide (18%); it was higher than in the placebo group (13%). No patient on abaloparatide or on placebo experienced a severe or serious hypercalciuria AE while for 1 patient (0.1%) on teriparatide a serious AE hypercalciuria considered related to treatment was reported. Approximately 89% of TEAEs of hypercalciuria in the abaloparatide treated group resolved with no medical treatment or any other intervention required. In the remaining proportion of subjects hypercalciuria was ongoing at the end of study.

Based on laboratory data, the overall incidence of urine calcium:creatinine ratio > 400 mg/g was lower with abaloparatide vs. teriparatide (19.6% vs. 24.4%). Similar results were obtained with the threshold of urine calcium:creatinine ratio > 300 mg/g (46.1% vs. 52.5%).

Renal impairment

In study BA058-05-003, the analyses of adverse events of renal impairment did not reveal significant differences between abaloparatide (7%), teriparatide (4%), and placebo groups (7%). Renal failure was reported in 6 patients treated with abaloparatide vs 2 teriparatide and 3 placebo treated patients. Upon medical review of individual patient data, the vast majority of patients with a preferred term of renal failure actually had decreases in creatinine clearance without any renal impairment signs and/or symptoms. Analysis of renal CT-scans in a subset of patients from study BA058-05-003 to assess kidney calcification did not reveal an increased incidence of calculi with abaloparatide. The mean change from baseline for 24-hour urine creatinine clearance was greater over time in the abaloparatide and teriparatide groups vs. placebo. By Month 18, mean change from baseline was -8.4 mL/minute for the abaloparatide- SC group, -6.8 mL/minute teriparatide group, and -3.3 mL/minute in the placebo group. The mean change from baseline levels for the Cockcroft-Gault estimated serum creatinine clearance over time was -0.3 mL/min for placebo, -2.6 mL/min for abaloparatide and -2.5 mL/min in teriparatide groups.

Clinically notable laboratory values for urine with > 50 RBC/high power field (hpf) were lower in the placebo group (18.8%) vs. abaloparatide, but comparable between the abaloparatide and teriparatide groups (25.1% vs. 24.0%, respectively).

Bone safety

In Study BA058-05-003, a subset of patients in the placebo (n=28), abaloparatide (n=30) and teriparatide (n=22) groups underwent bone biopsies of the anterior iliac crest between Visit 8 (Month 12) and the End-of-Treatment Visit (Visit 9, Month 18) for assessment of quantitative bone histomorphometry using a dual-labelling procedure. The histomorphometry was performed on 62 (77.5%) of the 80 specimens. The bone biopsy analysis did not indicate a pathological effect of abaloparatide on bone parameters, but histomorphometry also did not show evidence of bone anabolic effects by abaloparatide or teriparatide somewhat questioning the sensitivity of the analysis.

The objective of study BA058-05-020 was to evaluate the early effects of self-administrated 80µg abaloparatide on indices of bone formation and included 23 postmenopausal women with osteoporosis. Treatment with abaloparatide for 3 months stimulated bone formation on cancellous, endocortical, intracortical, and periosteal envelopes in transiliac bone biopsies obtained.

Injection site reactions, hypersensitivity

In study BA058-05-003, the incidence of events within the hypersensitivity AESI was across the 3 treatment groups was (9.9%, 12.7% and 12.4% in the placebo, abaloparatide and teriparatide groups, respectively).

No clinically relevant differences across treatment groups in local tolerance events for pain, swelling, or tenderness were reported in patient diaries from study BA058-05-003. Redness was slightly more often reported in the teriparatide than in the abaloparatide group, but teriparatide was applied open-label limiting the validity of the comparison.

In study BA058-05-002 the incidence of hypersensitivity AESIs did not increase as a function of the dose of abaloparatide. In study ITM-058-301, the incidence of AEs related to hypersensitivity reactions was higher in the abaloparatide group (14.3% [20/140]) than in the placebo group (8.3% [6/72]). Neither SAEs nor AEs leading to discontinuation of administration related to hypersensitivity occurred in the abaloparatide group.

Orthostatic hypotension

The incidences of any orthostatic hypotension, defined as a decrease in systolic blood pressure (SBP) of ≥20 mmHg from supine to standing or in diastolic blood pressure (DBP) of ≥10 mmHg from supine to standing in a post-dose blood pressure measurement was observed in 15.7.%, 12.7% and 13.1% abaloparatide, teriparatide, and placebo subjects, respectively. In addition, the incidences of, palpitations, nausea, and dizziness were higher on abaloparatide, than teriparatide or placebo and the percentage of subjects who discontinued treatment due to orthostatic hypotension adverse events was higher on abaloparatide compared to teriparatide and placebo.

Orthostatic hypotension as an adverse event of special interest (covering the PTs: Orthostatic hypotension, Dizziness, Nausea, Palpitations, Fatigue, Vertigo, Tachycardia Tinnitus, Muscular weakness, Syncope, Fall, Loss of consciousness, Presyncope, Sinus tachycardia, Vision blurred, Visual impairment, Arrhythmia, Balance disorder, Gait disturbance, Blood pressure orthostatic decreased, Confusional state, Visual acuity reduced) was higher for the abaloparatide group than for the placebo or the teriparatide group. In Study BA058-05-003, this occurred in 28.4% of patients on abaloparatide, 19.8% on teriparatide, and 14.4% on placebo. The percentage of patients reporting serious orthostatic hypotension AEs was low and comparable between groups (0.3%, 0.6%, and 0.3% on abaloparatide, teriparatide, and placebo, respectively). On the other hand, orthostatic hypotension reported as a single preferred term was reported in 1.0%, 0.4%, and 0.6% in abaloparatide, teriparatide, and placebo subjects, respectively. The percentage of subjects who discontinued treatment due to orthostatic hypotension AEs was 3.6%, 1.7%, and 0.9% on abaloparatide, teriparatide, and placebo, respectively.

In Study BA058-05-002, orthostatic hypotension AESIs were reported at a higher rate in the abaloparatide 40 and 80 ug groups than in the placebo and abaloparatide 20 ug group (26% and 22% vs. 7% and 0).

In Japanese study ITM-058-301, the incidence of AEs related to orthostatic hypotension in Study ITM-058-301 was 17.1% (24/140) in the abaloparatide- SC group and 9.7% (7/72) in the placebo group.

Increase in heart rate may be associated with orthostatic hypotension, since abaloparatide has vasodilating effect which may result in decreases in blood pressure and consequently in increases of the heart rate. In addition, abaloparatide has a direct chronotropic effect on the heart which can result in increased heart rate.

Table 38. Incidence of Adverse Events Associated With Orthostatic Hypotension in Studies 002 and BA058-05-003

	Study 003			Study 002				
	Placebo 0-18 mo N = 687 n (%)	ABL-SC 80 µg 0-18 mo N = 694 n (%)	Teriparatide SC 0-18 mo N = 686 n (%)	Placebo 0-28 wks N = 45 n (%)	ABL-SC 20 µg 0-28 wks N = 43 n (%)	ABL-SC 40 µg 0-28 wks N = 43 n (%)	ABL-SC 80 µg 0-28 wks N = 45 n (%)	Teriparatide SC 0-28 wks N = 45 n (%)
TEAE	99 (14.4)	197 (28.4)	136 (19.8)	3 (6.7)	0	11 (25.6)	10 (22.2)	5 (11.1)
Related TEAE	34 (4.9)	112 (16.1)	71 (10.3)	1 (2.2)	0	4 (9.3)	8 (17.8)	1 (2.2)
Severe TEAE	4 (0.6)	6 (0.9)	0	0	0	0	1 (2.2)	0
Serious TEAE	2 (0.3)	2 (0.3)	4 (0.6)	0	0	0	0	0
Serious Related TEAE	0	0	0	0	0	0	0	0
AE leading to death	0	0	0	0	0	0	0	0
AE leading to discontinuation[1]	6 (0.9)	25 (3.6)	12 (1.7)	0	0	1 (2.3)	0	0
Preferred Term								
Dizziness	49 (7.1)	77 (11.1)	56 (8.2)	2 (4.4)	0	4 (9.3)	5 (11.1)	2 (4.4)
Nausea	21 (3.1)	59 (8.5)	37 (5.4)	0	0	5 (11.6)	2 (4.4)	2 (4.4)
Palpitations	3 (0.4)	39 (5.6)	12 (1.7)	0	0	0	3 (6.7)	1 (2.2)
Fatigue	9 (1.3)	18 (2.6)	13 (1.9)	0	0	2 (4.7)	0	0
Vertigo	9 (1.3)	14 (2.0)	14 (2.0)	0	0	1 (2.3)	0	0
Tachycardia	2 (0.3)	9 (1.3)	3 (0.4)	0	0	0	0	0
Tinnitus	1 (0.1)	10 (1.4)	4 (0.6)	0	0	0	0	0
Orthostatic hypotension	4 (0.6)	7 (1.0)	3 (0.4)	0	0	0	0	0
Muscular weakness	2 (0.3)	6 (0.9)	4 (0.6)	0	0	0	0	0
Syncope	9 (1.3)	5 (0.7)	7 (1.0)	1 (2.2)	0	2 (4.7)	1 (2.2)	0
Fall	2 (0.3)	3 (0.4)	2 (0.3)	0	0	1 (2.3)	1 (2.2)	1 (2.2)
Loss of consciousness	2 (0.3)	2 (0.3)	2 (0.3)	0	0	0	0	0
Presyncope	0	2 (0.3)	0	0	0	0	0	0
Sinus tachycardia	1 (0.1)	2 (0.3)	0	0	0	0	0	0
Vision blurred	2 (0.3)	1 (0.1)	2 (0.3)	0	0	0	0	0
Visual impairment	0	2 (0.3)	1 (0.1)	0	0	0	0	0
Arrhythmia	2 (0.3)	1 (0.1)	2 (0.3)	0	0	0	0	0
Balance disorder	0	1 (0.1)	0	0	0	0	0	0
Gait disturbance	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	0	0
Blood pressure orthostatic decreased	0	0	1 (0.1)	0	0	0	0	0
Confusional state	1 (0.1)	0	0	0	0	0	0	0
Visual acuity reduced	1 (0.1)	0	3 (0.4)	0	0	0	0	0
Vertigo positional	0	0	0	0	0	1 (2.3)	0	0

1 In Study BA058-05-002, AEs leading to discontinuation were reported.
Each patient was counted once for the same MedDRA grouping level.

Palpitations

Palpitations AESI included the following PTs terms: palpitations, tachycardia, atrial fibrillation, extrasystoles, ventricular extrasystoles, sinus tachycardia, arrhythmia, atrial flutter, arrhythmia supraventricular, and sinus arrhythmia. The increased incidence of TEAEs associated with palpitations in the abaloparatide group of 8.5% (vs 3.5% teriparatide, 2.3% placebo) of Study BA058-05-003 was driven primarily by palpitations and tachycardia.

Palpitations were also observed in study ITM-058-301 and BA058-05-020. Study ITM-058-301 reported an elevated number of relevant TEAEs with treatment-related palpitations (n=7, 5.0 %) and supraventricular extrasystoles (n=4, 2.9 %) in the abaloparatide group compared to only one case of supraventricular extrasystoles (n=1, 1.4 %) in the placebo group. Furthermore, Study BA058-05-020 reported one serious case of atrial fibrillation and one mild case of palpitations.

Table 39. Incidence of Adverse Events Potentially Associated with Palpitation in Study BA058-05-003

	Placebo	Abaloparatide-SC	Teriparatide
	0-18 mo	0-18 mo	0-18 mo
	N = 687	N = 694	N = 686
	n (%)	n (%)	n (%)
TEAE	16 (2.3)	59 (8.5)	24 (3.5)
Related TEAE	4 (0.6)	35 (5.0)	13 (1.9)
Severe TEAE	0	1 (0.1)	1 (0.1)
Serious TEAE	0	1 (0.1)	2 (0.3)
AE Leading to Discontinuation	2 (0.3)	8 (1.2)	1 (0.1)
Preferred Term			
Palpitations	3 (0.4)	39 (5.6)	12 (1.7)
Tachycardia	2 (0.3)	9 (1.3)	3 (0.4)
Atrial Fibrillation	3 (0.4)	5 (0.7)	3 (0.4)
Extrasystoles	2 (0.3)	3 (0.4)	1 (0.1)
Ventricular extasystoles	4 (0.6)	3 (0.4)	4 (0.6)
Sinus tachycardia	1 (0.1)	2 (0.3)	0
Arrhythmia	2 (0.3)	1 (0.1)	2 (0.3)
Atrial flutter	0	1 (0.1)	1 (0.1)
Arrhythmia supraventricular	0	0	1 (0.1)

Each patient was counted once for the same MedDRA grouping level.

Cardiovascular events

A detailed review of CV-related AEs, including major adverse CV events (MACE) and heart failure (HF) was conducted to assess the CV safety profile of abaloparatide using HR, blood pressure (BP) measurements, and AEs potentially associated with changes in HR and BP and to determine the frequency of MACE after abaloparatide treatment.

Furthermore, in the observational study BA058-05-028, the safety objective was to evaluate the CV safety of abaloparatide for the treatment of osteoporosis in postmenopausal women in the real-world healthcare setting in the USA compared with teriparatide.

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

Heart rate

In Study BA058-05-003, treatment with abaloparatide and teriparatide was associated with an increase in HR, compared with placebo.

The mean increase in HR from baseline in the abaloparatide group ranged, from Day 1 to Month 12, between 6.9 and 7.8 bpm at one-hour post-injection. For teriparatide, the corresponding range was 5.5.to 6.7 bpm, and for placebo 1.0 to 1.9 bpm.

About 42% of patients experienced an increase in HR of >15 bpm from baseline at any time point in the abaloparatide group, compared to 31% in the teriparatide group and 10% for placebo.

The maximum 1-hour post-dose HR distributions for abaloparatide and teriparatide differ by a mean and median HR of 1.7 and 1.0 bpm respectively, higher for abaloparatide than for teriparatide. a higher percentage (greater frequency) of abaloparatide patients had high HRs than for teriparatide or placebo patients (HR ≥ 105 bpm, 3.2% abaloparatide, 1.6% teriparatide and 0.3% placebo).

Table 40. Patients with Increases in Heart Rate from Pre-dose to Post-dose at Any Visit (Study BA058-05-003 Safety Population, excluding the two excluded sites (data presented in the previous MAA)

Variable	Statistics[1]	Placebo (N=687) Increase (bpm)	Abaloparatide-SC (N=694) Increase (bpm)	Teriparatide (N=686) Increase (bpm)
> 5 bpm	n (%)	443 (64.5%)	620 (89.3%)	586 (85.4%)
	Median (Min, Max)	10.0 (6, 29)	15.0 (6, 58)	13.0 (6, 39)
	# occurrences/subject: Median (Min, Max)	2.0 (1, 6)	3.0 (1, 6)	3.0 (1, 6)
> 10 bpm	n (%)	208 (30.3%)	476 (68.6%)	408 (59.5%)
	Median (Min, Max)	14.0 (11, 29)	17.0 (11, 58)	16.0 (11, 39)
	# occurrences/subject: Median (Min, Max)	1.0 (1, 6)	2.0 (1, 6)	2.0 (1, 6)
> 15 bpm	n (%)	69 (10.0%)	288 (41.5%)	210 (30.6%)
	Median (Min, Max)	19.0 (16, 29)	20.0 (16, 58)	19.0 (16, 39)
	# occurrences/subject: Median (Min, Max)	1.0 (1, 3)	1.0 (1, 6)	1.0 (1, 6)
> 20 bpm	n (%)	22 (3.2%)	137 (19.7%)	75 (10.9%)
	Median (Min, Max)	24.0 (21, 29)	24.0 (21, 58)	23.0 (21, 39)
	# occurrences/subject: Median (Min, Max)	1.0 (1, 3)	1.0 (1, 6)	1.0 (1, 5)
> 25 bpm	n (%)	5 (0.7%)	55 (7.9%)	25 (3.6%)
	Median (Min, Max)	28.0 (26, 29)	30.0 (26, 58)	29.0 (26, 39)
	# occurrences/subject: Median (Min, Max)	1.0 (1, 1)	1.0 (1, 5)	1.0 (1, 5)
> 30 bpm	n (%)	0	27 (3.9%)	8 (1.2%)
	Median (Min, Max)	-	35.0 (31, 58)	34.0 (31, 39)
	# occurrences/subject: Median (Min, Max)	-	1.0 (1, 4)	1.0 (1, 2)
> 40 bpm	n (%)	0	5 (0.7%)	0
	Median (Min, Max)	-	45.0 (41, 58)	-
	# occurrences/subject: Median (Min, Max)	-	1.0 (1, 1)	-

Data source: Table 95-6-1 excluding the 2 EU sites
*Heart rate assessed by pre-dose and post-dose ECGs at each study visit.
[1] Percentages based on the number of patients in the Safety Population. Median, min and max based on the maximum increase for each subject.

Besides a post-injection increase in heart rate compared to placebo evaluations of electrocardiograms did not indicate clinically relevant changes.

Arrhythmia

Tachycardia and sinus tachycardia

An analysis of incidence of TEAEs related to tachycardia was done for Study BA058-05-003.

Table 41. At least one TEAE related to tachycardia in study BA058-05-003

At least one TEAE	Placebo N=687 n	Abaloparatide N=694 n	Teriparatide N=686 n
Tachycardia	2	9	3
Sinus tachycardia	1	2	0
TOTAL	3 (0.4%)	11 (1.6%)	3 (0.4%)

An analysis of incidence of TEAEs related to other arrhythmias (PT arrhythmia, arrhythmia supraventricular, atrial fibrillation, atrial flutter, extrasystoles, supraventricular extrasystoles, supraventricular tachycardia, and ventricular extrasystoles) was reported at similar frequencies in all three treatment groups, in the placebo group at 2.3%, abaloparatide at 2.6%, and teriparatide at 2.0%. None of the TEAEs were considered serious, and 2 subjects discontinued from the study, in the placebo group due to 1 incidence of arrhythmia and in the abaloparatide group due to 1 incidence of extrasystoles.

MACE and MACE plus HF

MACE was defined as non-fatal myocardial infarction, non-fatal stroke, CV death. Preferred terms for MACE included acute MI, basal ganglia stroke, cerebral thrombosis, cerebrovascular accident, haemorrhage intracranial, ischemic stroke, lacunar infarction, left ventricular failure, MI, aortic dissection, cardio-respiratory arrest, myocardial ischemia, sudden death, cardiac failure, cardiac failure chronic, cardiac failure congestive.

For Studies BA058-05-003, a post hoc analysis of CV outcomes was conducted and included the percentages of participants with AEs potentially associated with changes in HR and BP, MACE, MACE + HF, and time to first incidence of MACE and MACE + HF. Preferred terms for MACE included acute MI, basal ganglia stroke, cerebral thrombosis, cerebrovascular accident, haemorrhage intracranial, ischemic stroke, lacunar infarction, left ventricular failure, MI, aortic dissection, cardio-respiratory arrest, myocardial ischemia, sudden death, cardiac failure, cardiac failure chronic, cardiac failure congestive. Clinical judgement was used to group AEs that were increased with abaloparatide and teriparatide and were potentially associated with changes in HR or BP. Neither treatment with abaloparatide or teriparatide was associated with an increase in serious cardiac AEs.

Table 42. Incidences of MACE and HF in Study BA058-05-003

Study BA058-05-003 – 19 Months	Placebo	Abaloparatide	Teriparatide
MACE	8/687 (1.2%)	3/694(0.4%)	5/686 (0.7%)
K-M Estimated event rate (95% CI)	1.4 (0.69,2.75)	0.5 (0.18, 1.69)	0.8 (0.34, 1.96)
MACE + HF	12/687 (1.7%)	3/694 (0.4%)	5/686 (0.7%)
K-M Estimated event rate (95% CI)	2.1 (1.18, 3.63)	0.5 (0.18, 1.69)	0.8 (0.34, 1.96)

Results from the extension Study BA058-05-005, in which participants from the abaloparatide and placebo groups from Study BA058-05-003 were switched to alendronate for 24 months, indicated that the frequency of MACE and time to first incidence of MACE was similar between groups once abaloparatide was discontinued.

Study BA058-05-028

The retrospective observational Study BA058-05-028 analysed as a secondary endpoint, the specific risk for serious CV events after treatment with abaloparatide or teriparatide, respectively. Please see the efficacy section for full description and the integrated discussion of both efficacy and safety results.

2.5.8.3. *Serious adverse event/deaths/other significant events*

As regards deaths and serious adverse events the analyses did not indicate clinically relevant differences between groups. There were 75 SAEs in 62 (8.9%) subjects in the abaloparatide group, 80 SAEs in 64 (9.3%) subjects in the teriparatide group and 76 SAEs in 65 (9.5%) subjects in the placebo group reported in the 18 months pivotal Phase 3 Study BA058-05-003. None of the SAEs in patients receiving abaloparatide or placebo were assessed as treatment-related. In this study, 3 deaths occurred in patients on placebo and on abaloparatide each and 2 on teriparatide; none of these deaths were considered related to study medication.

During the first 6 months of study BA058-05-005 there was 1 death in a patient switched from abaloparatide and overall there were 2 additional AEs leading to death, 1 each in the placebo / alendronate and abaloparatide / alendronate group; none of these deaths were considered related to study medication. However, numbers are too small for a final assessment of differences in the incidence of death and serious adverse events possibly attributable to abaloparatide.

In the first 6 months of the follow-up study BA058-05-005, 6 events (brain neoplasm, colon cancer, intestinal adenocarcinoma, leiomyosarcoma, lung neoplasm malignant, renal cancer) were reported in the SOC 'neoplasms benign, malignant and unspecified (incl. cysts and polyps)' in patients previously on abaloparatide versus none in patients previously on placebo; however no difference was seen at later points during the trial.

2.5.8.4. Laboratory findings

Clinical chemistry

The percentage of patients with uric acid above upper normal limit was lower in the abaloparatide than in the teriparatide group but increased compared to placebo. Levels of 1,25 dihydroxyvitamin D, 25-hydroxyvitamin D, and PTH intact were also increased in line with the therapeutic effect of abaloparatide.

Vital signs

Vital sign measures included blood pressure (BP), heart rate (HR), body temperature and respiration rate. By end of treatment vital sign values were similar to baseline values and without notable differences between treatment groups. As discussed elsewhere in the report abaloparatide and teriparatide showed a marked increase in heart rate post injection versus placebo where no notable changes were seen.

Electrocardiograms and thorough QTC study

In study BA058-05-003, ECGs were performed pre-dose and 1-hour post-dose at regular intervals. The table below summarises the heart rate data at baseline and post-injection assessments.

Table 43. Study BA058-05-003. Heart rate at baseline and post-injection at Day 1, Month 1, Month 3 and Month 12

Visit: Timepoint Statistic	Placebo (N=687) Value	Placebo (N=687) Change from Baseline	Abaloparatide-SC (N=694) Value	Abaloparatide-SC (N=694) Change from Baseline	Teriparatide (N=686) Value	Teriparatide (N=686) Change from Baseline
Baseline						
n	687		694		686	
Mean (SD)	65.8 (9.56)		66.2 (10.13)		66.2 (9.43)	
Median	65.0		65.0		65.0	
Q1, Q3	59.0, 72.0		60.0, 72.0		60.0, 72.0	
Min, Max	41, 102		45, 99		43, 106	
Day 1: Post-Injection						
n	685	685	690	690	684	684
Mean (SD)	67.2 (10.08)	1.4 (7.11)	74.0 (11.36)	7.8 (8.60)	71.7 (10.45)	5.5 (7.40)
Median	66.0	2.0	73.0	7.0	71.0	5.0
Q1, Q3	60.0, 73.0	-3.0, 5.0	65.0, 81.0	2.0, 13.0	65.0, 77.0	1.0, 10.0
Min, Max	42, 107	-26, 25	49, 115	-33, 42	41, 118	-34, 38
Month 3: Post-Injection						
n	618	618	597	597	623	623
Mean (SD)	66.9 (9.54)	1.2 (8.65)	73.7 (11.31)	7.5 (9.69)	71.7 (10.20)	5.5 (8.96)
Median	66.0	1.5	72.0	7.0	71.0	6.0
Q1, Q3	60.0, 73.0	-4.0, 7.0	66.0, 80.0	2.0, 13.0	65.0, 78.0	0.0, 11.0
Min, Max	40, 116	-26, 27	44, 113	-31, 39	47, 109	-25, 39
Month 6: Post-Injection						
n	594	594	568	568	600	600
Mean (SD)	66.7 (9.57)	1.0 (8.50)	73.0 (10.95)	6.9 (10.12)	72.8 (10.52)	6.7 (9.28)
Median	66.0	1.0	72.0	6.0	72.0	6.0
Q1, Q3	60.0, 73.0	-4.0, 7.0	65.0, 79.0	1.0, 13.0	66.0, 79.0	0.0, 12.0
Min, Max	41, 99	-32, 33	42, 118	-23, 43	45, 112	-19, 37
Month 9: Post-Injection						
n	575	575	550	550	580	580
Mean (SD)	67.4 (10.18)	1.9 (8.95)	73.6 (11.08)	7.5 (10.26)	72.3 (10.62)	6.2 (9.78)
Median	66.0	1.0	72.5	7.0	71.0	6.0
Q1, Q3	61.0, 73.0	-4.0, 7.0	66.0, 81.0	2.0, 14.0	65.0, 78.0	0.0, 12.0
Min, Max	41, 117	-31, 48	48, 124	-25, 49	47, 119	-31, 48
Month 12: Post-Injection						
n	559	559	526	526	562	562
Mean (SD)	67.1 (9.47)	1.6 (8.71)	73.4 (10.92)	7.3 (10.53)	72.5 (10.52)	6.4 (8.70)
Median	66.0	2.0	72.0	7.0	72.0	6.0
Q1, Q3	61.0, 73.0	-4.0, 7.0	66.0, 79.0	1.0, 13.0	65.0, 79.0	1.0, 12.0
Min, Max	42, 107	-34, 27	51, 113	-24, 50	39, 105	-15, 35

Abaloparatide and teriparatide markedly increased heart rate post injection versus placebo. The mean increase from baseline in the abaloparatide group was stable and ranged (from Day 1 to month 12) between 6.9 and 7.8 bpm. For teriparatide the increase in heart rate post-dose was lower and ranged 5.5 to 6.7 bpm from Day 1 to month 12 during this period. The number of observations decreases over time. Study discontinuations due to palpitations may have contributed to this loss of observations which may have led to

an underestimation of the mean increase in heart rate post-injection. For placebo, the mean increase post-injection was 1.2 to 1.9 bpm. Pre-injection heart rate values were similar to baseline values for all time points in all three groups. Overall, 12.5%, 4.8%, and 0.6% of patients on abaloparatide, teriparatide, and placebo, respectively, had an increase in heart rate >25 bpm at any time.

Thorough QTC study

In addition to assessment of ECG parameters in phase I studies 127-001, 001, 001B, 010, and 011, a thorough QTC study (study BA058-05-012) in 48 healthy volunteers has been performed. In study 012, two different doses of abaloparatide were tested and compared with placebo and a positive control (moxifloxacin 400 µg orally). The table below summarizes the heart rate data (changes vs. baseline) up to 24 hours.

Table 44. Thorough QTC study (BA058-05-012). Changes in heart rate for abaloparatide 80 mcg and placebo

Timepoint (post dose)	Statistic	Abaloparatide 80 µg N=52	Placebo N=51
15 minutes	Mean (SD) Median (Min, Max)	14.6 (5.5) 14.6 (4.0, 29.1)	0.1 (2.3) 0.3 (-5.8, 5.0)
30 minutes	Mean (SD) Median (Min, Max)	13.7 (6.5) 12.6 (0.8, 32.2)	0.6 (3.0) -0.1 (-7.1, 6.8)
45 minutes	Mean (SD) Median (Min, Max)	10.8 (6.3) 10.6 (-2.1, 31.4)	0.5 (3.3) -0.4 (-5.8, 11.8)
1 hour	Mean (SD) Median (Min, Max)	9.5 (7.1) 8.6 (0.6, 39.3)	0.9 (3.0) 1.3 (-6.7, 6.8)
1.5 hour	Mean (SD) Median (Min, Max)	7.2 (6.7) 5.8 (-9.5, 28.8)	-0.0 (3.8) 0.1 (-9.7, 7.3)
2 hours	Mean (SD) Median (Min, Max)	6.1 (6.7) 4.9 (-10.5, 25.0)	0.9 (3.7) 0.3 (-9.4, 9.9)
2.5 hours	Mean (SD) Median (Min, Max)	5.0 (7.5) 3.5 (-15.9, 27.6)	0.0 (4.3) 0.6 (-11.1, 12.7)
4 hours	Mean (SD) Median (Min, Max)	5.1 (7.3) 3.4 (-9.5, 31.6)	1.4 (4.1) 1.3 (-14.1, 14.4)
6 hours	Mean (SD) Median (Min, Max)	11.1 (7.7) 10.7 (-5.2, 41.0)	8.8 (5.3) 7.9 (-2.2, 21.0)
8 hours	Mean (SD) Median (Min, Max)	8.1 (6.8) 8.3 (-6.5, 26.7)	4.1 (3.7) 3.4 (-2.0, 13.1)
12 hours	Mean (SD) Median (Min, Max)	9.5 (6.4) 9.5 (-9.4, 26.9)	7.3 (6.6) 7.7 (-11.4, 21.7)
24 hours	Mean (SD) Median (Min, Max)	3.6 (4.1) 3.5 (-4.7, 13.1)	3.7 (3.6) 3.1 (-2.0, 13.6)

In this single-injection study, abaloparatide caused a dose-related increase of heart rate, which peaked at 15 -30 min (the first two post-dosing assessment) with mean increases of ~15 bpm and ~20 bpm after dosing of 80 µg and 240 µg, respectively. The maximum increase in an individual subject in the 80 µg group was seen at 1 hour post-dose with 39.3 bpm. The mean increase 1-hour post-dose (9.5 bpm) in the 80 µg group was somewhat higher than in study BA058-05-003. Significant increases persisted in heart rate up to 12 hours (mean 9.5 bpm) in the QT study. However, elevations were seen also in the placebo group after 12 hours

(mean 7.3 bpm) but still less than for abaloparatide. The heart rate had almost returned to baseline and was comparable to placebo at 24 h, i.e. the proposed time point for the next injection in a clinical setting.

According to the study protocol, the primary PD endpoint was the time-matched, placebo-adjusted change from baseline in QTcF (Fridericia). The protocol allowed for switch to the "individualised" method if certain criteria were fulfilled which included a slope >|0.045| of the linear regression of QTcF versus RR and 2/3 of the subjects have their individual linear regression slopes >|0.045|.
Using Fridericia´s correction, the largest placebo-corrected ΔQTcF was observed 30 min after dosing and reached 6.8 ms (90% CI: 4.5 to 9.2) and 9.6 ms (90% CI: 7.3 to 12.0) in the 80 µg and 240 µg group, respectively. For the 80 µg dose of abaloparatide, using Fridericia´s correction, the study fulfilled the criterion for a negative QT study with an upper bound just below 10 ms. The 240 µg dose resulted in an upper bound above 10 ms.
When the "individualised" correction method was applied, the upper limit for the confidence interval on the corrected QT interval did not exceed 10 ms in either of the treatment groups. The largest placebo-corrected ΔQTcI was observed 30 min after dosing and reached 5.3 ms (90% CI: 2.7 to 8.0) and 7.1 ms (90% CI: 4.4 to 9.7) in the 80 µg and 240 µg group, respectively. Thus, by using this method the study fulfilled the criterion for a negative QT study (according to ICH E14 guideline) for both doses.

The marked mean post-dose increase in heart rate values observed in the thorough QT study and in study BA058-05-003 is of concern. In addition, the pivotal study had extensive exclusion criteria based on ECG findings and medical history of cardiovascular disease. Cardiovascular events have been studied post marketing in an observational study in the US but results from this study have limitations. Therefore, adequate wording in the PI is needed to mitigate the risks of cardiovascular events associated with the markedly increased heart rate in the general osteoporosis population where concomitant cardiovascular diseases are expected to be more common than in the pivotal clinical study.

2.5.8.5. Safety in special populations

<u>Age</u>

The majority (65%) of subjects were in the 65 to < 75 years age group (Study BA058-05-003). In the analysis by age groups <65 years, 65 to <75 years, and ≥75 years the SOC 'vascular disorders' occurred with a higher frequency in the abaloparatide than in the placebo group and showed an age-related trend; a higher percentage of patients ≥75 years of age in the abaloparatide group reported hypertension than in the teriparatide or placebo groups.
Only 4 patients (0.2%) were ≥85 years of age, 1 patient on abaloparatide (85 years) and 3 patients on placebo (85 and 86 years). The incidence of serious TEAEs (SAEs) generally increased with age group, with the exception of SAEs in teriparatide-treated patients where the incidence was similar in patients <65 and 65- 74 years of age; there were no SAEs reported in the 4 patients aged 85 or 86 years. TEAEs leading to drop-out were not significantly higher in patients 75-84 years of age as compared to those 65-74 years in any treatment group; the incidence was slightly lower in patients <65 years in all treatment groups. No patients aged ≥ 85 years dropped out of the study.

No significant clinically relevant trends were observed for the subgroups of age in Study BA058-05-003, see table below.

In Study ITM-058-301, a simple comparison of the incidence is not possible because the number of subjects aged ≥ 75 years was small, 21 subjects were aged ≥ 75 years.

In study BA058-05-028, the mean age was approximately 67,5 years and approximately 25% of the patients were ≥ 75 years.

Table 45. Summary of Treatment Emergent Adverse Events Observed in the study BA058-05-003 Safety Population Stratified by Age Group

MedDRA Terms	Treatment Group	All Ages n/N (%)	Age < 65 n/N (%)	Age65-74 n/N (%)	Age75-84 n/N (%)	Age 85+ n/N (%)
Total AEs	Placebo	607/687 (88.4)	85/101 (84.2)	406/453 (89.6)	114/130 (87.7)	2/3 (66.7)
	Abaloparatide-SC	627/694 (90.3)	88/101 (87.1)	412/454 (90.7)	126/138 (91.3)	1/1 (100)
	Teriparatide	614/686 (89.5)	90/99 (90.9)	392/443 (88.5)	132/144 (91.7)	0
Serious AEs - Total	Placebo	65/687 (9.5)	7/101 (6.9)	39/453 (8.6)	19/130 (14.6)	0
	Abaloparatide-SC	62/694 (8.9)	4/101 (4.0)	41/454 (9.0)	17/138 (12.3)	0
	Teriparatide	64/686 (9.3)	9/99 (9.1)	36/443 (8.1)	19/144 (13.2)	0
- Fatal	Placebo	3/687 (0.4)	0	2/453 (0.4)	1/130 (0.8)	0
	Abaloparatide-SC	3/694 (0.4)	0	0	3/138 (2.2)	0
	Teriparatide	2/686 (0.3)	0	1/443 (0.2)	1/144 (0.7)	0
- Hospitalisation/prolong existing hospitalisation	Placebo	58/687 (8.4)	7/101 (6.9)	34/453 (7.5)	17/130 (13.1)	0
	Abaloparatide-SC	56/694 (8.1)	3/101 (3.0)	39/454 (8.6)	14/138 (10.1)	0
	Teriparatide	61/686 (8.9)	9/99 (9.1)	34/443 (7.7)	18/144 (12.5)	0
- Life-threatening	Placebo	3/687 (0.4)	0	3/453 (0.7)	0	0
	Abaloparatide-SC	3/694 (0.4)	1/101 (1.0)	0	2/138 (1.4)	0
	Teriparatide	3/686 (0.4)	0	1/443 (0.2)	2/144 (1.4)	0
- Disability/incapacity	Placebo	1/687 (0.1)	0	0	1/130 (0.8)	0
	Abaloparatide-SC	3/694 (0.4)	1/101 (1.0)	1/454 (0.2)	1/138 (0.7)	0
	Teriparatide	2/686	1/99	1/443	0	0
- Other (medically significant)	Placebo	11/687 (1.6)	0	9/453 (2.0)	2/130 (1.5)	0

Category	Treatment					
	Abaloparatide-SC	11/694 (1.6)	1/101 (1.0)	5/454 (1.1)	5/138 (3.6)	0
	Teriparatide	14/686 (2.0)	5/99 (5.1)	5/443 (1.1)	4/144 (2.8)	0
Psychiatric disorders (SOC)	Placebo	32/687 (4.7)	6/101 (5.9)	19/453 (4.2)	7/130 (5.4)	0
	Abaloparatide-SC	34/694 (4.9)	4/101 (4.0)	23/454 (5.1)	7/138 (5.1)	0
	Teriparatide	21/686 (3.1)	4/99 (4.0)	14/443 (3.2)	3/144 (2.1)	0
Nervous system disorders (SOC)	Placebo	135/687 (19.7)	21/101 (20.8)	89/453 (19.6)	25/130 (19.2)	0
	Abaloparatide-SC	175/694 (25.2)	24/101 (23.8)	113/454 (24.9)	38/138 (27.5)	0
	Teriparatide	136/686 (19.8)	17/99 (17.2)	93/443 (21.0)	26/144 (18.1)	0
Accidents and injuries (SMQ)	Placebo	64/687 (9.3)	7/101 (6.9)	39/453 (8.6)	17/130 (13.1)	1/3 (33.3)
	Abaloparatide-SC	49/694 (7.1)	3/101 (3.0)	35/454 (7.7)	11/138 (8.0)	0
	Teriparatide	50/686 (7.3)	7/99 (7.1)	29/443 (6.5)	14/144 (9.7)	0
Cardiac disorders (SOC)	Placebo	37/687 (5.4)	3/101 (3.0)	24/453 (5.3)	10/130 (7.7)	0
	Abaloparatide-SC	81/694 (11.7)	10/101 (9.9)	59/454 (13.0)	12/138 (8.7)	0
	Teriparatide	43/686 (6.3)	7/99 (7.1)	27/443 (6.1)	9/144 (6.3)	0
Vascular disorders (SOC)	Placebo	56/687 (8.2)	5/101 (5.0)	40/453 (8.8)	11/130 (8.5)	0
	Abaloparatide-SC	81/694 (11.7)	12/101 (11.9)	45/454 (9.9)	23/138 (16.7)	1/1 (100)
	Teriparatide	69/686 (10.1)	9/99 (9.1)	46/443 (10.4)	14/144 (9.7)	0
Cerebrovascular disorders (SMQ)	Placebo	10/687 (1.5)	0	8/453 (1.8)	2/130 (1.5)	0
	Abaloparatide-SC	5/694 (0.7)	2/101 (2.0)	3/454 (0.7)	0	0
	Teriparatide	5/686 (0.7)	1/99 (1.0)	4/443 (0.9)	0	0

Infections and infestations (SOC)	Placebo	271/687 (39.4)	34/101 (33.7)	189/453 (41.7)	46/130 (35.4)	2/3 (66.7)
	Abaloparatide-SC	274/694 (39.5)	32/101 (31.7)	176/454 (38.8)	66/138 (47.8)	0
	Teriparatide	271/686 (39.5)	39/99 (39.4)	181/443 (40.9)	51/144 (35.4)	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures [1]	Placebo	81/687 (11.8)	6/101 (5.9)	56/453 (12.4)	19/130 (14.6)	0
	Abaloparatide-SC	99/694 (14.3)	12/101 (11.9)	66/454 (14.5)	21/138 (15.2)	0
	Teriparatide	76/686 (11.1)	9/99 (9.1)	51/443 (11.5)	16/144 (11.1)	0
Other AE appearing more frequently in older subjects [2]	Placebo	333/687 (48.5)	58/101 (57.4)	213/453 (47.0)	60/130 (46.2)	2/3 (66.7)
	Abaloparatide-SC	391/694 (56.3)	64/101 (63.4)	244/454 (53.7)	82/138 (59.4)	1/1 (100)
	Teriparatide	345/686 (50.3)	66/99 (66.7)	209/443 (47.2)	70/144 (48.6)	0

Coded by MedDRA v17.1. N: number of subjects treated. n: number of subjects with events.
[1] Includes PTs of Ataxia, Cerebellar ataxia, Cerebral ataxia, Vestibular ataxia, Orthostatic hypotension, Blood pressure orthostatic decreased, Fall, Loss of consciousness, Syncope, Dizziness, and Dizziness postural, plus HLGT of Fractures, excluding those with HLT Fracture complications.
[2] Includes PTs of Leukopenia, Nausea, Upper respiratory tract infection, Influenza, Nasopharyngitis, Creatinine renal clearance increased, Creatinine renal clearance decreased, Blood triglycerides increased, Blood urea increased, Dizziness, Urine calcium/creatinine ratio increased, Blood uric acid increased, Arthralgia, Osteoarthritis, Headache, Depression, Hypertension and Hypercalcaemia

Race

The analysis of ethnic subgroups in Study BA058-05-003 is limited by the low number of subjects of other than Caucasian origin (about 80%); only a comparison of study participants of Asian or Caucasian origin has been provided and even numbers in the Asian subgroup are small. Thus no definite conclusions can be drawn of differences in safety of abaloparatide between ethnic groups.
The percentage of patients who experienced adverse events was higher in Asian compared to Caucasian patients, but the pattern between treatment groups was comparable for the majority of adverse events. There was no difference in medical history or the average number of concomitant medication between the 2 groups, but Asian patients were slightly older and had lower body weight than Caucasian patients. The applicant claims that older age and lower body weight may partially explain the slightly higher incidence of AEs in Asian patients. The analyses of adverse events by body weight indicated a general decrease in the incidence of adverse events with increasing body weight, but analysis of adverse events by age showed no clear relationship of age with the incidence of adverse events.
The system organ classes 'cardiac disorders' and 'nervous system disorders' were reported with a higher frequency in Asian compared to Caucasian patients and occurred more often with abaloparatide compared to teriparatide and placebo; preferred terms with this pattern were palpitation and dizziness, while no system

organ class or preferred term were reported with a higher frequency in the abaloparatide versus the placebo group and with a lower frequency in Asian compared to Caucasian patients.

Weight

As regards weight an analysis by subgroups <54 kg, 54 to <68 kg, and ≥68 kg has been provided. Overall, the percentage of subjects with adverse events considered related across these groups decreased with increasing weight.

Baseline Renal Impairment

The incidence of hypercalcaemia adverse events increased with decreasing renal function in the abaloparatide and teriparatide groups; in patients on abaloparatide the incidence of hypercalcaemia was similar between the subgroups creatinine clearance <60 mL/min and 60 to <90 mL/min.

Baseline Hepatic Function

No analysis of adverse events by baseline hepatic function is possible since no patient with baseline hepatic impairment was included in study BA058-05-003.

Gender

Pivotal study BA058-05-003 included only women and the current MAA is limited to postmenopausal osteoporosis.

The abaloparatide study ITM-058-301 consisted of 14 men and 126 women. No substantial gender related differences were observed in the incidences of AEs and adverse reactions by PT in this small study.

A dedicated study in male osteoporosis was completed in September 2021. A summary of TEAEs that occurred within the Cardiac disorders SOC or MACE + HF during the male osteoporosis Study BA058-05-019 (Study 019) were presented as requested in the Day 150 answers of the procedure. The available data suggest that men and women treated with abaloparatide have similar frequency and pattern (i.e., type) of CV events. No new safety concern was identified.

Tobacco usage

No relationship between adverse events and current or previous tobacco use in the past 5 years before study entry in patients treated with abaloparatide has been identified.

2.5.8.6. Immunological events

The incidence of hypersensitivity adverse events was comparable between abaloparatide and teriparatide.

During 18 months in study BA058-05-003 about half of the patients developed anti-abaloparatide antibodies and about one third showed neutralising antibodies. All subjects who received abaloparatide and were confirmed ADA positive at the end of Study BA058-05-003 and who were included in the extension Study BA058-05-005 were retested at six-month intervals for up to 97 months until the subject seroconverted to antibody-negative or were lost to follow-up. The number of patients with anti-abaloparatide antibodies declined during the extension period in study BA058-05-005, about one quarter was still antibody positive after 6 months into the extension. One subject (Subject 1010198) remained ADA positive for more than 6 years following cessation of abaloparatide treatment, and Radius recently discontinued collecting the 6-monthly immunogenicity samples from this subject with the FDA's approval. The antibodies for this subject were not cross reactive to PTH or PTHrP and were not neutralising.

Compared to antibody negative subjects, no differences in safety were observed for subjects that were antibody positive or that were positive for neutralising antibodies and who were followed up to 97 months. A similar percentage of subjects in the ADA+/NAb+ and all ADA+ subgroups compared with the ADA- subgroup had at least one AE in Study BA058-05-003.

In Study BA058-05-005, a lower percentage of subjects in the ADA+/NAb+ and all ADA+ subgroups compared with the ADA- subgroup (79.2% and 78.9%, respectively versus 83.6%) had at least one AE. AEs reported in a higher percentage (>2%) of subjects in the ADA+ subgroup compared with the ADA- subgroup included upper respiratory infection, hypercalciuria, urinary tract infection, and back pain. Conversely, AEs reported in a lower percentage (< 2%) of subjects in the ADA+ group compared with the ADA- group included nausea and palpitations. No trends in AEs were observed between the subgroups.

A similar percentage of subjects in the ADA+/NAb+ and all ADA+ subgroups compared with the ADA- subgroup (7.5% and 8.6%, respectively, versus 9.1%) had at least one SAE in Study BA058-05-003. In Study BA058-05-005, a lower percentage subjects in the ADA+/NAb+ and all ADA+ subgroups compared with the ADA- subgroup (8.4% and 8.8%, respectively, versus 13.1%) had at least one SAE. No SAE was reported at a higher incidence (≥1.0%) for the ADA+/NAb+ and all ADA+ subgroups compared with the ADA- subgroup in either Study BA058-05-003 or Study BA058-05-005.

Of the 5 subjects who were positive for anti-PTHrP antibodies, 1 subject experienced 3 unrelated SAEs in Study BA058-05-003: influenza, cholangitis, and bronchiolitis. No SAEs were reported for the other 4 subjects who were positive for anti-PTHrP antibodies or the 1 subject who was positive for anti-PTH antibodies in Study BA058-05-003.

The percentage of subjects with AEs or SAEs suggestive of an immunologically-based reaction (i.e., hypersensitivity, anaphylaxis), were similar in subjects with and without anti-abaloparatide antibodies.

Overall, ADA+ antibodies had no apparent effect on the overall safety and efficacy profile of abaloparatide when subjects were followed on a 6-months interval basis for up to 97 months. Few subjects treated with abaloparatide-SC developed either ADA or NAb that were cross-reactive with PTH or PTHr.

Additionally, Study ITM-058-301 investigated the development of anti-abaloparatide antibodies after treatment with 80μg abaloparatide for a duration of 18 months. In the abaloparatide group, 40 subjects became positive for anti-abaloparatide antibody at any evaluation time point and 100 subjects remained negative for anti-abaloparatide antibody. There was no difference in incidence of AEs depending on the presence or absence of antibody production.

In summary, the incidence of hypersensitivity adverse events was comparable between abaloparatide and teriparatide treated patients. During 18 months in study BA058-05-003, the rate of antibody development was high; about 50% of the women treated with abaloparatide developed anti-abaloparatide antibodies, including about 30% with neutralising antibodies. The number of patients with anti-abaloparatide antibodies declined during the extension period in study BA058-05-005 when patients were treated with alendronate, about one quarter was antibody positive after 6 months into the extension. the percentage of subjects with ADA+ and NAb+ results steadily decreased over time in Study BA058-05-005. At Month 97 of follow-up, only 1 subject had ADA+ results. Overall, ADA+ antibodies had no apparent effect on the overall safety profile of abaloparatide when subjects were followed on a 6-months interval basis for up to 97 months. Few subjects treated with abaloparatide-SC developed either ADA or NAb that were cross-reactive with PTH or PTHr.

2.5.8.7. Safety related to drug-drug interactions and other interactions

Abaloparatide is a peptide with specific affinity to the parathyroid hormone receptor 1 (PTHR1) with no known affinity to PTHR2 or other molecular targets. Since there are no known secondary targets and no known effects on CYP induction or inhibition the likelihood of drug-drug interactions was considered low. Thus, no formal drug-drug interaction studies have been performed which is acceptable.

2.5.8.8. Discontinuation due to adverse events

In Study BA058-05-003, the number of patients who discontinued treatment and the incidence of adverse events leading to study discontinuation was higher in patients treated with abaloparatide 9.8% than those treated with teriparatide 6.7% or placebo 6.0%. Adverse event most frequently associated with discontinuation in patients on abaloparatide were nausea, dizziness, headache, and palpitations. Dizziness and headache were also among the most frequent adverse events associated with discontinuation in the teriparatide group but frequencies were lower than in the abaloparatide group.

A specific analysis has been performed to assess CV adverse events leading to study discontinuation in the abaloparatide group in Study BA058-05-003. There were a total of 12 patients in the abaloparatide group, with 13 CV events leading to discontinuation.

The majority of these events were palpitations/tachycardia (7/12 patients, 8/13 events) and myocardial ischaemic events (3/12 patients). Six out of the seven patients with palpitations/tachycardia had relevant medical history (e.g. hypertension, thyroid disorders). All patients (3/3) with ischaemic events (i.e. myocardial ischaemia) had relevant medical history (e.g. myocardial infarction, hypertension, hyperlipidaemia). All 13 events resolved except two, one ongoing and one fatal. The fatal event (myocardial ischaemia) occurred 136 days after treatment and was assessed by the investigator as not related to the study medication.

The overall incidence of AE leading to discontinuation was similar between the alendronate treatment groups after 6 months or 24 months of treatment in patients previously treated with placebo and abaloparatide in Study BA058-05-005. No clear pattern regarding Adverse Events Leading to Discontinuation was seen in the smaller clinical studies.

Table 46. Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (≥ 0.5% of Subjects in Any Treatment Group in Study BA058-05-003) by SOC and PTs in Subjects

with Osteoporosis; number of subjects (%), Studies BA058-05-003, BA058-05-002, BA058-007, BA058-05-020 and ITM-058-301

	Study BA058-05-003			Study BA058-05-002					Study BA058-05-007		Study BA058-05-020	Study ITM-058-301	
	PBO	ABL 80 µg	TPTD 20 µg	PBO	ABL 20 µg	ABL 40 µg	ABL 80 µg	TPTD 20 µg	PBO	ABL 80 µg	ABL 80 µg	PBO	ABL 80 µg
	0-18 mo	0-18 mo	0-18 mo	0-28 wks / 0-52 wks	0-28 wks / 0-52 wks	0-28 wks / 0-52 wks	0-28 wks / 0-52 wks	0-28 wks / 0-52 wks	0-24 wks	0-24 wks	0-3 mo	0-18 mo	0-18 mo
	N=687	N=694	N=686	N=45 / N=11	N=43 / N=13	N=43 / N=10	N=45 / N=7	N=45 / N=14	N=50	N=51	N=23	N=72	N=140
AE Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with a least 1 TEAE leading to discontinuation	41 (6.0)	68 (9.8)	46 (6.7)	0	1 (2.3) / 0	1 (2.3) / 1 (10)	2 (4.4) / 1 (14.3)	2 (4.4) / 0	0	7 (13.7)	0	4 (5.6)	4 (2.9)
Cardiac disorders	3 (0.4)	12 (1.7)	1 (0.1)	0	0	0	0	0	0	1 (2.0)	1 (4.3)	0	0
Palpitations	1 (0.1)	6 (0.9)	0	0	0	0	0	0	0	0	1 (4.3)	1 (0.7)	0
Gastrointestinal disorders	6 (0.9)	14 (2.0)	9 (1.3)	0	1 (2.3) / 0	1 (2.3) / 0	0	0	0	1 (2.0)	2 (8.7)	0	0
Nausea	2 (0.3)	11 (1.6)	3 (0.4)	0	0	1 (2.3)	0	0	0	0	1 (4.3)	1 (0.7)	0
Vomiting	0	0	0	0	0	0	0	0	0	0	1 (4.3)	0	0
General disorders and administration site conditions	6 (0.9)	6 (0.9)	3 (0.4)	0	0	1 (2.3) / 0	0	1 (2.2) / 0	0	2 (3.9)	0		0
Malaise	4 (0.6)	1 (0.1)	0	0	0	0	0	0	0	0	0	0	0
Investigations	5 (0.7)	7 (1.0)	4 (0.6)	0	0	0	0	0	0	0	0	0	0
Blood calcium increased	0	0	0	0	0	0	0	0	0	0	0	0	2 (1.4)
Metabolism and nutrition disorders	0	1 (0.1)	4 (0.6)	0	0	0	0	0	0	0	0	0	0
Hypercalcaemia	0	1 (0.1)	4 (0.6)	0	0	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	12 (1.7)	2 (0.3)	1 (0.1)	0	0	0	0 / 1 (14.3)	0	0	0	0	0	0
Osteoporosis	8 (1.2)	0	0 (0.0)	0	0	0	0	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4)	4 (0.6)	5 (0.7)	0	1 (2.3) / 0	0	0	0	0	0	0	0	0
Nervous system disorders	6 (0.9)	18 (2.6)	13 (1.9)	0	0	0 / 1 (10.0)	2 (4.4) / 0	1 (2.2) / 0	0	1 (2.0)	0	0	0
Dizziness	3 (0.4)	10 (1.4)	8 (1.2)	0	0	0	0	0	0	0	0	0	0
Headache	2 (0.3)	8 (1.2)	4 (0.6)	0	0	0	2 (4.4) / 0	1 (2.2) / 0	0	1 (2.0)	0	0	0
Psychiatric disorders	3 (0.4)	4 (0.6)	0	0	0	0	0	0	0	0	0	0	0

Skin and subcutaneous tissuedisorders	3 (0.4)	4 (0.6)	5 (0.7)	0	0	0	0	1 (2.2) 0	0	2 (3.9)	0	0	0
Vascular disorders	1 (0.1)	6 (0.9)	3 (0.4)	0	0	0	0	0	0	0	0	0	0

Source: BA058-05-003, Appendix 2, Table 6; Study BA058-05-003-Add, Table 14.3.1.6.2 Excluding Sites 131 and 132. Note that if there is no subject reporting TEAEs during the initial 6 months treatment period (0-28 weeks) and the extension period (0-52 weeks) in Study BA058-05-002, "0" is noted only once. CSR BA058-05-020, Table 14.3.1.6 and Listing 14.3.2.4; CSR ITM-058-301, Table 14.3.1 2 5 1

ABL=abaloparatide; PBO=placebo; TPTD=teriparatide

2.5.8.9. Study BA058-05-028

The retrospective observational Study BA058-05-028 analysed the specific risk for serious CV events after treatment with abaloparatide or teriparatide, respectively, as a secondary endpoint. The methods are described and discussed in detail in the efficacy section.

The overall mean duration of abaloparatide and teriparatide exposure was 301.0 and 314.5 days (10 months), respectively, with >45% of patients in both treatment cohorts exposed to treatment >12 months. The mean cumulative duration of abaloparatide and teriparatide exposure was 257.6 and 270.2 days, respectively, with >33% of patients in both treatment cohorts exposed to treatment >12 months. The percentage of patients in both treatment cohorts who were exposed >12 months of consecutive treatment was >34%. Consecutive treatment duration is determined from the index date to the last drug supply date without any gap exceeding 60 days.

Table 47. Cohort Drug Exposure, Cumulative Treatment Duration (the sum of all cohort drug supply days recorded on the pharmacy data). (Overall PS-Matched)

Parameter	Abaloparatide-SC N=11027	Teriparatide N=11027
Cumulative Treatment Duration n (%) [3]		
≤1 Month	1999 (18.1)	1936 (17.6)
>1 to ≤3 Months	1846 (16.7)	1542 (14.0)
>3 to ≤6 Months	1312 (11.9)	1273 (11.5)
>6 to ≤9 Months	1042 (9.4)	1016 (9.2)
>9 to ≤12 Months	1136 (10.3)	1012 (9.2)
>12 Months	3692 (33.5)	4248 (38.5)

The mean cumulative treatment duration was 257.6 days for abaloparatide and 270.2 days for teriparatide-treated patients. In line with the clinical study, there were more early discontinuations (shorter exposures) in the abaloparatide group. Overall, the mean exposure of 10 months in the observational study was considerably shorter than the mean exposure in the clinical study that was >15 months.

66% of abaloparatide-treated patients and 62% of teriparatide-treated patients had a cumulative treatment duration shorter than 12 months.

This was considerably shorter than in study BA058-05-003.

Secondary endpoints - safety

Table 48. Time to First Incidence of Cardiovascular Event During Treatment (Secondary Composite Endpoints = MI/Stroke/Hospital CV Death and MI/Stroke/Heart Failure/Hospital CV Death) (Overall PS-Matched)

Time-to-Event Variable	Parameter	Statistic	Abaloparatide-SC (N=11027)	Teriparatide (N=11027)
MI/Stroke/Hospital CV Death	K-M Estimated Event Rate at 18 Months [1]	%	3.00	2.90
	Number of Patients with Event	n (%)	221 (2.0)	211 (1.9)
	Number of Patients Censored [2]	n (%)	10806 (98.0)	10816 (98.1)
	HR vs Teriparatide [3]	HR (95% CI)	1.08 (0.89, 1.30)	
	P-value vs Teriparatide [4]		0.4428	
MI/Stroke/HF/ Hospital CV Death	K-M Estimated Event Rate at 18 Months [1]	%	6.54	6.20
	Number of Patients with Event	n (%)	495 (4.5)	471 (4.3)
	Number of Patients Censored [2]	n (%)	10532 (95.5)	10556 (95.7)
	HR vs Teriparatide [3]	HR (95% CI)	1.08 (0.95, 1.22)	
	P-value vs Teriparatide [4]		0.2384	

Source: Section 14.3, Table 14.3.1

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; K-M = Kaplan-Meier; MI = myocardial infarction; PS = propensity score

ICD-10-CM was used to define the event: MI= I21.X, I22.X; Stroke= I61.X-I63.X; HF=I50.X (exclude I50.X2, I50.8X). Hospital discharge status code (20, 40, 41 and 42) will be derived for hospital death. Patients with hospital CV death derived from indirect approach 2 [Xie F. et al., 2018].
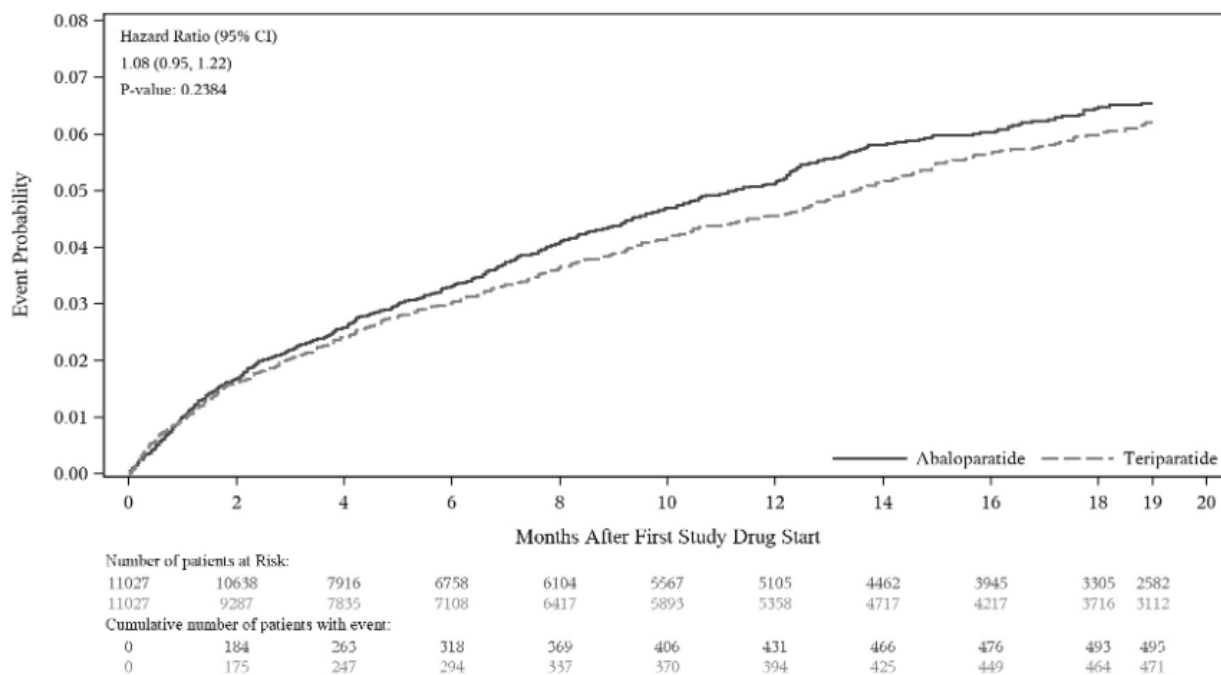
[1] The observation period was 18 months (540 days) plus 30 days follow-up after the index date.

[2] Patients are censored at the earlier of 30 days after treatment end, death, or 570 days after index date, if no cardiovascular event before that.

[3] Cox proportional hazard model was used to calculate the hazard ratio with teriparatide as reference.

[4] P-values were from the log rank test.

Figure 17. Kaplan-Meier Plot for Time to First Incidence of Cardiovascular Event (Composite Endpoint = MI/Stroke/Heart Failure/Hospital CV Death) (Overall PS-Matched)

Source: Section 14.3, Figure 14.3.1
CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; PS = propensity score
The AT analysis observation period was from the index-date to the 30 days after end of treatment (up to 18 months).

Table 49. Time to First Incidence of Cardiovascular Event During Treatment (Overall PS-Matched)

Time-to-Event Variable	Parameter	Statistic	Abaloparatide (N=11616)	Teriparatide (N=11616)

Time-to-Event Variable	Parameter	Statistic	Abaloparatide-SC (N=11027)	Teriparatide (N=11027)
MI/Stroke	K-M Estimated Event Rate at 18 Months [1]	%	3.00	2.87
	Number of Patients with Event	n (%)	221 (2.0)	209 (1.9)
	Number of Patients Censored [2]	n (%)	10806 (98.0)	10818 (98.1)
	HR vs Teriparatide [3]	HR (95% CI)	1.09 (0.90, 1.31)	
	P-value vs Teriparatide [4]		0.3879	
MI/Stroke/HF	K-M Estimated Event Rate at 18 Months [1]	%	6.54	6.17
	Number of Patients with Event	n (%)	495 (4.5)	469 (4.3)
	Number of Patients Censored [2]	n (%)	10532 (95.5)	10558 (95.7)
	HR vs Teriparatide [3]	HR (95% CI)	1.08 (0.96, 1.23)	
	P-value vs Teriparatide [4]		0.2139	
MI	K-M Estimated Event Rate at 18 Months [1]	%	0.96	1.13
	Number of Patients with Event	n (%)	70 (0.6)	77 (0.7)
	Number of Patients Censored [2]	n (%)	10957 (99.4)	10950 (99.3)
	HR vs Teriparatide [3]	HR (95% CI)	0.94 (0.68, 1.30)	
	P-value vs Teriparatide [4]		0.7000	
Stroke	K-M Estimated Event Rate at 18 Months [1]	%	2.13	1.88
	Number of Patients with Event	n (%)	157 (1.4)	140 (1.3)
	Number of Patients Censored [2]	n (%)	10870 (98.6)	10887 (98.7)
	HR vs Teriparatide [3]	HR (95% CI)	1.15 (0.92, 1.45)	
	P-value vs Teriparatide [4]		0.2271	
HF	K-M Estimated Event Rate at 18 Months [1]	%	4.40	4.08
	Number of Patients with Event	n (%)	330 (3.0)	310 (2.8)
	Number of Patients Censored [2]	n (%)	10697 (97.0)	10717 (97.2)
	HR vs Teriparatide [3]	HR (95% CI)	1.09 (0.94, 1.28)	
	P-value vs Teriparatide [4]		0.2610	
Hospital CV Death	K-M Estimated Event Rate at 18 Months [1]	%	0.00	0.07
	Number of Patients with Event	n (%)	0	4 (0)
	Number of Patients Censored [2]	n (%)	11027 (100)	11023 (100)
	HR vs Teriparatide [3]	HR (95% CI)	N/A	
	P-value vs Teriparatide [4]		0.0509	
Hospital All-Cause Death	K-M Estimated Event Rate at 18 Months [1]	%	0.17	0.12
	Number of Patients with Event	n (%)	10 (0.1)	9 (0.1)
	Number of Patients Censored [2]	n (%)	11017 (99.9)	11018 (99.9)
	HR vs Teriparatide [3]	HR (95% CI)	1.15 (0.47, 2.84)	

Time-to-Event Variable	Parameter	Statistic	Abaloparatide-SC (N=11027)	Teriparatide (N=11027)
	P-value vs Teriparatide [4]		0.7573	

Source: Section 14.3, Table 14.3.1

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; K-M = Kaplan-Meier; MI = myocardial infarction; PS = propensity score

ICD-10-CM was used to define the event: MI= I21.X, I22.X; Stroke= I61.X-I63.X; HF=I50.X (exclude I50.X2, I50.8X). Hospital discharge status code (20, 40, 41 and 42) will be derived for hospital death. Patients with hospital CV death derived from indirect approach 2 [Xie F. et al., 2018].

[1] The observation period was 18 months (540 days) plus 30 days follow-up after the index date.

[2] Patients are censored at the earlier of 30 days after treatment end, death, or 570 days after index date, if no cardiovascular event before that.

[3] Cox proportional hazard model was used to calculate the hazard ratio with teriparatide as reference.

[4] P-values were from the log rank test.

Time to First Incidence of Cardiovascular Event During Treatment (MI/Stroke/Hospital CV Death and MI/Stroke/Heart Failure/Hospital CV Death) in the overall PS-Matched population was comparable in abaloparatide and teriparatide treated patients.
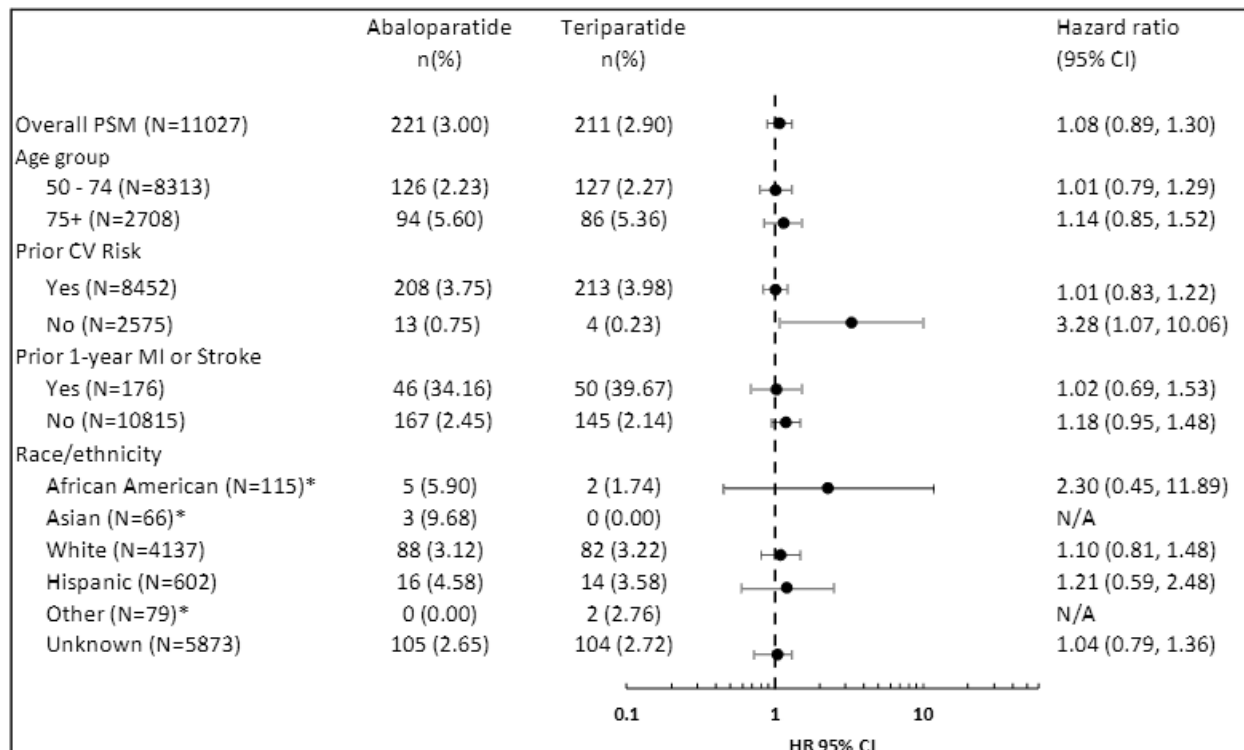
Most event were heart failure followed by stroke that was recorded in twice as many patients as MI. Only 10 respectively 11 hospital all cause deaths were recorded.

Considering the safety concern of increased heart rate, the applicant analyzed arrhythmia (defined as ICD-10-CM of I47.X, I48.X, I49.X, R00.0), atrial fibrillation (ICD-10-CM of I48.X), and other arrhythmia (ICD-10-CM of I47.X, I49.X, R00.0) events in study BA058-05-028 as a response to D120 LoQ. The three arrhythmia incidence rates were comparable between abaloparatide and teriparatide (arrhythmia: 10.69 vs 10.74, respectively; atrial fibrillation: 5.70 vs 5.81, respectively; and other arrhythmia: 6.80 vs 6.60, respectively).

Subgroup Analyses

Some Subgroup analysis are presented below:

Figure 18. Forest Plot of Hazard Ratios of MI/Stroke/Hospital CV Death for Abaloparatide vs Teriparatide

	Abaloparatide n(%)	Teriparatide n(%)		Hazard ratio (95% CI)
Overall PSM (N=11027)	221 (3.00)	211 (2.90)		1.08 (0.89, 1.30)
Age group				
50 - 74 (N=8313)	126 (2.23)	127 (2.27)		1.01 (0.79, 1.29)
75+ (N=2708)	94 (5.60)	86 (5.36)		1.14 (0.85, 1.52)
Prior CV Risk				
Yes (N=8452)	208 (3.75)	213 (3.98)		1.01 (0.83, 1.22)
No (N=2575)	13 (0.75)	4 (0.23)		3.28 (1.07, 10.06)
Prior 1-year MI or Stroke				
Yes (N=176)	46 (34.16)	50 (39.67)		1.02 (0.69, 1.53)
No (N=10815)	167 (2.45)	145 (2.14)		1.18 (0.95, 1.48)
Race/ethnicity				
African American (N=115)*	5 (5.90)	2 (1.74)		2.30 (0.45, 11.89)
Asian (N=66)*	3 (9.68)	0 (0.00)		N/A
White (N=4137)	88 (3.12)	82 (3.22)		1.10 (0.81, 1.48)
Hispanic (N=602)	16 (4.58)	14 (3.58)		1.21 (0.59, 2.48)
Other (N=79)*	0 (0.00)	2 (2.76)		N/A
Unknown (N=5873)	105 (2.65)	104 (2.72)		1.04 (0.79, 1.36)

0.1   1   10
HR 95% CI

Source: Section 14.3, Table 14.3.1, 14.3.1.1, 14.3.1.2, 14.3.1.3, 14.3.1.4, 14.3.1.5, 14.3.1.6, 14.3.1.7, 14.3.1.8, 14.3.1.9, 14.3.1.10, 14.3.1.11, 14.3.1.12

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; PSM = propensity score matching

[1] N is number of matched pairs in each subgroup; n is number of events and % is K-M estimate at the end of 19 months since index date.
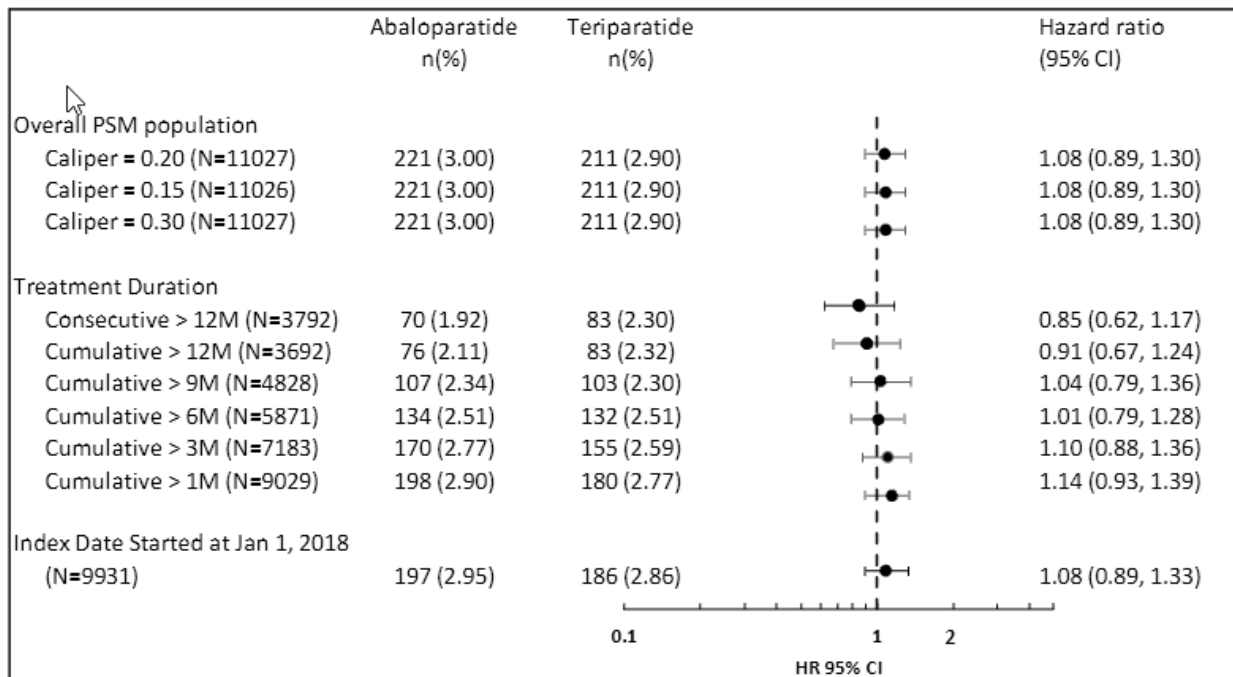
[2] Patients were censored at earliest of 30 days after treatment end, 30 days after 18 months of treatment, or the date of death, if no event happened before that.

*Subgroup did not meet matching expectation (ie, standardized difference for some covariates >0.10).

The risk of MI/Stroke/Hospital CV Death was doubled in patients >75 years compared to age group 50-74.

Figure 19. Forest Plot of Hazard Ratios of MI/Stroke/Heart Failure/Hospital CV Death for Abaloparatide vs Teriparatide

	Abaloparatide n(%)	Teriparatide n(%)		Hazard ratio (95% CI)
Overall PSM population				
Caliper = 0.20 (N=11027)	221 (3.00)	211 (2.90)		1.08 (0.89, 1.30)
Caliper = 0.15 (N=11026)	221 (3.00)	211 (2.90)		1.08 (0.89, 1.30)
Caliper = 0.30 (N=11027)	221 (3.00)	211 (2.90)		1.08 (0.89, 1.30)
Treatment Duration				
Consecutive > 12M (N=3792)	70 (1.92)	83 (2.30)		0.85 (0.62, 1.17)
Cumulative > 12M (N=3692)	76 (2.11)	83 (2.32)		0.91 (0.67, 1.24)
Cumulative > 9M (N=4828)	107 (2.34)	103 (2.30)		1.04 (0.79, 1.36)
Cumulative > 6M (N=5871)	134 (2.51)	132 (2.51)		1.01 (0.79, 1.28)
Cumulative > 3M (N=7183)	170 (2.77)	155 (2.59)		1.10 (0.88, 1.36)
Cumulative > 1M (N=9029)	198 (2.90)	180 (2.77)		1.14 (0.93, 1.39)
Index Date Started at Jan 1, 2018				
(N=9931)	197 (2.95)	186 (2.86)		1.08 (0.89, 1.33)

Source: Section 14.3, Table 14.3.1, 14.3.2.1, 14.3.2.2, 14.3.2.3, 14.3.2.4, 14.3.2.5, 14.3.2.6, 14.3.4.1, 14.3.4.2, 14.3.4.3

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; PSM = propensity score matching

[1] N is number of matched pairs in each subgroup; n is number of events and % is K-M estimate at the end of 19 months since index date.

[2] Patients were censored at earliest of 30 days after treatment end, 30 days after 18 months of treatment or the date of death if no event happened before that.

Only a minority of the patients had a treatment duration of >12 months.

Discussion of CV safety in study BA058-05-028:

CV Safety of Abaloparatide

The effects of abaloparatide versus teriparatide on the incidence of the composite CV events were measured in PS-matched cohorts based on time to the first incidence of nonfatal MI, nonfatal stroke, and hospital CV death within the 19 months after treatment initiation while still on therapy. An additional composite endpoint including heart failure events was also assessed. Of note, there are no contraindications for cardiovascular disorders in the FDA approved product labels for abaloparatide and teriparatide.

Representativeness of the study population vs European population:

The following table was submitted by the applicant:

Comparison of the Patients Characteristics on Anabolic Therapies in US vs. EU

Patient Characteristics	ABL US[†] (n=11,021)	ABL US[‡] (n=193)	TPTD US[†] (n=14,285)	TPTD US[†] (n=1,527)	TPTD US[†] (5,882)	TPTD US[‡] DANCE (n=4,085)	TPTD EU EFOS[‡] (n=1,645)	TPTD EU ExFOS[‡] (n=1,607)
Referenced Study	[Williams S. et al., 2019]	Data on File, Radius Health, Inc., November 2020	[Burge R.T. et al., 2017]	[Bonafede M.M. et al., 2015]	[Boytsov N. et al., 2015]	[Silverman S. et al., 2013]	[Rajzbaum G. et al., 2008]	[Ljunggren O. et al., 2014]
Age Mean (±SD)	67.3 (9.2)	67.4 (8.6)	68.4 (±12.0)	69.5 (±10.6)	69.2(±10.9)	68.0 (±11.7)	71.5 (±8.4)	70.3 (±9.8)
Fracture History	40%	34%	30%	26%	34%	57%	70% with ≥2 Fx	85.8% 64.7% ≥2 Fx
BMD Lumbar Spine Total Hip Femoral Neck	Not Available	-2.6 -2.0 -2.4	Not Available	Not Available	Not Available	-2.48 (±1.38) -2.18 (±0.99) -2.44 (±0.92)	-3.3 (±1.2) -2.6 (±1.04) -2.7 (±0.96)	-3.0(±1.24) -2.4 (±1.00) -2.5 (±0.92)
OP Tx Hx	60%	63%	52%	64%	65%	85.7%	91.7%	89%
Comorbid Conditions	CVD (69%) GI (41%) OA (27%) Respiratory (26%) T2DM (18%) Renal (14%)	HPT (28%) GERD (28%) OA (11%) DM (7%) RA (5%) CHD (4%) Stroke (3%) Cardiac arrhythmia (2%) No comorbidities (22%)	CCI 0.99 (1.42)	Thyroid Disease (14%) GERD (11%) Diabetes (10%) RA (8%) GI (6%)	CVD (75%) GI (69%) Metabolic dx (59%) Antihypertensive (43%) Thyroid dx (28%) COPD (24%) RA (10%)	No comorbidities (17%)	Antihypertensives (37%) RA (12%) COPD (9%) Anti-arrhythmic (8%) Oral anticoagulants/ heparin (7%) DM (5%) Stroke (3%) No comorbidities (67%)	Antihypertensives (42%) RA (11%) Respiratory disease (9%) Diabetes (5%) No comorbidities (66%)

The patients treated with teriparatide in EU are in general older and have more severe osteoporosis.

Time to First Incidence of Cardiovascular Event During Treatment (MI/Stroke/Hospital CV Death and MI/Stroke/Heart Failure/Hospital CV Death) in the overall PS-Matched population was comparable in abaloparatide and teriparatide treated patients. The incidence of the composite of MI, stroke, heart failure, and hospital CV death [HR (95% CI): 1.08 (0.95, 1.22)]. The event rate for stroke was HR (95% CI) 1.15 (0.92, 1.45). The point estimates of Hazard Ratios were below 1.2 in most of the sensitivity and subgroup analyses. Among the events included in the composite endpoint, the most frequent events were heart failure followed by stroke that was recorded in twice as many patients as MI. Only 10 respectively 11 hospital all cause deaths were recorded. It seems to be that the study likely included patients with somewhat higher CV risk than the main clinical study. Incidences of MACE in Study BA058-05-003 were 0.5-1.2% whereas in this observational study the incidences were 2%. Of note, patients were somewhat younger than in the clinical study. A particular weakness of the study was that mortality data in the study was derived from mortality recorded on the hospital (medical facility) discharge status that covers only about one-third of the total death records.

Considering the safety concern of increased heart rate, the applicant analyzed arrhythmia (defined as ICD-10-CM of I47.X, I48.X, I49.X, R00.0), atrial fibrillation (ICD-10-CM of I48.X), and other (non-AF) arrhythmia

(ICD-10-CM of I47.X, I49.X, R00.0) events in study BA058-05-028 as a response to D120 LoQ. The arrhythmia incidence rates were comparable between abaloparatide and teriparatide (arrhythmia: 10.69 vs 10.74, respectively; atrial fibrillation: 5.70 vs 5.81, respectively; and other arrhythmia: 6.80 vs 6.60, respectively).

The mean cumulative treatment duration was 258 days for abaloparatide and 269 days for teriparatide treated patients. In line with the clinical study, there were more early discontinuations (shorter exposures) in the abaloparatide group. The difference in persistence between the 2 cohorts became apparent in the first few months but thereafter was similar between cohorts. The reason for the difference in persistence is difficult to assess in the current study. Overall, the mean exposure of 10 months in the observational study was considerably shorter than the mean exposure in the clinical study that was >15 months.

66% of Abaloparatide treated patients and 62% of teriparatide treated patients did have a treatment duration shorter than 12 months. This was considerably shorter than in study BA058-05-003.

CV safety outcomes were evaluated using an as-treated (AT) analysis based only on events occurring while on therapy (until end of treatment) for up to 18 months plus 30 days follow-up, regardless of the anabolic drug possession gap between any 2 prescription fills. Abaloparatide treated patients had a higher frequency of early treatment discontinuations both in the clinical trial 003 and in the study 028. Frail patients are more likely to discontinue. Safety analysis based only on events occurring while on therapy is therefore not necessarily the most conservative one. However, safety evaluation using an "intent-to-treat (ITT) analysis" was in line with that presented for effectiveness.
In the analysis presented from the current study, the risk of MI/Stroke/Hospital CV Death was doubled in patients >75 years compared to age group 50-74. Numerically, there were more events in the abaloparatide group 5.6% vs 4.7% in the subgroup of >75 year old. Of note, age of 80 was used in all analyses for patients aged 80 and above. Before matching, the number of patients age ≥80 was 1465 (13.3%) and 3386 (15.2%) in the abaloparatide and teriparatide groups, respectively. After propensity-score matching, the percentages of patients age ≥80 are 13.3% and 13.7% for abaloparatide and teriparatide, respectively, a difference of 0.4% between the 2 treatment cohorts. The distribution of patients age ≥80 is unknown.

Other subgroup analyses were generally supportive of the primary findings as were sensitivity analyses examining subgroups with at least 12 months of consecutive or cumulative exposure. Of note, the incidence of serious CV events was similar in abaloparatide- and teriparatide-treated patients with a history of stroke or MI within the year before the index date or those with CV risk factors representing approximately 75% of patients in this study.

The incidence of CV events was greater in abaloparatide-treated patients compared with teriparatide-treated patients with no identified CV risks [HR (95% CI): 3.28 (1.07, 10.06)]. Overall, the incidence of CV events in the cohort was low relative to patients with CV risks, and because no effect modification was observed in patients with identified CV risks this may have been a chance finding. Among the race subgroups, the incidence of CV events was higher in abaloparatide-treated Asian and African American patients relative to teriparatide-treated Asian patients. The small number of patients in each cohort and low number of events was very low making it difficult to draw any firm conclusions. There is no obvious biologic plausibility for the response in these subgroups.

Different regions and types of clinics were included as a variable in the propensity score matching that was used in the study but, for example, socioeconomic or retiree status, as well as other factors (e.g., family

history, smoking status, alcohol intake, BMD) characterising the disease state and/or being prognostic for fractures or CV safety was not.

Mortality data recorded on the hospital (medical facility) discharge status covers only about one-third of the total death records. Consequently, the mortality numbers from this observational study underestimate the total death rate. In the Day 120 LoQ, the applicant was asked to comment or if there are any particular known characteristics and what are the main causes of death for women 50 to 65 years that are not found in medical facility discharge records and if this could lead to bias in the study design. For example, a cheaper drug could be more used in patients with lower socioeconomic status and deaths in this patient group might occur more often outside medical facilities. The applicant confirmed that mortality data outside of the hospitals is not available. Rate of out of hospital deaths may be higher for those with lower socioeconomic status due to poor access to healthcare or lower education regarding warning signs of a serious event. Geographic region, prescriber physician specialty, and insurance type as proxy for socioeconomic status is not optimal. However, although the wholesale acquisition cost (WAC) for each abaloparatide pen was discounted at 50% to the teriparatide pen, the actual differences in patient's out of pocket cost were much less. No access to mortality data outside of the hospitals is an important limitation of study BA058-05-028. The applicant was not able to confirm deaths using the National Death Index.

No access to income and education data in the study is also a limitation. it is difficult to estimate potential bias caused by different price settings of abaloparatide/teriparatide.

2.5.8.10. Post marketing experience

The currently available postmarketing safety information includes cumulative events from the international birth date (IBD) of abaloparatide (27 April 2017) through a data cut-off date of 27 April 2022. At this time, abaloparatide is only marketed in the United States. Abaloparatide has been approved in the United States for the treatment of postmenopausal women with osteoporosis at high risk for fracture since 2017.

The last PBRER/PSUR prepared for the annual time period 28 April 2021 to 27 April 2022 was included in this MAA. The AEs reported were generally consistent with the safety profile of abaloparatide observed in the clinical settings.

During the cumulative postmarketing surveillance in the United States, a total of 27 safety signals were identified for further evaluation. The signals related to hot flush, flushing, chest pain, chest discomfort, atrial fibrillation, alopecia, and weight increased/waist circumference increased were identified, assessed, and refuted due to insufficient evidence to support causative association with abaloparatide administration. The remaining twenty signals were added to the Company Core Data Sheet (CCDS) and were submitted to the FDA to revise the USPI. FDA approved the revised USPI (USPI Oct 2020) to include the following AEs in the "Postmarketing section": abdominal pain, abdominal distension, arthralgia, asthenia, back pain, bone pain, constipation, diarrhoea, dyspnoea, hypersensitivity/anaphylaxis, injection site reactions, insomnia, lethargy, malaise, muscle spasms of leg/back, pain, pain in extremity, pruritus, rash, vomiting.

Since there is an outstanding concern that transient increase in HR may be a potential risk for serious CV events such as myocardial infarction, cerebrovascular accident, CV death, heart failure and arrhythmia-related events, a qualitative review of all serious CV events reported with TYMLOS (trade name for abaloparatide in the US) via ongoing clinical trials and postmarketing surveillance was conducted through 31 March 2022. To capture serious CV events reported with TYMLOS® in the postmarketing experience, a

customised search was conducted in the Radius Central Safety Database to focus on major adverse CV events (MACE) including death using Medical Dictionary for Regulatory Activities (MedDRA) terms.

The pivotal trial (BA058-05-003) and its pivotal extension (BA058-05-005), both which were completed, concluded that abaloparatide was associated with transient increases in HR in postmenopausal women with osteoporosis but there was no association of increased risk of serious cardiac AEs, MACE, or heart failure with abaloparatide therapy. Two recently completed studies (BA058-05-019 and BA058-05-021) identified three reported cases of MACE. All three reports were confounded by the subject's concurrent illness or prior medical history of cardiac disorder or MI. No new safety concern was identified.

The estimated postmarketing patient exposure to abaloparatide from launch through 31 March 2022 was 47,618 patient-years of treatment. The cumulative search in the safety database identified 57 cases reporting 60 MACE and accounted for approximately 0.33% of all post-marketing reports. In 34 of 57 cases, confounding factors such as prior medical history may have contributed to the MACE. In the remaining 23 cases, insufficient information regarding abaloparatide treatment (dose, duration, action taken), concomitant medication use, relevant history and clinical course/event details prevented a full medical assessment. In conclusion, no safety signal was identified for CV events with abaloparatide treatment from the available data including completed and ongoing clinical studies, and approximately 5 years of postmarketing experience data from the United States.

In addition, the US FDA Adverse Event Reporting System (FAERS) data was reviewed for abaloparatide, teriparatide, and romosozumab and did not identify any disproportionality safety signals with regards to serious CV events for teriparatide or abaloparatide, in contrast to romosozumab, known to have a CV safety concern. However, as seen in the table below, The EB05 ranges are overlapping and lower bound of 90% CI is the same for all three substances.

Table 50. Disproportionality Safety Signals (Cardiovascular Safety) from FAERS

	Number of MACE Cases	EB05 Range[a]
Abaloparatide	63	0.18 to 0.45
Teriparatide	2,780	0.09 to 1.22
Romosozumab	192	0.07 to 4.00

[a] EB05, lower bound of 90% confidence interval for the Empiric Bayes Geometric Mean; threshold for signal detection is EB05≥2%

2.5.9. Discussion on clinical safety

Safety data for abaloparatide were derived from 10 clinical trials, but the primary evaluation is based on the pivotal trial BA058-05-003 with up to 18 months of exposure to abaloparatide compared to placebo and teriparatide. In the extension study BA058-05-005 participants were switched to alendronate.

In the pivotal study BA058-05-003, 694 patients received abaloparatide 80 µg SC daily and 507 (73%) completed 18 months of exposure, while on teriparatide 546 out of 686 (80%) and on placebo 531 out of 687 (77%) completed the trial; patients on abaloparatide dropped out early, with drop-out ≤1 month and >1 month to ≤3 months being 7.9% and 3.8% on abaloparatide, respectively and 3.9% and 3.6% on teriparatide, respectively. In the analysis of the data from the follow-up study BA058-05-005 in which patients were switched to alendronate no differences in adverse events were seen between patients previously treated with abaloparatide and those previously treated with placebo.

In general, the highest incidence of adverse events was seen within the first 2 months of treatment and differences in occurrence of adverse events were most pronounced in this time period; differences were no longer apparent from 6 months onwards. The diminishing differences in frequency of adverse events in the system organ classes 'cardiac disorders', 'gastrointestinal disorders', and 'nervous system disorders' might be partly attributable to the differential drop-out between treatment groups.

Around 80% of adverse events were considered mild to moderate and the distribution of severity was comparable between treatment groups for mild to moderate adverse events; frequencies of severe adverse events were too low for a reliable comparison between groups.

The number of patients who discontinued treatment and the incidence of adverse events leading to study discontinuation were higher in patients treated with abaloparatide than those treated with teriparatide or placebo. Adverse event most frequently associated with discontinuation in patients on abaloparatide were nausea, dizziness, headache, and palpitations.

As regards deaths and serious adverse events the analyses did not indicate clinically relevant differences between groups. In the 18 months pivotal phase 3 study BA058-05-003, 3 deaths occurred in patients on placebo and on abaloparatide each and 2 on teriparatide; none of these deaths were considered related to study medication. During the first 6 months of study BA058-05-005 there was 1 death in a patient switched from abaloparatide and overall there were 2 additional AEs leading to death, 1 each in the placebo / alendronate and abaloparatide / alendronate group; none of these deaths were considered related to study medication. Numbers are too small for a conclusive assessment of differences in the incidence of death and serious adverse events possibly attributable to abaloparatide.

In the analysis of adverse events by system organ class relevant differences were seen for 'cardiac disorders', and 'nervous system disorders' with higher frequencies on abaloparatide compared to teriparatide, and placebo; the higher frequency of abaloparatide in the system organ class 'cardiac disorders' was mainly driven by the increased rate of palpitations.

Marked post-injection increases in HR with abaloparatide were observed in healthy volunteers in the thorough QT-study with a maximum mean increase of 14.6 bpm 15 min after the therapeutic dose of 80 µg. Significant increases in HR seemed to persist for several hours. In this context, it should be noted that abaloparatide was proposed to be given once daily as a subcutaneous injection. Besides a post-injection increase in heart rate compared to placebo evaluations of electrocardiograms did not indicate clinically relevant changes.

In the pivotal study, the 1-hour post-dose HR increased more in abaloparatide treated patients compared to teriparatide. For example, 20% of patients treated with abaloparatide experienced an increase in HR by >20 bpm at any time point vs. 11% of patients treated with teriparatide. Patients that experienced highest increases in HR by >40 bpm (n=5, 0.7%) were all in the abaloparatide group.

Associated adverse events such as palpitations (6% vs. 2%), tachycardia (1.3% vs. 0.4%), dizziness (11% vs. 8%), nausea (9% vs. 5%) and discontinuations due to adverse events (10% vs 7%) were also reported more frequently in patients treated with abaloparatide compared to teriparatide. There were earlier (≤1 month) drop-outs in the abaloparatide arm, see above. The adverse event dizziness appeared to show a dose-response effect in patients treated with abaloparatide. The percentage of subjects who discontinued treatment due to orthostatic hypotension adverse events was higher on abaloparatide compared to teriparatide and placebo.

The analyses of adverse events of renal impairment did not reveal significant differences between abaloparatide, teriparatide, and placebo groups. The incidence of hypercalcaemia adverse events increased

with decreasing renal function in the abaloparatide and teriparatide groups. In general, the incidence of hypercalcemia was more pronounced with teriparatide than with abaloparatide (4.8% vs 2.2%).

The analysis of renal CT-scans in a subset of patients from study BA058-05-003 to assess kidney calcification did not reveal an increased incidence of calculi with abaloparatide. Hypercalcaemia and hypercalciuria occurred somewhat less frequently in patients on abaloparatide than on teriparatide but more often than on placebo. The percentage of patients with uric acid above upper normal limit was lower in the abaloparatide than in the teriparatide group but increased compared to placebo. Levels of 1,25 dihydroxyvitamin D, 25-hydroxyvitamin D, and PTH intact were also increased in line with the therapeutic effect of abaloparatide.

The bone biopsy analysis did not indicate a pathological effect of abaloparatide on bone parameters.

No clinically relevant differences across treatment groups in local tolerance events for pain, swelling, or tenderness were reported in patient diaries from study BA058-05-003. Redness was slightly more often reported in the teriparatide than in the abaloparatide group, but teriparatide was applied open label limiting the validity of the comparison.

In the analysis by age groups (<65 years, 65 to <75 years, and ≥75 years) a higher percentage of patients ≥75 years of age in the abaloparatide group reported hypertension than in the teriparatide or placebo groups. Only 4 patients (0.2%) were ≥85 years of age, 1 patient on abaloparatide (85 years) and 3 patients on placebo (85 and 86 years).

The analysis of ethnic subgroups in study BA058-05-003 was limited by the low number of subjects of other than Caucasian origin (about 80%). The system organ classes 'cardiac disorders' and 'nervous system disorders' were reported with a higher frequency in Asian compared to Caucasian patients and occurred more often with abaloparatide compared to teriparatide and placebo; preferred terms with this pattern were palpitation and dizziness. No unexpected safety findings were identified in study ITM-058-301 in postmenopausal women and men with osteoporosis in Japan.

No analysis of adverse events by baseline hepatic function is possible since no patient with baseline hepatic impairment was included in study BA058-05-003.

No clinically relevant differences across treatment groups in local tolerance were seen and the incidence of hypersensitivity adverse events was comparable between abaloparatide and teriparatide treated patients. About half of the patients developed anti-abaloparatide antibodies and about one third neutralising antibodies; antibody titres declined during the extension period on alendronate but remained high. The long-term data did not indicate an influence of the development of anti-abaloparatide antibodies as well as neutralising antibodies on the efficacy or safety of abaloparatide.

Abaloparatide is a peptide with specific affinity to the parathyroid hormone receptor 1 (PTHR1) with no known affinity to PTHR2 or other molecular targets. Since there are no known secondary targets and no known effects on CYP induction or inhibition the likelihood of drug-drug interactions was considered low. Thus, no formal drug-drug interaction studies have been performed which is considered acceptable.

Abaloparatide was authorised in the US in April 2017. Cumulatively, as of 31 March 2022, there has been a total of 482,890 abaloparatide prescriptions and 571,415 pens have been dispensed. The estimated post-marketing patient exposure to abaloparatide from launch through 31 March 2022 was 47,618 patient-years of treatment. No disproportionality safety signals with regards to serious CV events for teriparatide or abaloparatide, as opposed to romosozumab. CV events commonly occurs in the osteoporosis population, underreporting and biases are likely, and it is therefore difficult to draw any firm conclusions based on adverse event reporting data.

Since the previous procedure, the risk for adverse cardiovascular outcomes associated with heart rate increase in a real-life osteoporosis population has now been investigated in a registry study. This study used anonymized patient claims data from PRA's Symphony Health Patient Source Integrated Dataverse (IDV) database with the inclusion of enhanced hospital data, which are claims and remittance from the inpatient hospital setting and proprietary Patient Transactional Dataset (PTD) claims and prescription data. This retrospective observational Study BA058-05-028 analysed the specific risk for serious CV events after treatment with abaloparatide or teriparatide, respectively, as a secondary endpoint. The study used anonymized patient claims data from the US for the period from 01 May 2012 to 31 January 2021. Since the previous procedure, the risk for adverse cardiovascular outcomes associated with heart rate increase in a real-life osteoporosis population has now been investigated in a retrospective observational study BA058-05-028 performed in the USA using claims databases. The data from this observational study indicates that the MACE (MI/Stroke/heart failure/hospital CV death) event rates were not significantly increased in abaloparatide treated patients compared to teriparatide HR (95% CI): 1.08 (0.95, 1.22). The event rate for stroke was HR (95% CI) 1.15 (0.92, 1.45). The point estimates of Hazard Ratios were below 1.2 in most of the sensitivity and subgroup analyses. In addition, arrhythmia incidence rates were comparable between abaloparatide and teriparatide. The main limitation of the study is that mortality data outside of the hospitals was not recorded. No access to income and education data in the study is also a limitation. It is difficult to estimate any potential bias caused by different price settings of abaloparatide/teriparatide (each abaloparatide pen was discounted at 50% to the teriparatide pen).

2.5.10. Conclusions on the clinical safety

Abaloparatide is intended for a maximum 18 months of treatment. The main clinical study had an exposure of 18 months in comparison to teriparatide and placebo plus 24 months of open-label follow-up on alendronate without comparator for patients who finished the base study and were treated with either abaloparatide or placebo; no follow-up of patients previously on teriparatide is available although this might have delivered important information for the safety evaluation. However, in principle, the extent and duration of exposure as well as the chosen comparator teriparatide are considered adequate. Results from this study were already available at the time of previous procedure, where CHMP considered the B/R of abaloparatide to be negative.

Relevant differences were seen in the incidences of the adverse events of orthostatic hypotension, palpitations, nausea, dizziness, and headache, which occurred more often in abaloparatide treated patients compared with those receiving teriparatide or placebo.

Marked post-injection increases in HR with abaloparatide were observed in healthy volunteers in the thorough QT-study. Significant increases in HR seemed to persist for several hours. An increase in heart rate of the magnitude seen in the clinical trials with abaloparatide may theoretically have clinical consequences in vulnerable patients. The pivotal study had extensive exclusion criteria based on ECG findings and medical history of cardiovascular disease. Consequently, the number of cardiovascular adverse events in the study population may have been too low to conclude on any possible risks related to the post-baseline heart rate and blood pressure measurements in the study. In addition, the percentage of subjects who discontinued treatment due to palpitations, nausea, and dizziness occurred more frequently in the abaloparatide arm compared to teriparatide and placebo arms leading to possible follow-up bias and a lower number of reported cardiovascular AEs in this group over the study period.

To mitigate risks associated with orthostatic hypotension and tachycardia, the applicant proposed already in the previous procedure to monitor patients in after the first dose of abaloparatide for heart rate and blood

pressure. Patients either particularly responsive to haemodynamic effects or vulnerable to adverse events like ischemia or syncope may be detected with medical staff nearby although this does not prevent events of increased heart rate or hypotension during the later course of the treatment. It was proposed that patients at increased cardiovascular risk e.g. due to coronary artery disease, pronounced atherosclerosis, symptomatic heart failure NYHA II or III, or hypertrophic cardiomyopathy would have been monitored frequently during the course of treatment. However, the risk of increased heart rate and orthostatic hypotension in vulnerable patients exists throughout treatment and the risk cannot fully be eliminated by monitoring patients after the first dose.

In contrast to the previous procedure, post-marketing data from the US is available covering 47,618 patient-years of treatment. No signal of MACE and no cases of osteosarcoma have been identified.

Furthermore, the applicant has now submitted a retrospective, observational cohort study evaluating the effectiveness and cardiovascular safety of abaloparatide. Two additional smaller studies have been submitted that are new for this application. A clinical study in Japanese subjects and a bone biopsy study. These studies did not provide additional insights in the cardiovascular safety of abaloparatide. A dedicated study in male osteoporosis was completed in September 2021. A summary of TEAEs that occurred within the Cardiac disorders SOC or MACE + HF during the male osteoporosis Study BA058-05-019 (Study 019) were presented as requested in the Day 150 answers of the procedure. The available data suggest that men and women treated with abaloparatide have similar frequency and pattern (i.e., type) of CV events. No new safety concern was identified.

Regarding the RMP, it is acknowledged that study data regarding hepatic impairment is limited. However, no further studies are planned, and routine post-market surveillance is planned which is agreed. Inclusion of hepatic impairment in the RMP is not considered necessary but can be followed in future PSURs.

In summary, the new data has not confirmed that increases in heart rate associated with abaloparatide would be associated with increase of serious CV events. However, both the observational study and postmarketing data have important limitations. Still, for a majority of osteoporosis patient, abaloparatide is well tolerated and the safety seems acceptable. Patients who experience concurrent events with palpitations and orthostatic hypotension are likely to discontinue with the treatment. However, patients who suffer from untreated heart disease, rhythm disturbances or blood pressure are likely most vulnerable for sudden serious adverse events. It seems important to identify these patients and monitor them before they get symptoms that may have serious consequences. Strict contraindications may not be necessary but additional revisions of the SmPC section 4.4 are proposed.

Pharmacovigilance plan

As additional pharmacovigilance activities, the applicant proposed a DUS to obtain further information on the real-world drug utilisation of abaloparatide in EU as well as a physician survey to evaluate the effectiveness of risk minimisation measures (RMMs). As only routine risk minimisation in the labelling is proposed by the CHMP, no DUS or survey are not considered necessary. There will likely be some differences in abaloparatide target population characteristics between EU population and the US population and performing a DUS to investigate this further is not considered meaningful. In contrast, the need for a post-authorisation safety study (PASS) to quantify the risk of MACE has been identified. A post marketing study using European registries regarding CV risks could be feasible as such studies have been previously performed for other osteoporosis products. Such a study might provide more comprehensive safety data, e.g. all-cause mortality would be available. Of note, routine pharmacovigilance is expected to provide only little useful information

about this risk in a post marketing setting and may therefore not be sufficient in case more information is required. The Applicant is therefore requested to conduct an EU-based PASS to further quantify the potential risk of serious cardiovascular events and arrhythmias with a relevant comparator/control group.

2.6. Additional expert consultations

Two expert meetings were held during the previous abaloparatide MAA Procedure No. EMEA/H/C/004157/0000.

Expert group meeting on 1 March 2018

CHMP requested an ad hoc expert meeting to obtain the opinion of experts in the field of cardiology, osteoporosis and geriatrics, as well as from patient representatives, on the issue of observed heart rate accelerations post injection of abaloparatide in the context of a single pivotal phase 3 trial. Questions were addressed to the ad hoc expert group. The corresponding answers are presented below:

Question 1

Which data are available regarding the possible impact of an intermittent increase in heart rate (as seen in the clinical trial with abaloparatide) on cardiovascular risk in general and in the target population "postmenopausal women" in particular?

Epidemiologic data and clinical trials show an association of increased heart rate (HR) with an increased prevalence of cardiovascular (CV) disease. In most studies this represents a single measurement of HR at the onset of the study. In the experts' view such a link does not establish causality, may be due to various underlying diseases, and, in any case, is not directly comparable to the pattern of increase of HR seen with abaloparatide. Equally, examples of physiological short term acceleration of HR, such as due to exercise, food ingestion etc., cannot be seen as equivalent to HR increases induced by pharmacological intervention. There seem to be also no similar examples of pharmacologically-induced increase of HR where data of impact on CV risk would be available. Overall, the possible impact of the type of increase in HR seen with abaloparatide on CV risk in general and in postmenopausal women in particular remains unknown. However, experts pointed out the potential vulnerability of the elderly and very elderly, due to high prevalence of cardiovascular disease.

The experts voiced concern about how little was known about the cause of the HR increase with abaloparatide, which could in principle be caused by a number of mechanisms, such as catecholamine driven, vagus tone related, or reflex tachycardia due to vasodilation. One hypothesis offered by the applicant is that PTHrP analogues (and PTH) activate extra-osseous PTHrP receptors and may lead e.g. to smooth muscle relaxation, vasodilation, and consequential reflex tachycardia. The experts found a further understanding of the cause of the HR acceleration would be important to better appreciate any potential CV risk of this HR acceleration; the experts would be much more reassured about limited CV risk if the cause of the HR acceleration would be due to reflex tachycardia following vasodilation. Some experts suggested that a mechanistic study, including monitoring of heart rate and blood pressure, and preferably in the target population, could be helpful to alleviate concerns regarding potential CV risk.

Question 2

Based on the answer to question 1, please consider the extent of the possible cardiovascular risk associated with the intermittent increase in heart rate seen in the clinical trial with abaloparatide and the active comparator (teriparatide).

Regarding the potential CV risk associated with the HR increase induced by abaloparatide, the experts considered the Thorough QT study 012 in healthy volunteers: There was overall less concern with the temporary mean HR increase vs. control, which decreased to < 5 bpm difference by 2.5 hours post injection; more concerning was the substantial HR increase in individual probands in that study, e.g. up to 41 bpm with abaloparatide vs. 21 bpm with the control at 6 hours post injection, with the max. HR increase at most time points ca. twice as high as the control. Overall, a lack of more comprehensive PK/PD data was also noted. In the pivotal clinical study BA058-05-003, a higher percentage of patients treated with abaloparatide exceeded certain thresholds of HR increase (e.g. > 20 bpm post vs. pre injection) compared to both placebo and the comparator, teriparatide; higher rates of AE orthostatic hypotension and AEs leading to discontinuation were observed with abaloparatide. The experts found it not possible to draw firm conclusions regarding the potential impact of such HR changes on CV events in an osteoporosis patient population. They also pointed out the limitation of pivotal trial BA058-05-003 in that regard, as several CV diseases were exclusion criteria and it included a placebo arm, making it likely that "real world" patients (likely to have a high risk of fracture often associated with a high CV risk) would have a higher CV risk profile than the population studied in the trial.

Considering these uncertainties, and as several CV conditions were exclusion criteria in the pivotal study BA058-05-003, the cardiologists among the experts suggested to consider to contraindicate the use of abaloparatide for certain common conditions; these could include: Tachyarrhythmia, including atrial fibrillation, supraventricular tachycardia and ventricular tachycardia; sinus tachycardia; angina pectoris (both symptomatic stable, and unstable); significant valvular stenosis; heart failure; recent myocardial infarction (< 3 months).

The experts noted that teriparatide, considered as a same in class product, as comparator in the pivotal study BA058-05-003 did exhibit also HR increases, albeit to a lesser extent, and that no concerning CV safety signal has emerged for teriparatide since its authorisation in 2003, although such signals may be difficult to detect in an elderly population.

The experts further noted the availability of post authorisation safety data from the US, where abaloparatide has been approved in April 2017 (with use in up to 3600 pats. as of January 2018); however, the experts had doubts regarding the usefulness of such data to be informative on the CV safety profile, in particular in the likely absence of important patient baseline data.

Question 3

How do you consider the feasibility and effectiveness of the currently proposed risk minimisation measures in general practice? Should other risk minimisation measures, including ways to identify patients most susceptible to cardiovascular adverse events, be considered?

The applicant explained that their data did not point to any parameters which identify patients most susceptible to HR increase a priori, i.e. before treatment with abaloparatide, including e.g. no differences in pattern according to age or according to having diabetes (with potentially some degree of autonomic neuropathy).

In the pivotal study BA058-05-003, patients with a HR increase of ≤ 20 bpm HR after the first injection experienced less cardiac TEAEs, mainly palpitations (with comparable TEAEs and other parameters and outcomes), and subsequent occurrences of HR increases of >20 bpm were reduced. As a possible measure to mitigate the potential risk arising from HR increase, the applicant proposed the identification of patients experiencing an increase in HR of >20 bpm at 1 hour post first injection with abaloparatide, to employ a different follow up strategy for these patients during subsequent treatment with abaloparatide. These

patients should then be seen more frequently, which would be needed to be further specified in the product information.

The experts were critical whether there could be a meaningful rational of different treatment strategy for patients with a HR of >20 bpm at 1 hour post first injection. Cardiologist experts raised the question whether such patients identified as having a higher risk of repeated heart rate increases exceeding a certain threshold should be considered for a more comprehensive investigation to exclude CV disease (including echocardiography and Holter monitoring), or may in some cases discontinue the medication overall.

The practicality of assessing the HR at 1 hour post injection and a more frequent follow up was, however, not questioned, and considered by the majority of osteoporosis experts as unproblematic, as this kind of treatment is with specialists in most health care systems, although with some exceptions. However, it was seen as problematic to base such a decision on a single, quite variable, measurement at individual patient level, and also because such a strategy would be based on a post hoc assessment with all its limitations.

According to the osteoporosis experts, short term side effects observed at time of HR increase, such as tendency to hypotension / dizziness, and a subsequent risk of falling, could be mitigated by moving injection time point to bed time, based on experience with teriparatide injections (although, risk of falls during night time might still be an issue). The majority of the osteoporosis experts considered side effects manageable, in particular considering that as a PTH-related osteoanabolic agent the length of treatment is limited to maximal total duration of 18 months. Patient representatives voiced concerns in case quite frequent follow-up visits would be needed and whether side effects might impact compliance longer-term.

The applicant is proposing a post authorisation safety study (PASS), using a population-based health care data base, with as primary outcome major adverse cardiovascular events (MACE) (global, but in particular US-based). While details of such a PASS proposal were not part of the briefing or discussion of the AHEG meeting, the experts had nevertheless a number of general comments: In general, in the presence of only one single pivotal trial, a second randomised controlled trial could be desirable, but it was acknowledged that an RCT specifically for such a safety concern would be quite large. Although the absence of CV disease-related contraindications in the US labelling might allow inclusion of high CV risk patients in a US study, there may be major differences, for instance use of such osteoanabolic therapy in the EU might be mostly in severe osteoporosis, representing a different population. In any such study extensive cardiovascular baseline data should be recorded, which may not be available in existing registries. Moreover, evaluation of risk mitigation measures could be also a consideration. Therefore, an EU-centric focus of such a PASS might be preferable.

Report from the 2nd Ad Hoc expert Group meeting held on 10 July 2018, Re-examination procedure

Question 1

Do you consider the efficacy sufficiently established in the applied indication based on the provided data? Moreover, how do you view the supportive value of the PP population results as primary analysis as well as the results at 43 months in the ITT population based on the linear extrapolation model for the application?

Although this application is based on a single study only, the 18- month Phase 3 study BA058-003 ACTIVE study, the experts were of the view that efficacy of treatment with abaloparatide over 18 months regarding the incidence of new radiologically detected vertebral fractures was demonstrated in the pivotal study (abaloparatide 0.51% vs. placebo 4.2%; the absolute risk reduction in the abaloparatide treated group compared to placebo was 3.65 (95% CI: 2.00;5.59 ; p<0.0001). The osteoporosis experts considered

demonstration of such an effect on vertebral fractures as highly relevant for an osteoporosis product. The extension study BA058-05-005 was considered supportive by the experts.

With regards to the efficacy for non-vertebral fractures, the majority of the experts were of the view that, even though the pivotal study failed to demonstrate a statistically significant effect on non-vertebral fractures versus placebo (abaloparatide 2.2% vs. placebo 3.1%), relevant effects on major osteoporotic fractures, BMD (total hip, femoral neck, lumbar spine) and biomarkers were demonstrated. While the study was not designed for direct in- study comparison with teriparatide, similarities of the mechanism of action might allow some extrapolation. Therefore, taking together all the data and from a clinical perspective, the majority of experts was of the view that an effect of abaloparatide on reduction of non-vertebral fractures is expected. The data on BMD would support this. The methodology expert was not favouring this approach and was of the view that the current data are not robust to establish a positive effect on reduction of non-vertebral fractures.

Reservations were expressed regarding the use of the PP population because of selection risk and the use of the linear extrapolation model (for placebo) was also questioned.

Question 2

With regard to the observed heart rate increase upon administration of abaloparatide, do you consider that:

    a. **the HR measured at one hour post-dose represents the relevant value to discuss a potential safety issue or are other time-points post-dose better suited?**

    b. **do you consider the observed HR increase to infer a potential safety risk for the target population?**

    If so,

        i. **can you envision an osteoporosis patient population in which this would not be the case and how can the patients be described?**

        ii. **do you consider that the proposed risk minimisation measures and the cardio-vascular contra-indications to adequately address the safety risk associated with the HR increase?**

        iii. **how do you view the potential CV risk associated with heart rate increase of abaloparatide compared to teriparatide?**

2.a. Overall, the experts considered HR measurement within one hour post-dose (as was done in the clinical study) to be an appropriate timepoint. They discussed as well 15 minutes as a first timepoint.

In contrast, one expert even questioned the need of systematic HR measurement at all.

2.b. The observed increase in heart rate could possibly infer a safety risk to certain groups of patients, such as patients who have pre-existing heart disease.

The cardiology experts referred to some of the animal data presented by the applicant at the current expert meeting, where the applicant explained that (at least) part of the HR response is due to a direct effect on the sinus node. This chronotropic effect together with a vasodilation effect as the main underlying MoA for the

increase in HR with abaloparatide, reassured the experts with regards to a potential safety risk. The experts are of the view that the proposed contraindications which exclude certain groups of patients where increased heart rate may infer a safety risk are important and could be considered reassuring. The osteoporosis experts as well found the explanation on the mechanism of action for the observed heart rate increase reassuring. The lack of CV safety signals from the pivotal study was considered reassuring, although due to the very small number of MACE events these results should be interpreted with caution.

It was acknowledged that the data from the randomised trial represent a selected (healthier) population; a PASS study would be useful to provide information on real-word patients (e.g. elderly patient on multiple medications)

i. The target population could be described by a list of contraindications to exclude patients for whom increased heart rate may pose a safety risk.

ii. The experts believe that risk minimisation measures as proposed in the product information (4.3 contraindications and 4.4 Special precautions and warnings for use), would address the potential safety risk associated with HR increase.

The experts found a screening of heart rate (within 1 hour after first administration of abaloparatide), as described in the SmPC, a reasonable proposal. This should allow capturing those patients with a relevant increase of the HR. One expert mentioned that for some patients HR increase may appear later (i.e. not after the first administration) though; those patients may be offered HR /ECG screening, on a as needed basis, at the time when tachycardia symptoms are reported.

iii. The experts considered that the potential CV risk associated with increased heart rate could be expected to be somewhat similar, to a certain extent, for abaloparatide and teriparatide.

However, they pointed out that uncertainties remain and a greater potential of an increased CV risk for abaloparatide exists. In the pivotal study, the 1-hour post-dose heart rate increased more in the abaloparatide treated patients compared to teriparatide. Also associated adverse events such as palpitations, tachycardia, dizziness, nausea and discontinuations due to adverse events were also reported more frequently in the abaloparatide than in the teriparatide study arm. The open-label design of the teriparatide makes it difficult to interpret the comparison between the two treatment groups.

Question 3

Please discuss to what extent the results from the post marketing setting and from the planned PASS obtained in the US are relevant for the EU patients. This should include, but need not be limited to the following topics:

> a. **Is the anticipated EU population the same as the one that would currently use teriparatide?**

> b. **Is their risk of CV events comparable to the EU target population?**

There was support for a Drug Utilisation Study in particular since this could provide useful information on the EU and US populations and could inform the design of the PASS study.

It is expected that the EU and US patient population is different based on differences in availability of healthcare and reimbursement. A further difference in the risk of CV events is expected from the fact that the abaloparatide US label contains no CV contraindications.

Therefore, the experts call for a PASS sized to have adequate participation from both a US and a European population.

The experts recommended to ensure the inclusion of sufficient frail and elderly patients.

The experts discussed the appropriate comparator in the PASS. Teriparatide and denosumab were mentioned to obtain more comparable populations, but there was no conclusion regarding this point. One expert voiced concern that there is considerable GP use of denosumab in rather mild osteoporosis.

Other comments

One patient representative made a call for the applicant to collect information on patient reported outcome/QoL parameters. In particular the effect on pain relief was mentioned.

The experts did not raise further comments on the grounds for refusal adopted by the CHMP in its opinion of March 2018).

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP version 0.5:

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

2.7.2. Pharmacovigilance plan

Summary of additional PhV activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Abaloparatide PASS:	To evaluate the potential risk of serious CV events of MI, stroke, all-cause	Serious cardiovascular events (i.e. MACE, arrhythmia)	Final PASS protocol submission	Within 3 months post abaloparatide approval

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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	mortality including CV death and arrhythmias associated with the use of abaloparatide in routine clinical practice compared with other available OP medications		Interim reports on an annual basis	For the entire study period until the final study report is submitted
			Final report	2029-2030

2.7.3. 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.

Safety concern	Routine risk minimisation activities
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. 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.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.04.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Eladynos (abaloparatide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Abaloparatide subcutaneous daily injection is intended for treatment of postmenopausal osteoporosis to increase bone mineral density (BMD) and consequently reduce the risk of vertebral and non-vertebral fractures. The proposed therapeutic indication for abaloparatide is treatment of osteoporosis in postmenopausal women at increased risk of fracture.

In Europe, it is estimated that 4.3 million new fragility fractures occur every year. Most fractures occur at the spine, wrist and hip. The vast majority of osteoporotic fractures occur in postmenopausal women and the incidence increases markedly with age.

Abaloparatide is a synthetic, 34 amino acid analogue of PTHrP(1-34) and belongs to the same class as teriparatide (approved for osteoporosis almost 20 years ago) and stimulates the production and activity of osteoblasts, increasing BMD by building new bone.

3.1.2. Available therapies and unmet medical need

The primary aim of pharmacological treatment is the reduction of the risk of osteoporotic fractures. Currently, there are two therapeutic approaches for the treatment of osteoporosis; one is to decrease bone loss with an antiresorptive drug and the other is to increase new bone formation and BMD with a bone anabolic therapy. Antiresorptive agents include oestrogens and selective oestrogen receptor modulators, anti-RANK ligand antibodies, and bisphosphonates. They inhibit the bone-resorbing activity of osteoclasts. In contrast, anabolic therapy like teriparatide and abaloparatide stimulate the production and activity of osteoblasts, increasing BMD by building new bone. Romosozumab is a monoclonal antibody that acts by inhibiting sclerostin with a mixed anabolic/antiresorptive effect on bone that was approved in 2019.

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.

3.1.3. Main clinical studies

The abaloparatide clinical programme consists of 12 studies with a total of 1305 subjects receiving at least one dose of abaloparatide, including Phase 1 studies in healthy postmenopausal women, healthy volunteers, subjects with renal impairment and postmenopausal women with osteoporosis and two Phase 2 studies.

The basis for the MAA of abaloparatide-SC is the 18 months pivotal Phase 3 study BA058-05-003 (ACTIVE study) in postmenopausal women with osteoporosis. This is the only study that meets the criteria for pivotal study in osteoporosis with fractures as primary efficacy variable. Based on the deviations found during the GCP inspections in the previous 2015 procedure, data from two sites were excluded when assessing the abaloparatide marketing authorisation application. The clinical efficacy and safety of daily 80 µg abaloparatide was studied in comparison to a matched placebo and an open-label active control daily teriparatide 20 µg SC. A total of 2070 patients were randomised into three treatment arms of approximately 690 patients in each

group. The 18 months period was followed by extension study BA058-05-005, where a total of 963 patients who previously received placebo (n=494) or abaloparatide (n=469) received 18 months of alendronate therapy.

In addition to above data that was already submitted and assessed in the previous 2015 procedure, the applicant has now submitted:

- Study ITM-058-301: placebo-controlled study, approximately 200 postmenopausal women and men with osteoporosis in Japan, BMD as primary endpoint

- Study BA058-05-020: 3 month open-label study, 23 US patients with bone biopsies

- In a sub-population of pivotal study BA058-05-003, an additional retrospective post-hoc analysis on hip dual-energy X-ray absorptiometry (DXA) images and bone mineral density (BMD) was conducted (3D-DXA study).

- Study BA058-05-028: A prospectively planned, retrospective observational cohort study using US claims data from >11,000 patients

- Post-marketing safety reporting from United States since approval in 2017, approximately 47,618 patient-years of treatment.

3.2. Favourable effects

Abaloparatide administered at a dose of 80 µg SC daily over up to 18 months significantly reduced the risk of experiencing new vertebral fractures compared to placebo in postmenopausal women in the main study BA058-05-003; the active comparator teriparatide also showed a significant reduction in the incidence of new vertebral fractures compared to placebo. New vertebral fractures (mainly non-clinical) occurred in 3 (0.5%) patients treated with abaloparatide, in 25 (4.2%) patients on placebo, and in 4 (0.7%) patients on teriparatide. After 6 months of alendronate treatment in the extension study BA058-05-005, no patient previously on abaloparatide and 6 patients previously on placebo experienced new vertebral fractures while after 24 months these numbers were 2 patients previously on abaloparatide and 13 on placebo. The absolute risk reduction in the abaloparatide treated group compared to placebo was -3.65, (95% CI: (-5.59, -2.00) in study BA058-05-003 at month 18 (p<0.0001). In the extension study BA058-05-005, the risk reduction versus placebo (95% CI) was -1.23 (-2.65, -0.16; p=0.0313) at Month 6 and -2.22 (-4.08, -0.64; p=0.0074) at Month 24.

The percent changes in BMD at total hip, femoral neck, and lumbar spine from baseline to 18-month were statistically significantly higher with abaloparatide compared to placebo and the results demonstrate a relevant increase in BMD in patients on abaloparatide; teriparatide also increased BMD from baseline to 18 months at all three sites. BMD decreased with placebo at all three sites.

Comparable absolute BMD increases were seen in abaloparatide treated subjects in study ITM-058-301, performed in Japan.

In the open label extension study BA058-05-005 where patients previously on abaloparatide or placebo (but not those on teriparatide) were switched to alendronate, further increases in BMD from the BA058-05-003 baseline were observed in both groups. Statistically significant differences favouring the abaloparatide/alendronate group were observed at the total hip, femoral neck, and lumbar spine for all timepoints.

Retrospective analysis of hip DXA images from study BA058-05-003 using three-dimensional (3D) modelling methods demonstrated increases in trabecular volumetric BMD (vBMD) and cortical thickness and increased cortical vBMD compared to baseline after 18 months treatment with abaloparatide.

In study BA058-05-003, percent changes in the anabolic serum bone marker s-P1NP were higher for abaloparatide versus placebo at all time-points, while the increase with teriparatide was higher than with abaloparatide from 3 months onwards. The bone resorption marker s-CTX showed a transient increase for abaloparatide versus placebo from 3 to 12 months and increases in s-CTX were highest with teriparatide. Activities of BALP and s-osteocalcin were higher with abaloparatide versus placebo and highest in participants using teriparatide.

Study BA058-05-028 was a retrospective observational cohort study using administrative claims data for the period from 01 May 2012 to 31 January 2021. According to the analysis presented by the applicant, non-inferiority for abaloparatide versus teriparatide was demonstrated for the endpoint "first incidence of non-vertebral fractures", in the dataset including 11616 patients in both treatment cohorts.

3.3. Uncertainties and limitations about favourable effects

GCP related serious findings lead to exclusion of two study sites in the main study BA058-05-003, reducing the original total study population by 16% from 2463 to 2070 participants. All assessments in this report were therefore based on this smaller subset of study participants.

A significant and clinically relevant efficacy of abaloparatide compared to placebo on non-vertebral fractures could not be established in the main study [log-rank p=0.3675; HR (95% CI) 0.74 (0.38, 1.43)] and there was no statistically significant difference between abaloparatide and teriparatide on the time to first incidence of non-vertebral fracture [p=0.4919; HR (95%CI) 1.30 (0.61, 2.79)]. Furthermore, the analysis of this key secondary endpoint non-vertebral fracture was changed in the statistical analysis plan that was finalised two days prior to database lock and further changes to the analysis were introduced after database lock, upon a request from the US FDA.

The active comparator teriparatide was not blinded due to commercial availability of teriparatide. For the analysis of differences in effects between teriparatide and abaloparatide as well teriparatide and placebo, it has to be considered that patients and physicians have been aware of the treatment applied in patients on teriparatide.

Discontinuation and the percentage of patients with no post-treatment x-ray were different between groups; discontinuation was highest with abaloparatide and lowest with teriparatide and the percentage of patients with no post-treatment x-ray was higher in patients on abaloparatide compared to both placebo and teriparatide.

The time to first incidence of other fractures defined as clinical fracture, major osteoporotic fracture, wrist fracture, non-vertebral fracture including any level of trauma, and clinical spine fracture was numerically increased for abaloparatide compared to teriparatide but differences were mostly not statistically significant and are not considered clinically relevant.

It is not clear if and how the differences in changes in serum bone markers s-P1NP, s-CTX, BALP, and s-osteocalcin relate to difference in the reduction of fracture risk between abaloparatide and teriparatide.

There were only minimal numerical differences in change and percent change in vertical height between groups and differences were neither statistically significant nor clinically relevant.

Other randomised clinical studies did not assess abaloparatide efficacy on fracture reduction. In the Japanese study ITM-058-301, with its limited number of participants, no new vertebral fractures were identified in the abaloparatide group versus 3/70 (4.3%) in the vehicle group. In the abaloparatide group there were 3 (2.2 %) new non-vertebral fractures up to the last visit and 2 (2.9%) in the placebo group. The number of fractures was thus too low to draw any conclusions on efficacy in fracture reduction.

The new histomorphometry (Study BA058-05-020) and 3D analysis (Study BA058-05-003) do support an anabolic effect of abaloparatide on bone. However, it is unclear how this data can be translated into fracture risk reduction.

Comprehensive additional efficacy analyses that were requested from study BA058-05-028 support initial analyses and comparable effectiveness vs teriparatide in a US population. Observational studies are prone to biases impossible to completely master reliably. It is still reasonable to conclude that no lack of effectiveness was identified.

3.4. Unfavourable effects

In the pivotal Phase 3 study BA058-05-003, relevant differences were seen in the incidences of the adverse events orthostatic hypotension (abaloparatide, teriparatide, placebo: 28.4%, 19.8%, and 14.4%, respectively), palpitations (5.6%, 1.7%, and 0.4%, respectively), nausea (8.5%, 5.4%, and 3.1%, respectively), dizziness (11.1%, 8.2%, and 7.1%, respectively), and the increase in heart rate (maximum mean (SD) increase of 7.8 (8.60) bpm, 6.7 (9.28) bpm, and 1.9 (8.95) bpm, respectively) which occurred more often in abaloparatide treated patients compared with those receiving teriparatide or placebo; the adverse event dizziness showed also a dose-dependent effect in patients treated with abaloparatide (20 µg, 40 µg, 80 µg: 0%, 9%, and 11%, respectively).

Hypercalcaemia and hypercalciuria occurred less frequently in patients on abaloparatide (2.2%, 15.6%) than on teriparatide (4.8%, 18.1%) but more often than on placebo (0.6%, 12.5%); the incidence of hypercalcaemia adverse events increased with decreasing baseline renal function (CL$_{CR}$ ≥90 ml/min, ≥60 <90 ml/min, <60 ml/min: 0.6%, 1.9%, 1.9%).

There were no significant differences between abaloparatide, teriparatide, and placebo in adverse events leading to death and serious adverse events.

In general, the highest incidences of adverse events as well as differences between groups were seen within the first 2 months of treatment; differences were no longer apparent from 6 months onwards.

Abaloparatide injection is followed by an increase in heart rate. In study BA058-05-003, abaloparatide and teriparatide markedly increased heart rate measured 1-hour post injection compared to placebo. The mean increases from baseline in the abaloparatide group ranged between 6.9 and 7.8 bpm from day 1 to month 12. For teriparatide, the mean increases in heart rate post-dose were lower, between 5.5 to 6.7 bpm from day 1 to month 12, and for placebo, the mean increases post-injection were 1.2 to 1.9 bpm. Overall, 12.5%, 4.8%, and 0.6% of patients on abaloparatide, teriparatide, and placebo, respectively, had an increase in heart rate >25 bpm at any time. About 20% of patients experienced an increase in HR by >20 bpm at any time point; only patients on treatment with abaloparatide experienced HR increases by more than 40 bpm (n=5) and there were even single cases were the increase in heart rate was >50 bpm. These observations were paralleled by a higher rate in cardiac related TEAEs in the abaloparatide group than in the teriparatide or the placebo group (12%, 6% and 5%, respectively). The difference between groups was driven by higher incidences of palpitations and tachycardia in the abaloparatide group.

In line with the findings in the pivotal study BA058-05-003, marked post-injection increases in heart rate for abaloparatide were observed in healthy volunteers in the thorough QT-study BA058-05-012. The maximum mean increase of 14.6 bpm was noted 15 min after the therapeutic dose of 80 µg vs. 0.1 bpm in the placebo group. Mean increases of 9.5 bpm were seen 1 h post-dose. Mean increases of 9.5 bpm were seen 1 h post-dose and lasted up to approximately 6 hours and returned to baseline at 24 hours, i.e. the proposed time point for the next injection in a clinical setting.

Theoretically, an increase in heart rate due to vasodilation and possibly coronary vasodilation leading to coronary steal effects may precipitate myocardial ischemia in vulnerable patients. Orthostatic hypotension, defined as a decrease in SBP of ≥20 mmHg from supine to standing or in DBP of ≥10 mmHg from supine to standing 1 hour post-dose, was reported in all treatment groups (7 AEs in abaloparatide, 3 in placebo and 3 in teriparatide).

About half of the patients developed anti-abaloparatide antibodies and about one third neutralising antibodies; antibody titres declined during the extension period on alendronate. Since pharmacologic activity or efficacy were not negatively impacted by ADA or NAb formation, there is no clinical concern related to this finding.

3.5. Uncertainties and limitations about unfavourable effects

Clinical trial safety data for abaloparatide are limited to an exposure of 18 months in comparison to teriparatide and placebo plus 24 months of open-label follow-up on alendronate without comparator for patients who finished the base study and were treated with either abaloparatide or placebo; no follow-up of patients previously on teriparatide is available although this might have delivered important information for the safety evaluation.

The haemodynamic effects of abaloparatide raise a concern that they might be associated with adverse cardiac effects in subjects with ischemic heart disease or other significant cardiovascular disease. Regarding major adverse cardiac events (MACE), the number of events during 18 months was too limited for any firm conclusions on differences between groups. There were 4 (0.6%) cases of myocardial ischemia / acute myocardial infarction in the abaloparatide group versus 5 (0.7%) in the teriparatide and 1 (0.1%) in the placebo group. However, it is notable that patients with uncontrolled hypertension, heart rate abnormalities, orthostatic hypotension or significant cardiovascular disease were excluded from the pivotal trials. Therefore, there is a remaining uncertainty about the impact of abaloparatide associated hemodynamic effects in patients with significant cardiovascular disease. Two additional smaller studies have been submitted that are new for this application: A clinical study in Japanese subjects and a bone biopsy study. These studies did not provide additional insights in the cardiovascular safety of abaloparatide. A dedicated study in male osteoporosis was completed in September 2021. A summary of TEAEs that occurred within the Cardiac disorders SOC or MACE + HF during the male osteoporosis Study BA058-05-019 (Study 019) were presented in the data provided by the applicant. The available data suggest that men and women treated with abaloparatide have similar frequency and pattern (i.e., type) of CV events. No new safety concern was identified.

Since the previous procedure, the risk for adverse cardiovascular outcomes associated with heart rate increase in a real-life osteoporosis population has now been investigated in a retrospective observational study BA058-05-028 performed in the USA using claims databases. The data from this observational study indicates that the MACE (MI/Stroke/heart failure/hospital CV death) event rates were not significantly increased in abaloparatide treated patients compared to teriparatide HR (95% CI): 1.08 (0.95, 1.22). The

event rate for stroke was HR (95% CI) 1.15 (0.92, 1.45). The point estimates of Hazard Ratios were below 1.2 in most of the sensitivity and subgroup analyses. In addition, the arrhythmia incidence rates were comparable between abaloparatide and teriparatide.

Mortality data, as well as other outcomes in the study was derived from mortality recorded on the hospital (medical facility) discharge status that covers only about one-third of the total death records. Moreover, as in all studies of this kind, channelling bias cannot be excluded. For instance, the cost of teriparatide is substantially higher than that of abaloparatide. Notably, the rate of out of hospital deaths may be higher for those with lower socioeconomic status due to poor access to healthcare or lower education regarding warning signs of a serious event. No access to mortality data outside of the hospitals is an important limitation of study BA058-05-028. No access to income and education data in the study is also a limitation.

Overall, the risk and directionality of potential bias in this study, due to the abovementioned factors and others, is not easy to assess; consequently, the same goes for the sensitivity of this study to detect any difference in cardiovascular safety between the products. However, given the outcome, a large detrimental effect relative to teriparatide may be considered unlikely.

Teriparatide has been evaluated in hypertensive women and in patients with stable heart failure. No such studies were included in this MAA for abaloparatide.

The thorough QT study produced data which fulfilled, although borderline, the criterion for a negative QT study.

No analysis of adverse events by baseline hepatic function is possible since no patient with baseline hepatic impairment was included in study BA058-05-003.

The diminishing differences in frequency of adverse events over the course of the study might be attributable to the differential drop-out between treatment groups; fewer patients on abaloparatide than on either teriparatide or placebo completed the 18-month trial BA058-05-003 and patients on abaloparatide dropped out earlier than on teriparatide or placebo, most frequently during the first month of the study. The pattern of shorter mean duration of treatment with abaloparatide compared to teriparatide and placebo was also seen in the phase 2 study BA058-05-002 as well as in the observational cohort study BA058-05-028.

The analysis of ethnic subgroups in study BA058-05-003 was limited by the low number of subjects of other than Caucasian origin (about 80%). The system organ classes 'cardiac disorders' and 'nervous system disorders' were reported with a higher frequency in Asian compared to Caucasian patients and occurred more often with abaloparatide compared to teriparatide and placebo; preferred terms with this pattern were palpitation and dizziness. No unexpected safety findings were identified in study ITM-058-301 in postmenopausal women and men with osteoporosis in Japan.

The analysis of renal CT scans in a subset of patients from study BA058-05-003 to assess kidney calcification did not reveal an increased incidence of calculi with abaloparatide compared to placebo but organ calcification has been identified in preclinical trials. Hypercalcemia and hypercalciuria can contribute to the development of nephrolithiasis which has been identified as ADRs with abaloparatide therapy and is described in the proposed SmPC. No clinical safety signal has been identified regarding other organ calcification related events.

3.6. Effects Table

Table 51/ Effects Table for abaloparatide in the treatment of osteoporosis in postmenopausal women, study BA058-05-003 (database lock: 10 December 2014, last patient completed: 7 October 2014)

Effect	Short Description	Unit	Abalo	Teri	Plb	Uncertainties / Strength of evidence	References
	Favourable Effects						
Incidence new vertebral fractures	% patients with new vertebral fracture abalo vs plb baseline to 18 months, mITT	n (of numbers analysed) (%) RR (95% CI) p	3 (583) (0.51) **abalo vs plb** -3.65 (-5.59, -2.00) <0.0001	4 (600) (0.67) **teri vs plb** -3.50 (-5.45, -1.82) <0.0001	25 (600) (4.17)	significant and clinically relevant effect vs. placebo limitations concerning statistical analysis and definition of endpoints effect size might be overestimated	see discussion on clinical efficacy
Time to first incident non-vertebral fracture	K-M estimated event rate (%), 19 months, ITT	n, K-M % HR (95% CI) p (log-rank test) HR (95% CI), p (log-rank test)	15 2.7 **abalo vs plb** 0.74 (0.38, 1.43) 0.3675 **abalo vs teri** 1.30 (0.61, 2.79) 0.4919	12 2.0 **teri vs plb** 0.56 (0.28, 1.15) 0.1095	21 3.6	effects not statistically significant and not clinically relevant especially considering one pivotal trial significant uncertainties regarding statistical analysis and definition of endpoint	
	Unfavourable Effects						
Neutralising antibodies		%	~30	N/A	N/A	plb and comparator (teri) controlled study teri not blinded only 18 months of exposure to abalo	see discussion on clinical safety
Orthostatic hypotension		%	28	20	14		
Discon. due to orthostatic hypotension		%	3.6	1.7	0.9		
Palpitation		%	5.6	1.6	0.4		
Increase HR >20 bpm		%	19.7	10.9	3.2		
Increase HR >30 bpm		%	3.9	1.2	0		

Effect	Short Description	Unit	Abalo	Teri	Plb	Uncertainties / Strength of evidence	References
Increase HR >40 bpm		%	0.7	0	0		
Nausea		%	8.5	5.4	3.1		
Dizziness		%	11.1	8.2	7.1		
Headache		%	8.5	7.1	5.8		
Discon. due to AEs		%	9.8	6.7	6.0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The main clinical consequence of osteoporosis is an increased risk of fragility fractures. Radiological vertebral fractures are a common finding in postmenopausal women and usually asymptomatic (approximately 60%). A typical symptomatic vertebral fracture causes acute pain and decreased mobility that lasts about one month. Fractures that require surgery are the most dangerous aspect of osteoporosis. Hip fracture and the following surgery are associated with serious risks, permanent disability, and increased mortality. Radiological vertebral fractures on the other hand are considered as important markers of osteoporosis severity. BMD is a surrogate marker for osteoporosis severity and included in the osteoporosis definition by the WHO criteria.

Abaloparatide significantly reduces the risk of developing new vertebral fractures. However, the CHMP guideline on osteoporosis requests that for the demonstration of efficacy of a new anti-osteoporotic drug effects on non-vertebral fractures should also be shown, preferably in a separate, adequate powered study. Abaloparatide has only been studied in one trial BA058-05-003 with non-vertebral fractures as key secondary endpoint. In this trial no effect of abaloparatide on non-vertebral fractures was established. Such an effect could possibly be extrapolated from knowledge of the effects of teriparatide (same molecule class, same mode of action) only. Teriparatide was used as a comparator both in main clinical study BA058-05-003 and in the retrospective, observational cohort study BA058-05-028. In study BA058-05-003, the benefit in prevention of new vertebral fractures was comparable to teriparatide. In study BA058-05-028, preliminary analyses indicated similar effectiveness of abaloparatide to teriparatide in the prevention of non-vertebral fractures in propensity score matched cohorts. Other endpoints investigated in clinical programme, e.g. BMD and serum bone markers, are in line with the primary finding of a reduction in the risk of osteoporotic fractures and endpoints investigated primarily show the same trend of an advantage of abaloparatide over placebo. However, these endpoints are only supportive surrogates, they do not establish effects in their own right, and do not allow a valid conclusion on efficacy of abaloparatide over teriparatide.

The identified risks of nausea, dizziness, and palpitations did not increase the number of syncopes or falls in study BA058-05-003 but led to more discontinuations in the abaloparatide-treated patients.

Hypercalcaemia and hypercalciuria occurred less frequently in patients on abaloparatide than on teriparatide but more often than on placebo. Similar precautions regarding hypercalcemia are proposed in the SmPC of abaloparatide than for teriparatide which is endorsed.

The increase in heart rate was more pronounced in patients treated with abaloparatide compared with teriparatide. There is a concern that an increase in heart rate of the magnitude seen in the clinical trials with abaloparatide may have clinical consequences in vulnerable patients, such as those with ischemic heart disease or undiagnosed/untreated cardiovascular disease.

The pivotal study had extensive exclusion criteria based on ECG findings and medical history of cardiovascular disease. Consequently, the number of cardiovascular adverse events in the study population was too low to conclude on any possible risks related to the post-baseline heart rate and blood pressure measurements in the study. In addition, the percentage of subjects who discontinued treatment due to palpitations, nausea, and dizziness was higher in the abaloparatide compared to the teriparatide and placebo arms leading to possible follow-up bias and a lower number of reported cardiovascular AEs in this group over the study period.

The data from the retrospective study BA058-05-028 indicates that the MACE (MI/Stroke/heart failure/hospital CV death) event rates were not significantly increased in abaloparatide treated patients compared to teriparatide in a US-osteoporosis population. In addition, the arrhythmia incidence rates were comparable between abaloparatide and teriparatide. While the BA058-05-028 study provides some reassurance that large detrimental effects in a broad population are unlikely, patients who suffer from untreated heart disease, rhythm disturbances or blood pressure, may not tolerate the hemodynamic effects of abaloparatide. The product information must clarify that cardiovascular risks must be weighed against anticipated benefits in such patients. Moreover, appropriate clinical monitoring after a first dose would help further identify patients that do not tolerate the hemodynamic effects of abaloparatide. In addition, patients with cardiac disease should be monitored for worsening of their disease. If severe orthostatic hypotension or severe cardiovascular symptoms occur, treatment should be discontinued.

3.7.2. Balance of benefits and risks

Efficacy of treatment with abaloparatide over 18 months regarding the incidence of new radiologically-detected vertebral fractures was demonstrated in the pivotal study (abaloparatide 0.51% vs. placebo vs 4.2%). However, the study failed to demonstrate statistically significant efficacy on non-vertebral fractures versus placebo (abaloparatide 2.2% vs. placebo 3.1%). Only one hip fracture occurred in the study (on placebo). Similarity of the mechanism of action with teriparatide might allow some extrapolation regarding efficacy but direct in-study comparison with teriparatide was based on very few fracture events. New vertebral fractures occurred in 3/583 (0.51%) patients on abaloparatide versus 4/600 (0.67%) patients on teriparatide. Non-vertebral fractures occurred in 15/696 (2.2%) patients on abaloparatide versus 12/686 (1.7%) patients on teriparatide. There are no studies comparing abaloparatide with bisphosphonates, the current standard therapy osteoporosis.

Regarding the grounds for refusal during the previous procedure; there is still only one randomised controlled trial conducted with fractures as the primary endpoint (BA058-05-003/005). There were GCP-related findings during the procedure which led to a significantly reduced study population in the pivotal study with the

consequence that no statistically significant effect on the non-vertebral fractures could be demonstrated vs placebo. However, additional supportive data has been submitted; a placebo-controlled Phase 3 study in Japan, a histomorphometric study in patients, an additional analysis of the hip DXA images, and an observational cohort study using US claims data giving some support of comparable effectiveness vs teriparatide in a US population.

In summary, the applicant has demonstrated reduction of radiological vertebral fractures compared to placebo. The effect of abaloparatide versus placebo on non-vertebral fractures was not statistically significant but the data were indicative of a trend in favour of abaloparatide. The results regarding increasing BMD compared to placebo in lumbar spine, hip and femoral neck are convincing. Therefore, in this particular case, there seems not to be a scientific reason to presume efficacy only for vertebral but not for non-vertebral fractures, regardless of statistical significance being demonstrated for vertebral (but not for non-vertebral) fractures. From the totality of information, including both the data from the pivotal study and supportive studies as well as knowledge of the effects of teriparatide (same molecule class, same mode of action), the efficacy of abaloparatide could be considered sufficiently demonstrated in the applied indication.

Some concerns about the impact of the hemodynamic effects of abaloparatide remain, despite a large observational study showing no impact on MACE events compared to teriparatide. The benefits and risks of treatment must be carefully weighed in vulnerable patients, and appropriate precautions and monitoring generally applied.

As additional pharmacovigilance activities, the applicants proposed a DUS to obtain further information on the real-world drug utilisation of abaloparatide in EU as well as a physician survey to evaluate the effectiveness of risk minimisation measures (RMMs). As only routine risk minimisation in the labelling is proposed by the CHMP, no DUS or survey are not considered necessary. There will likely be some differences in abaloparatide target population characteristics between EU population and the US population and performing a separate study to investigate this further is not considered meaningful. In contrast, the need for a post-authorisation safety study (PASS) to quantify the risk of MACE has been identified. A post marketing study using European registries regarding CV risks could be feasible as such studies have been previously performed for other osteoporosis products. Such a study might provide more comprehensive safety data, e.g. all-cause mortality would be available in contrast to the US-based study. The Applicant is requested to conduct an EU-based PASS to further quantify the potential risk of serious cardiovascular events and arrhythmias with a relevant comparator/control group.

3.7.3. Additional considerations on the benefit-risk balance

Initial MAA application for abaloparatide was received by the EMA on 17 November 2015. On 22 March 2018, the CHMP issued a negative opinion for granting a marketing authorisation to Eladynos. This negative opinion remained at the re-examination on 26 July 2018. Two expert group meetings were held, 1 March 2018 and 10 July 2018. See section 2.6. "Additional expert consultations".

3.8. Conclusions

The overall benefit/risk balance of Eladynos is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Eladynos is favourable in the following indication(s):

Treatment of osteoporosis in postmenopausal women at increased risk of fracture

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that abaloparatide is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 13 October 2022