EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2018
EMA/CHMP/581111/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eladynos

International non-proprietary name: abaloparatide

Procedure No. EMEA/H/C/004157/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ABL	Abaloparatide
ABL-IV	Abaloparatide intravenous
ABL-SC	Abaloparatide subcutaneous
ABL-TD	Abaloparatide transdermal
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active Pharmaceutical Ingredient (=Active Substance)
AS	Active Substance
AST	Aspartate aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APD	Action Potential Duration
$AUC_{(0\text{-last})}$	Area under the plasma concentration-time curve from time zero to the last measurable concentration
$AUC_{(0\text{-inf})}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity
AUCD	Dose-adjusted area under the concentration-time curve
BMD	Bone mineral density
BMI	Body Mass Index
BALP	Bone alkaline phosphatase
cAMP	Cyclic AMP release
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CL	Total clearance
CL/F	Apparent total clearance of drug
C_{max}	Maximum observed plasma concentration
$C_{max}D$	Dose-adjusted maximum observed plasma concentration
CrCL	Creatinine clearance
CPK	Creatine phosphokinase
CSR	Clinical study report
CTX	C-telopeptide of type 1 collagen crosslinks
DSMB	Data Safety Monitoring Board
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FRAX	Fracture Risk Assessment Tool

GCP	Good Clinical Practice
hERG	Human Ether-a-Gogo related gene
h	Hour(s)
hpf	High power field
hPTH	Human parathyroid hormone
hPTHrP(1-34)	Human parathyroid hormone-related peptide(1-34)
HR	Heart rate
ICH	International Conference on Harmonisation
IIR	Integrated inspection report
INR	International normalised ratio
IRB	Institutional Review Board
Kel	Apparent first-order terminal-elimination rate constant
LDH	Lactate dehydrogenase
LFT	Liver function test
LLOQ	Lower limit of quantification
MCV	Mean corpuscular volume
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
min	Minute(s)
msec	Millisecond(s)
MTD	Maximum tolerated dose
N/A	Not applicable
NAS	New Active Substance
NMR	Nuclear Magnetic Resonance
NS	Non-significant
NTX	Collagen type 1 cross-linked N-telopeptide
NVF	Non-vertebral fracture
OC	Osteocalcin
OOS	Out of Specifications
PD	Pharmacodynamic(s)
P1CP	C-terminal propeptide of type I procollagen
P1NP	N-terminal propeptide of type I procollagen
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PMW	Postmenopausal women
PT	Preferred term
PTH	Parathyroid hormone
PTHR1	Parathyroid hormone receptor 1
PTHrP	Parathyroid Hormone related protein
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using Fridericia’s formula

ΔQTcF	Baseline-adjusted QTcF
ΔΔQTcF	Baseline-adjusted, placebo-corrected QTcF
QTcI	Individually corrected QT interval
ΔQTcI	Baseline-adjusted QTcI
ΔΔQTcI	Baseline-adjusted, placebo-corrected QTcI
RBC	Red blood cell
RH	Relative Humidity
RP-HPLC	Reverse Phase High performance liquid chromatography
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
s-CTX	Serum C-telopeptide of type I collagen
SD	Standard deviation
SOC	System organ class
s-P1CP	Serum C-terminal propeptide of type I procollagen
s-P1NP	N-terminal propeptide of type I procollagen in serum
SERMs	Selective estrogen receptor modulators
SmPC	Summary of Product Characteristics
sMTS	Solid microstructured transdermal system
SOC	System organ class
SSPS	Standard solid phase peptide synthesis
TAMC	Total Aerobic Microbial Count
TEAE	Treatment emergent adverse event
T_{last}	Time to the last measurable plasma concentration
T_{max}	Time to attain maximum observed plasma concentration
$t_{1/2}$	Half-life
TYMC	Total Combined Yeasts/Moulds Count
ULN	Upper limit of the standard reference range
UPLC	Ultra performance liquid chromatography
USP	United States Pharmacopoeia
UV	Ultraviolet
VF	Vertebral fracture
Vz	Volume of distribution (IV)
Vz/F	Apparent volume of distribution (SC)
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Radius International Ltd submitted on 17 November 2015 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 January 2015.

The applicant initially applied for the following indication:

Treatment of osteoporosis in postmenopausal women (see Section 5.1). In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures has been demonstrated.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that abaloparatide was considered to be a new active substance.

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 tests or studies.

Information on Paediatric requirements

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

Information relating to orphan market exclusivity

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.

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.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 June 2010 and 22 March 2011. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Harald Enzmann Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 17 November 2015.
- The procedure started on 4 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 February 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 22 February 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 2 March 2016.
- During the meeting on 1 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 October 2016.
- Requested GCP inspections were conducted between February and April 2016 at six sites: five investigator sites in Hong Kong P.R. China, Lithuania, Czech Republic and Denmark and at the CRO site in Denmark. The outcome of the inspections carried out was issued on 29 September 2016.
  In parallel with the CHMP requested inspections, national inspections were conducted in Czech Republic.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 November 2016.
- During the PRAC meeting on 1 December 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 15 December 2016, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 6 July 2017.
- During the CHMP meeting on 20 July 2017, the CHMP agreed on a second list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 14 November 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 29 November 2017.
- During the CHMP meeting on 13 December 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 14 December 2017, the CHMP agreed on a third list of outstanding issues to be sent to the applicant.

- The applicant submitted the responses to the CHMP third List of Outstanding Issues on 21 February 2018.
- During the Expert group meeting on 1 March 2018 experts were convened to address questions raised by the CHMP. The CHMP considered the views of the Expert group as presented in the minutes of this meeting.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the thirds List of Outstanding Issues to all CHMP members on 7 March 2018.
- During the CHMP meeting on 20 March 2018, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22 March 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Eladynos.

1.3. Steps taken for the re-examination procedure

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

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Andrea Laslop

- The applicant submitted written notice to the EMA on 9 April 2018 to request a re-examination of Eladynos CHMP opinion of 22 March 2018.
- During its meeting on 26 April 2018, the CHMP appointed Paula Boudewina van Hennik as Rapporteur and Andrea Laslop as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 28 May 2018 (Appendix 2 of Final Opinion). The re-examination procedure started on 29 May 2018.
- The rapporteur's re-examination assessment report was circulated to all CHMP members on 19 June 2018. The co-rapporteur's assessment report was circulated to all CHMP members on 18 June 2018.
- During a meeting of the Expert group meeting on 10 July 2018, experts were convened to consider the grounds for re-examination .The CHMP considered the views of the Expert group as presented in the minutes of this meeting.
- During the CHMP meeting on 24 July 2018, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 26 July 2018, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommended the refusal of the granting of the marketing authorisation.

2. Scientific discussion

2.1.1. Disease or condition

A definition from 1993 states osteoporosis is a "disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk". A more recent definition from the NIH Consensus Development Panel on Osteoporosis defines osteoporosis as a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture (Szulc & Bouxsein, 2010).

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. This is comparable with the risk of fracture for a 50 year old woman at one of these three sites. By the age of 80 years, 70% of women are osteoporotic at the hip, lumbar spine, or distal forearm. The prevalence of osteoporosis, assessed 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 adult women (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 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 in contrast stimulates the production and activity of osteoblasts, increasing BMD by building new bone.

2.1.6. 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 Becton Dickinson, while the to-be-commercialised pen will be manufactured by Ypsomed AG.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that there are currently a number of available treatment options for patients with osteoporosis, such as bisphosphonates,

denosumab and teriparatide and based on available data, it could not be concluded that abaloparatide would contribute additional benefits to patients that would support an accelerated assessment.

2.2. Quality aspects

2.2.1. 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 and acetic acid (for pH adjustment).

The product is available in cartridge (siliconised Type I glass) with a plunger (chlorobutyl rubber), crimp cap (bromobutyl rubber seal)/aluminium assembled into a disposable pen.

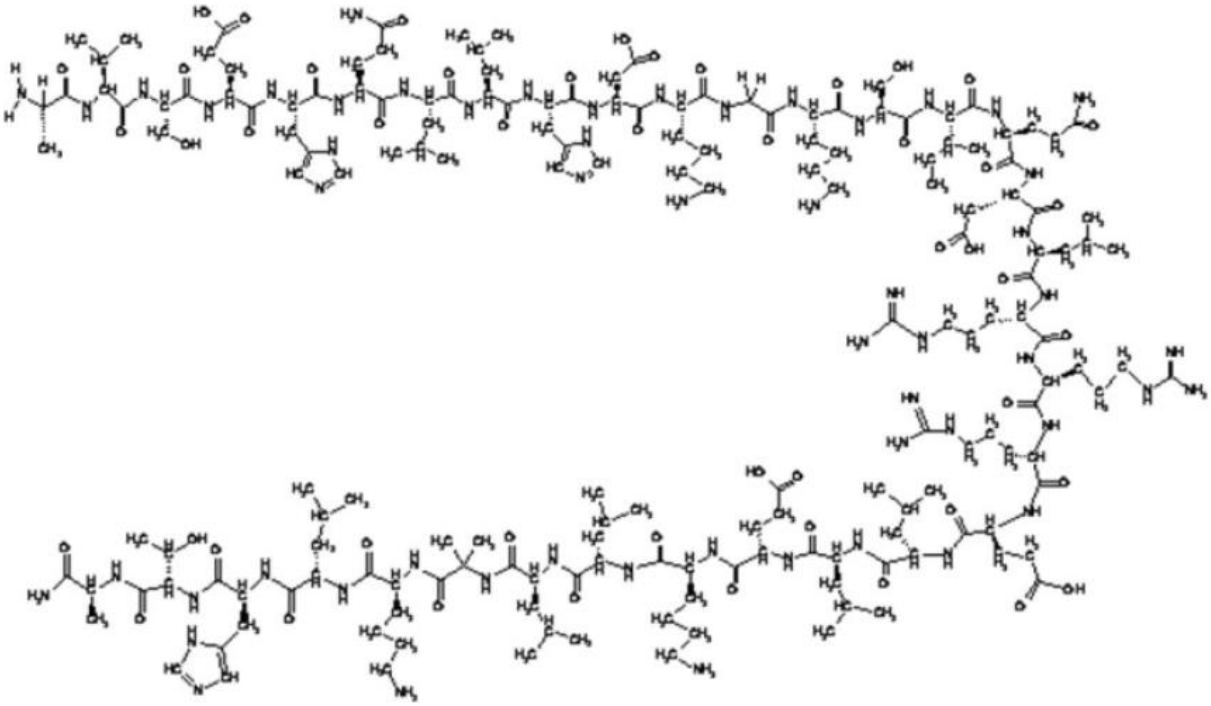
Each pre-filled pen contains 1.5 ml of solution, a volume sufficient to allow administration of 30 doses of 80 micrograms of abaloparatide (per 40 microliters).

2.2.2. Active Substance

General information

The chemical name of abaloparatide is L-Alaninamide, L-alanyl-L-valyl-L-seryl-L-alpha-glutamyl-L-histidyl-L-glutaminyl-L-leucyl-L- leucyl-L-histidyl-L-alpha-aspartyl-L-lysyl-glycyl-L-lysyl-L-seryl-L-isoleucyl-L-glutaminyl-L- alpha-aspartyl-L-leucyl-L-arginyl-L-arginyl-L-arginyl-L-alpha-glutamyl-L-leucyl-L-leucyl-L- alpha-glutamyl-L-lysyl-L-leucyl-L-leucyl-2-methylalanyl-L-lysyl-L-leucyl-L-histidyl-L-threonyl corresponding to the molecular formula $C_{174}H_{300}N_{56}O_{49}$ and a molecular mass of 3961Daltons (Da). It has the following structure:

Figure 1 Structure of abaloparatide



The active substance abaloparatide is a synthetic peptide consisting of 34 amino acids, of which 32 are L-amino acids, Gly and Aib are non-chiral. Abaloparatide is an analogue of the first 34 amino acids of human parathyroid hormone-related peptide [hPTHrP(1-34)], and 20 amino acids are exchanged compared to the natural counterpart.

The peptide sequence 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

The structure elucidation of the peptide was performed using 2D NMR spectroscopy. UV and IR spectroscopy and Fourier Transform Infra-Red (FT-IR) experiments and amino acid analysis were also conducted.

The primary structure of the active substance has been confirmed by electrospray ionisation mass spectrometry (ES-MS-CAD-MS) and N-terminal sequencing analysis.

Enantiomeric purity has been studied by chiral GC-MS, which confirms that all the amino acids of the fully assembled peptide are indeed in the right configuration.

Structural characterisation by Circular Dichroism (CD) spectroscopy (secondary structure) and Differential Scanning Calorimetry (DSC) (tertiary structure) were also carried out. The active substance is an amorphous white to off white hygroscopic powder. Its isoelectric point is 9.51. It is practically insoluble in acetone, acetonitrile, ethanol and tetrahydrofuran; soluble in methanol; and freely soluble in 0.1 N acetic acid and water.

Abaloparatide exhibits stereoisomerism. Enantiomeric purity is controlled routinely in the active substance (AS) starting materials by chiral GC-MS HPLC. The specific optical rotation of abaloparatide is also controlled as a routine test of the active substance specification.

The applicant has performed comparative structural analysis to show that abaloparatide is to be regarded as a new active substance (NAS) in itself and that it is not a salt, complex, derivative or isomer (nor mixture of isomers) of a previously authorised substance.

The parathyroid hormone (PTH) is a natural human peptide of 84 AA (MW about 9500Da), of which only the sequence of the 34 N-terminal Amino acids binds to PTH1 and PTH2 receptors. The full sequence of the human PTH is: SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQR PRKKEDNVLVESHEKSLGEADKADVNVLTKAKSQ.

The PTH (1-34) is the peptide fragment that contains the 34 N-terminal residues of hPTH (1-84) (Sequence in bold given above).

The PTH related protein (PTHrP) is a 139 to 173 AA protein (different isoforms in human) with N-terminal sequence analogy to PTH.

Teriparatide is a recombinant human PTH(1-34) marketed in Europe under the name of Forsteo™.

Although abaloparatide shares some sequence homology with PTH(1-34) and teriparatide, the applicant claimed that it is significantly different from them. This was substantiated by a comparison of abaloparatide and teriparatide amino acid sequence, which showed the differences at 20 positions (1, 5, 8, 10, 11, 14, 15, 16, 17, 18, 19, 21, 23, 25, 27, 29, 30, 31, 33, 34). Table 2 is a presentation of the sequences, with differences in sequence highlighted in red. The amino acid (X) at the position 29 is Aib, 2-aminoisobutiric acid, alias 2-methylalanine, a non-natural amino acid.

Table 2 Primary amino acid sequence of abaloparatide and teriparatide.

Teriparatide:	SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF
Abaloparatide:	AVSEHQLLHDKGKSIQDLRRRELLEKLLXKLHTA

X=AIB

It was also demonstrated that the amino acid sequence of abaloparatide differs significantly from PTH (1-34) or PTHrP (1-34) in different species.

In addition, the secondary structure of abaloparatide was evaluated by Nuclear Magnetic Resonance (NMR) and Circular Dichromism (CD) methods. The differences in the secondary structure of teriparatide and abaloparatide, including differences in the proportions and positions of α-helix and β-sheet structures, led to the conclusion that the secondary structure of abaloparatide and teriparatide differ substantially.

These studies were supplemented by receptor affinity tests (see non-clinical part of the report).

Manufacture, characterisation and process controls

The active substance is manufactured using a standard solid phase peptide synthesis (SPSS) which comprises four main steps using well defined starting materials with acceptable specifications, which correspond to N-α Fluorenylmethyloxycarbonyl-protected amino acids (Fmoc-X-OH where X stands for the amino acid). A specification for the resin used as the solid support has also been provided. The manufacturing steps include: (1) a standard solid phase peptide synthesis (SPPS) of the protected peptide which comprises loading of the protected Fmoc-Ala-aminoacid to the resin and incorporation of

successive protected Fmoc-aminoacids; (2) synthesis of crude peptide (deprotection and cleavage from the resin); (3) purification and desalting through a preparative HPLC process; and (4) isolation (evaporation, filtration and lyophilisation).

Coupling reactions are critical and are controlled by specific-tests. Depending on the result a recoupling step also controlled may be performed.

No reprocessing is anticipated during the course of the regular manufacturing process of abaloparatide. However if a batch fail specifications, reprocessing would be triggered after initial root cause evaluation and appropriate justification.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.
Potential and actual impurities were well discussed with regards to their origin and characterised. These have been divided into three categories depending on their origin: i) impurities linked to the synthesis of the protected peptide on the resin, ii) impurities linked to the final cleavage and side-chain deprotection, and iii) impurities linked to the peptide storage in solution during downstream process.

The enantiomeric purity of the active substance is acceptable and comparable to other synthetic peptides. Residual solvents, residual reagents and by-products, leachables from purification columns and elemental impurities have been sufficiently addressed.

Due to the extensive resin washing and the purification steps practically any residual reagents or by-products of peptide coupling reagents or reaction by-products are separated from the active substance. Only impurities with a very close structure to the active substance structure are collected during each purification step. Related compounds are controlled by the proposed active substance specification.

Related impurities that have been observed in abaloparatide do not contain structural alerts for genotoxicity. In addition, as discussed above, purification steps used to manufacture abaloparatide can be expected to remove potential process impurities below levels of concern from ICH M7 taking into account the allowed daily dose of 80µg for abaloparatide.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The history of the manufacturing process changes during development has been presented in sufficient detail and the changes have been justified.

The active substance is packaged in wide-mouth bottles ranging from 30 to 1000 mL made of high-density polyethylene (HDPE) and closed by a polypropylene screw cap. This primary packaging provides good protection against moisture and oxygen. Its suitability for abaloparatide is demonstrated by the stability data (discussed below). The material which complies with the EU regulations 10/2011 and 202/2014 as amended.

Specification

The active substance specification includes tests for appearance and colour (visual), identification (monoisotopic mass by LC-MS and co-elution with reference sample by UPLC), purity (UPLC), related substances (UPLC), assay (UPLC), mass balance, residual solvents (HPLC, GC), water content (KF), specific optical rotation (Ph. Eur.), endotoxins (Ph. Eur.), total aerobic microbial count (TAMC) (Ph. Eur.) and total combined yeasts and moulds (TYMC) (Ph. Eur.).

All critical quality attributes (CQAs) have been included in the active substance specification. A justification for each attribute and the respective acceptance criteria has been provided. The proposed specification limits are acceptable and have been justified by batch analysis data. Batch analysis data have been presented. The results are within the specifications and consistent from batch to batch.

The overall purity and level of impurities is assessed using different test methods. The limit for the specified impurity is based on batch and stability data. The limits for peptide-related impurities have been toxicologically justified. As per requirement of the Ph. Eur. monograph 'Substances for Pharmaceutical Use' impurities above 0.1% are reported and impurities above 0.5% will be identified.

The process related impurities have been found during development and are identified as truncated peptides. A single specification has been established based on historical batch data.

Justifications for not including bioassay, elemental impurities and benzene in the specification have been provided and were considered acceptable. The justification for the omission of bioassay was based on the nature of the abaloparatide molecule, its robust manufacturing process, the consistency of structural conformation and of biological activity in different active substance batches with different ages. Results from CD spectroscopy, DSC analysis and potency assay demonstrated that the structure and activity of abaloparatide active substance is reproducible between batches and over time for aged samples. This supports the conclusion that the routine use of a bioassay for release and stability testing is not necessary.

Limits for elemental impurities were not included in the active substance specification since its manufacturing process does not involve use of catalysts nor processing aids that contain any of the elements listed in ICH Q3D Elemental Impurities. Two active substance batches were tested to assess levels of elemental impurities, and showed that the levels are well within the ICH limits.

The potential sources of benzene contamination during manufacturing of the active substance were assessed and identified to be limited. Benzene that may have been present is removed during subsequent washing, purification and evaporation steps

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the abaloparatide and impurity reference standards used for assay testing and validation of the analytical methods has been presented.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions at -20°C ± 5°C and for up to 6 months under accelerated conditions at +5°C ± 3°C and +25°C ± 2°C/60% RH ± 5% RH, according to the ICH guidelines, were provided. Samples were stored in HDPE bottles with screw-cap polypropylene closure of the same quality as those used for bulk storage.

The following parameters were tested: powder appearance, water content, purity and related substances, API content, acetic acid content, mass balance, microbial contamination and bacterial endotoxins. In general, the analytical methods used were the same as for release and were stability indicating.

Supportive stability data from three development batches stored for up to 60 months under long term (-20°C ± 5°C) and accelerated conditions (+ 5°C ± 3°C) were also submitted.

No change in appearance of the powder was observed for any batch at any storage condition.

With regards to purity and related substances, for all three primary batches, no significant change was detected after storage at -20°C ± 5°C. At +5°C ± 3°C a slight decrease overall purity was observed and additional impurities were detected over time; but for both initially present impurities and impurities emerging over time, individual and total impurity levels remained below the specification limit. However, when stored at the accelerated storage condition of 25°C / 60% RH a significant decrease was observed for purity, from the start of the study through to 6 months, and levels of both initially present impurities and emerging impurities increased significantly over 6 months.

The API (peptide) content showed no trend when stored at -20°C. However, at +5°C ± 3°C and at 25°C / 60% RH the API content decreased over time. This decrease was greater at the higher stress condition of 25°C / 60% RH. The observed decrease of API content was consistent with the concomitant increase in the level of impurities, as well as an increase in water content, observed over the 6 months of storage.

The water content results met the specification for all tested storage conditions for all 3 batches. At +5°C and +25°C /60% RH storage conditions the water content increased over time, with a significant increase observed at the higher temperature. These increases were attributed to the hygroscopicity of the active substance, influenced by the storage temperature used.

The acetic acid content results were stable and met the specification at all tested storage conditions for all batches. The mass balance and microbial contamination and bacterial endotoxins results also met the specifications under all storage conditions.

In addition, a photostability study following the ICH guideline Q1B was performed on one development batch. Samples were tested for appearance, purity and related substances, peptide content and water content. The purity results obtained showed a slight decrease on the sample exposed to light, but no significant degradation was observed. No significant change was observed for the impurity profiles, including main single impurity and total impurity levels, appearance, peptide content and water content.

Results on stress conditions under acid (1M HCl), base (0.01 M, NaOH), oxidation (3% H_2O_2), heat (+80°C), and UV-light were also provided on one development batch, which demonstrated the stability indicating properties of the UPLC method used for purity testing.

Overall, the stability results obtained for the three primary batches and three supporting stability batches stored at under the long-term stability condition of – 20°C, confirm that the drug substance, abaloparatide manufactured by the proposed manufacturer is stable when stored under the recommended storage conditions of – 20°C.

The results generated at +5°C ± 3°C over 6 months (accelerated storage condition) and from the stress with UV light, demonstrate that the stability of abaloparatide is maintained in the event of short term excursions outside the recommended storage condition.

In conclusion, the stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months at -20°C ± 5°C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Eladynos is 80 micrograms/dose solution for injection in pre-filled pen for subcutaneous delivery of abaloparatide. The pen is a multi-dose, fixed dose, disposable pen injector for single patient use. Each injector is provided as a fully assembled unit, ready for use. Within the pen injector, the abaloparatide solution is contained in a siliconized glass non-replaceable cartridge with a rubber plunger closure at one end a crimp seal with a rubber septum at the other end. The cartridge is a siliconized glass cartridge of Type 1 USP/Ph. Eur. glass with a plunger made of a chlorobutyl rubber 4432/50. Additionally the crimp seal has a septum made of a bilayer of rubber consisting of 4780/40 bromobutyl rubber formulation (product contact side) and an isoprene rubber 7778/40 backing.

The pen should only be used with specified needles. No needles are supplied with the medicinal product.

The fill volume is approximately 1.5 ml per cartridge (target 1.56 ml) with no headspace. Based on 30 days of dosing at 40 µl, the total volume administered to the patient is 1.20 ml.

Abaloparatide is a 34 amino acid peptide. Abaloparatide is freely soluble in water. The stability of abaloparatide has been demonstrated at selected pH by both laboratory, clinical and registration stability at a storage temperature of 2-8°C.

There are only four excipients in the formulation. The excipients concentrations used have been used in similar sterile subcutaneous formulations. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients or excipients of human or animal origin used in the finished product formulation. The list of excipients was included in section 6.1 of the proposed SmPC and in paragraph 2.1.1 of this report.

Critical quality attributes of the finished product have been defined as: the release parameters, the bioburden prior to sterile filtration (defined as critical in-process test), the correct assembly of the pen (leading to correct locking of interrelated parts).

During the early stages of development of Eladynos, two types of finished product formulations were considered: (1) lyophilized (freeze dried); and (2) solution. For the initial Phase 1 clinical trial, a lyophilized formulation was developed and used, since it could be developed and tested more quickly than the solution formulation. All subsequent clinical studies that have been conducted used the solution formulation, which is the intended commercial formulation.

During the course of development of the solution form, evaluations were made of different pH levels, excipients, preservatives, buffers and anti-microbial agents. For each of these formulations, several alternatives were evaluated and tested. Based on the results of the performed studies the formulation was chosen. In this regard, a study was conducted to demonstrate that the final formulation met the antimicrobial preservation requirements as defined by the US and European Pharmacopoeia for multi-use parenterals. This study was performed during stability study of the solution and results showed to be compliant, demonstrating efficacy of antimicrobial preservative for up to 36 months at 5°C. Although the applicant did not perform any study to show that the amount of the preservative is the lowest feasible to uphold the antimicrobial effectiveness, confirmation that the amount of this excipient is within a safe range with regards to possible toxic effect has been provided and is considered acceptable.

Three different solution strengths were used during clinical trials. The formulation containing 2.0 mg/ml abaloparatide is the one proposed for marketing.

The excipients in the final finished product formulation maintain abaloparatide pH at acceptable levels. Antimicrobial preservative and other excipients in the formulation do not influence the performance of the active substance.

There are no overages in the formulation. During manufacture of the finished product, a specified amount of the solution is filled into the glass cartridge to ensure that the total dose volume of 40 µl (equivalent to 80 µg of abaloparatide) is achieved over the full 30-day treatment period. The target fill volume is based on the capabilities of the manufacturing equipment.

The manufacturing process development was explained in detail. The bulk solution mixing process is a simple process of mixing the excipients, adding the abaloparatide active substance, q.s to final concentration and then sterile filtering and filling into prepared multidose pen cartridge assembly. The cartridge is later assembled into a functioning pen system and labeled for patient use.

The manufacturing process is standard for this kind of product, containing a peptide and comprises formulation buffer preparation, formulated drug product preparation, sterile filtration, aseptic filling, stoppering and pen assembly. The basic steps of this process remained unchanged during development. The differences were described and justified. A Becton Dickenson Pen II was used through Phase II and III clinical studies. The changes of the manufacture of the finished product solution are not considered to have a negative impact on the quality. Comparability of the product manufactured for clinical trials and manufactured using the commercial process has been demonstrated by batch analysis results.

The choice of the sterilisation method has been justified by the applicant in accordance with the decision tree for selection of sterilisation methods (CPMP/QWP/054/98). The formulation is an aqueous solution of a synthetic peptide - abaloparatide. The applicant stated that it is not possible to carry out terminal sterilization by heating due to formulation instability, as evidenced by stability studies and forced degradation studies using heat. Autoclaving at 121° C or at F0>8 minutes will lead to degradation of abaloparatide in aqueous formulation. The formulation can be filtered through a microbial retentive filter. Therefore, a combination of aseptic filtration and aseptic processing is proposed. Results for impurities and peptide content during stability studies at 25°C and 40°C are out of specification. Therefore, based on the data presented, the applicant's justification to use aseptic processing and sterile filtration is accepted.

Two different studies were performed to demonstrate the stability and compatibility of the finished product solution.

Study 1 was conducted to show the compatibility of the solution with the contact materials during the manufacturing process and with all the in process materials used. No negative impact on product quality was observed with the maximum allowed hold/process times. No increased levels of impurities were detected during this study.

Study 2 was conducted to show the compatibility of the concentrated abaloparatide solution in the delivery HDPE container. No negative impact in product quality was observed when product was manufactured with the worst case incubation time. The impurity profile at the start of incubation was identical to the impurity profile after that time .

The product is filled in clear, USP and Ph. Eur. Siliconized Type I glass cartridges, fitted with an aluminium crimp cap on one end, and a grey, chlorobutyl rubber plunger on the other end. The rubber components meet the requirements of USP <381>, Physicochemical Tests for Elastomeric Closures,

Ph. Eur. monograph 3.2.9 Rubber Closure for Containers for Aqueous Parenteral Preparations, and JP Section 59 Test for Rubber Closure for Aqueous Infusions. Studies for leachable and extractable substances showed that potential extractable substances are not found as leachable substances in finished product.

The cartridge complies with ISO 11608-3: 2012, "Needle-based injection systems for medical use – Requirements and test methods – Part 3: Finished Containers". The prefilled cartridges are permanently fitted into a multi-dose, disposable pen.

During development abaloparatide was administered to patients by syringe, and by a pen manufactured by by another manufacturer. The major difference between the pens used for development and proposed for marketing is that the user placed the cartridges into the reusable development pen, while the to-be marketed pen is provided with the cartridge permanently fitted into the pen. Both pens have the same dose accuracy. The disposable pen-injector is an integral part of the finished product and together with the drug solution in the cartridge, are intended to be used exclusively in combination and form a single finished medicinal product. The pen is to be used with compatible pen needles, which are not supplied with it. The pen allows the delivery of at least 30 doses, which sum up to a nominal deliverable volume of 1.2 ml. The overfill volume is available for priming the pen. The abaloparatide dose (80 µg) is indicated in the display window. The manufacturing process and quality control of the components and the subassembly of the components have been satisfactorily described. Product verification and validation comprised conformance to ISO 11608-1:2014 general requirements and dose accuracy testing, needle compatibility testing, leakage testing, injection time, functional and force testing, shelf life testing, conformance to ISO 10993-1 biocompatibility testing and usability engineering and testing. The provided information is in general considered sufficient. The pen corresponds to system designation C of ISO 11608-1:2014 "Needle-based injection systems for medical use – Requirements and test methods".

Seal integrity of the crimp cap after multiple punctures was also studied. Patient use was simulated with 10 cartridges by attaching a pen needle to a pen, priming the pen and then removing the needle. The cycle was repeated to 60 punctures. Crimp caps used in this study consisted of single layer and bilayer stoppers. Particles were observed in some of the cartridges with single layer stopper and no particles were observed in the cartridges with bilayer stoppers. Therefore bilayer stopper crimp caps were selected.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Eladynos is designed and manufactured in order to maintain a sterile product throughout its shelf life (stored at 2-8°C) and during the 30 day usage period (stored at typical room temperatures of approximately 25°C) during which doses are removed once a day.

A container closure integrity test of the cartridge has been performed which demonstrates that the pen container closure does not allow ingress of dye under stress conditions and that the product will remain sterile once packaged.

Confirmation of the sterility is demonstrated by release testing and scheduled tests on stability (Ph. Eur. 2.6.1).

Since the product is a multidose injection system, the formulation contains an antimicrobial preservative. An antimicrobial effectiveness test (AET) was performed as per USP<51> and Ph. Eur. 5.1.3 which demonstrated that the preservative remains effective at the proposed concentrations. Additionally, stability data up to 36 months at 2-8°C supports its specification. AET studies in

combination with antimicrobial assay are being performed on the registration batches as part of the stability protocol to demonstrate the control of microbial contamination during long term stability.

In-use testing has been performed on stability which demonstrates that after multiple entries using the disposable sterile needle and mimicking the patient use conditions, the product remains sterile.

Manufacture of the product and process controls

The manufacturing process is typical for this kind of drug product containing a peptide and consists of six main steps: compounding of excipient solution and drug product solution, sterile filtration, aseptic filling into cartridges, stoppering and pen assembly, and pen assembly. The process is considered to be a non-standard manufacturing process.

The classification of all operating parameters and ranges has been justified concerning their potential effect on the product CQAs has been justified. Although the manufacturer of the finished product uses an in-house terminology for the criticality of process parameters, during the evaluation it was clarified that all parameters categorized as critical operational parameters and non-key parameters are critical These have been described in the dossier.

The proposed in-process controls are considered adequate for this type of manufacturing process.

A batch size range has been defined for the bulk drug product solution. The exact batch size will be determined during the process by an assay so that a target protein content is reached.

Process validation comprised filter validation, validation of aseptic processing by media fill and validation of compounding and filling manufacturing operations.

Process validation batches were manufactured at the commercial site, covering both the minimum and maximum batch size. Validation of the finished product manufacturing process comprised all unit operations of the finished product process including hold times as defined in the dossier. The first and the second validation batch showed a large number of major defects during visual inspections. An investigation identified the root cause for the defects. Following its correction, the defect was no longer observed. The proposed holding times have been validated and are thus acceptable.

The assembly step of the pens during finished product manufacturing has also been sufficiently validated.

The manufacturing process and quality control of the components and the subassembly of the components are satisfactorily described. Product verification and validation comprised conformance to ISO 11608-1:2014 general requirements and dose accuracy testing, needle compatibility testing, leakage testing, injection time, functional and force testing, shelf life testing, conformance to ISO 10993-1 biocompatibility testing, and usability engineering and testing. The provided information is considered sufficient.

Altogether, the provided validation data for the manufacture of the filled cartridges are considered sufficient to demonstrate that the finished product manufacturing process is under control and provides a product of consistent quality.

Product specification

A justification has been provided for the attributes in the specification as necessary.

The proposed release specification for abaloparatide content (assay) and the proposed end of shelf-life specification have been adequately justified. This is based on experience from batches manufactured for clinical Phases II and III, registration and validation, and the resulting stability data. The predicted efficacy of the lower limit abaloparatide was estimated based on pharmacokinetic (PK) modelling data. The results suggested that there are no significant differences in abaloparatide C_{max} or AUC parameters for both target and lower limit doses across these patient populations. The exposures associated with the lower dose are well within the 95% confidence interval for the efficacious 80 µg dose, which strongly suggests the lower dose would behave similarly to an 80 µg dose in terms of biological activity.

With respect to purity testing, the degradation product has been the only impurity identified and qualified. This degradant was identified and separated in the drug product by a method developed and improved during development. Batch analysis data from aged clinical batches and registration batches (all stored at 5°C) provided information on degradation process. These together with the results of simulated in-use storage at 25°C for one month and toxicological evaluation including its immunogenicity (see non-clinical section), justify the shelf-life limit for this impurity.

The release and shelf life specification limit for individual impurities is the identification threshold for peptides obtained by chemical synthesis in accordance with the Ph. Eur. monograph "Substances for pharmaceutical use".

Total related impurities at end of shelf life are limited, in accordance with the assay limits are defined.

The proposed specification for pH is acceptable for subcutaneous injections as well as to maintain solubility and stability of abaloparatide. pH remained unchanged during stability.

A functionality test is included to verify correct assembly of the pen and cartridge. The acceptance criterion is justified as it confirms the pen is capable of delivering the intended number of doses.

All tests required by standard ISO-11608-1 have been shown to pass. Based on the extensive verification on the full assembled pen it is proposed not to conduct a dose accuracy test at time of release.

A justification for omission of bioassay from the specification was presented. This was based on the demonstration that the structure and activity of abaloparatide drug product are reproducible consistent between batches and over time for aged samples. CD spectroscopy and DSC were used to determine the secondary and higher order structures for abaloparatide drug product, including batches of varying age. No change in structure was observed in aged finished product batches. Abaloparatide finished product was also characterized by potency assay. The relative potencies observed for finished product batches of varying age were all within specifications.
These results demonstrate that activity of abaloparatide does not change, from batch to batch and for aged batches, and therefore confirm that the routine use of a bioassay for release and/or stability testing is not necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines where applicable.

Batch analysis results for three registration commercial scale stability batches, and three development batches produced according to process 1 have been provided. The results confirm consistency and uniformity of the finished product and indicate that the manufacturing process for the cartridges is under control. Data for the test on verification of function of the assembled pen has also been included.

Stability of the product

Stability data of three commercial scale batches of finished product stored for 24 months under long term conditions of 5°C ± 3°C /ambient RH and at accelerated condition of 25°C ± 2°C/60% RH ± 5%RH, according to the ICH guidelines were provided. Data for 6 months are available under stress conditions at 40ºC ± 2°C/75% ± 5%. Furthermore, four commercial scale validation batches of "naked" cartridges (not incorporated in the pen) containing abaloparatide solution were placed on stability at long term 5°C ± 3°C /ambient RH and accelerated 25°C /60% RH conditions.

The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The following tests have been applied for stability testing: appearance, clarity, colour, pH, extractable volume, sub-visible particles (≥10 µm, ≥25 µm), preservative content, assay (peptide content), specified identified impurity, specified unidentified impurities, total related impurities. The following additional tests were conducted at 2-8°C and 25°C /60% RH, but not at 40ºC/75% RH: sterility, bacterial endotoxins, antimicrobial effectiveness testing, break loose force and glide forces.

No significant changes of the quality attributes occurred at long term conditions except for the specified identified impurity degradant for which a clear trend of increase was observed. The rate of its formation increased with increase in temperature. At 25°C/60%RH and 40°C/75/RH out of specification results were observed for impurities and assay at the six months' time point.

The increase in the specified identified impurity and total impurities was accompanied by a decrease in abaloparatide content. Based on this observation and on completed qualification of this analogue, the specification of abaloparatide, the specified identified impurity and total impurities was defined.

The specified identified impurity was determined in older clinical batches (up to 54 months old) and registration batches (24 month) through contemporary testing using a revised HPLC method. All batches had been stored at 5°C. The levels of this impurity found were reported. Additionally, storage at room temperature (equivalent to in-use storage) has been demonstrated to contribute to its formation.

Based on these observations, the estimated amount of this impurity after 35 months when stored at 5°C followed by 1 month storage at 25°C/60%RH is expected to be well below the specification limit.

The stability data, including the predictability of this impurity formation which accounts for essentially all abaloparatide degradation, the comparison of levels in registration stability batches and in aged clinical batches, the goodness of fit of predicted degradation to actual in clinical lots greater than 54 months old, and the high predictability of the degradation of abaloparatide at 5ºC, 25ºC and 40ºC, the extrapolation of the shelf-life to 36 months is considered acceptable.

With regards to the fully assembled pens, no changes in appearance and pen functionality was observed after 9 month storage under long term storage conditions.

In addition, in order to mimic patient use, stability data have also been generated from an in-use stability study (storage at room temperature for duration of in-use period) and an in-use cycling stability study (removal and return to refrigeration, daily during in-use period) on the three stability batches used for the long term, accelerated and stress studies.

Specifically, for the in-use stability study, samples were pulled from the 5°C ± 3°C/ambient RH storage condition at defined time points. Some samples were punctured 30 times to mimic patient use, and the remaining samples were left un-punctured. All samples were then placed in storage under the

condition of 25°C ± 2°C/60% RH for 30 days. Data from up to 23 months of storage at 5°C ± 3°C/ambient RH condition and 30 days at 25°C ± 2°C/60% RH ± 5% condition were presented.

For the in-use cycling stability study, samples were stored at 5°C ± 3°C /ambient RH condition. During the in-use period, samples were cycled daily to ambient room temperature for 30 minutes, after this time samples were returned to storage at 5°C±3°C/ambient RH. This cycle was repeated for 30 days. During the 30-minute excursion, a defined set of samples was punctured once, daily to mimic patient use. Data up to 18 months storage is available.

The tests performed on the punctured samples are: appearance/visible particles, sub-visible particles (≥10 µm, ≥25 µm), in-use sterility test, assay, specified identified impurity, specified unidentified impurities, total related impurities. The tests performed on the punctured samples are: clarity, colour, pH, extractable volume, phenol content, antimicrobial effectiveness testing and break loose force and glide forces.

Although an increasing trend in the specified identified impurity content and total impurities accompanied by a decrease in assay was observed in both in-use studies, all parameters remained within the specification limits. The in-use stability data currently support the proposed claim that the pen can be stored below 25°C during one month use. Therefore, the pen must be discarded 30 days after it is removed from refrigeration for initial use, regardless of the number of doses that have been delivered or remain in the pen.

Results of a photo stability study in accordance with ICH Q1B Option 2 have been provided on one validation batch of "naked" cartridges containing abaloparatide solution demonstrating that the finished product is not photosensitive. There is thus no need for any storage restriction concerning light protection.

Based on available stability data, the proposed shelf-life of 36 months when stored in a refrigerator (2°C - 8°C) and not freezed, followed by 1 month of continuous storage below 25°C as stated in the proposed SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance is the synthetic peptide abaloparatide, which is an analogue of the first 34 amino acids of human parathyroid hormone-related peptide [hPTHrP(1-34)]. It is manufactured by standard solid phase peptide synthesis. The finished product is solution for injection in pre-filled pen. Each pre-filled pen contains 1.5 ml of solution, a volume sufficient to allow administration of 30 doses of 80 micrograms of abaloparatide (per 40 microliters). The pen is a multi-dose, fixed-dose, disposable pen injector system which should be used by a single patient and the pen must be discarded 30 days after it is removed from refrigeration for initial use, regardless of the number of doses that have been delivered or remain in the pen.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

2.2.5. 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 that were defined in the proposed SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. 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 (Aib). 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 characterise the pharmacological activity of abaloparatide.

Primary pharmacodynamics

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 (≤ 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 ± 0.06 versus 0.40 ± 0.16 and 0.48 ± 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. The Applicant was asked to comment, what is known about the binding characteristics of abaloparatide to PTH1 receptors or their analogues in the animal species used in in vivo studies for investigation of pharmacology and toxicity. 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 mobilisation in rat plasma

In calcium-deficient, parathyreoidectomised (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.

The applicant was asked to discuss the differentiation profile of abaloparatide compared to teriparatide in terms of efficacy and risk of hypercalcaemia. Given that both compounds 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 hypercalcaemia 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 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.

Secondary pharmacodynamics

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).

Safety pharmacology

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 in the pentylenetetrazole-induced seizure test (up to 125 µg/kg) were unaffected by abaloparatide administration. The applicant concludes an NOEL of Abaloparatide in the CNS of 125 µg/kg/day subcutaneously which was considered 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 and one non-GLP compliant study investigating hERG currents in human embryonic kidney (HEK) cells. The Applicant was asked to justify the absence of GLP compliance and the studies were complemented by an additional 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 initially submitted non-GLP study abaloparatide, slightly blocked the hERG current without showing an 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 indicate an IC_{50} for abalopratide > 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 arrythmogenic 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. In addition the Applicant provides a nonclinical summary of the cardiovascular effects of abaloparatide (Expert Cardiac Safety Report) which mainly summarizes the non-clinical data presented in the Assessment Report.

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 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 increased 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).

The applicant has tried to replace missing pharmacokinetic data by pharmacokinetic modelling and simulation analysis. Overall the estimated plasma concentration profile has a high degree of uncertainty and should generally not be acceptable. The estimated margins of exposure obtained in dogs are rather low (≤4.6 fold compared to human exposure) indicated that even higher doses should have been evaluated in the cardiovascular safety studies. The systemic calcium levels were not measured in the two dog cardiovascular safety pharmacology studies, which in turn would have been valuable information since hypercalcaemia has been suggested to be a risk factor for QT shortening.

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 humans. 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.

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.

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 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.

2.3.2. 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 clinical 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 specific 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 (bioiavailability 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 which 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 on page 25 of the non-clinical overview 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 cynomlogus 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 antibody formation (ADA), 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 points out further 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 points out further 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 of ^{125}I-abaloparatide, followed by rapid clearance and a renal route of elimination. However, this study does not necessarily 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, hypothesised 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 woman). 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.

Pharmacokinetic drug interactions

Three drug interaction studies have been provided. Abaloparatide did not inhibit the drug transporters phospho-glycoprotein (P-gp) in HEK293 cells and breast cancer resistance protein (BCRP) in Caco-2 cells, indicating that abaloparatide is not expected to affect the distribution or elimination of drug substrates of these transporters.

Abaloparatide had neither time-dependent direct nor metabolic-dependent inhibitory activity on the CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 isoenzymes, in the presence of human hepatic microsomes. In summary, abaloparatide had neither inhibitory nor inducing effect on any of the CYP enzymes tested. For further discussion, see Clinical Pharmacokinetics.

2.3.3. Toxicology

The toxicity profile of abaloparatide was characterised 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 months 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.

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.

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 weeks 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 tachypnea 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 tachypnea, 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 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 as well coagulation time was shortened and, as in the monkey studies seen as well, 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 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 weeks 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 weeks 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 mineralisation. 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 weeks 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 euthanised 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 asked to discuss how abaloparatide can be safely used in patients without exposing patients to the risks of organ mineralisation. Occurrence of tissue mineralisation 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 mineralisation in patients during clinical use. A renal CT Scan Sub-study did not yield evidence of increased mineralisation 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 mineralisation (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 mineralisation 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.

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.

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 mineralisation 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 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 localised 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.

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-fetal 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.

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.

Antigenicity

Occurrence of anti-drug antibodies (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 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 specific impurity of abaloparatide appeared 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 specific 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 this impurity of abaloparatide of ≤ 5% 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 ≤ 5% 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 with the 80 ug dose at the proposed ≤ 5% specification limit.

In response to a request which was based on the concern of possibly higher antigenicity of this impurity compared to abaloparatide due to the structural difference, the applicant re-evaluated data from phase 3 clinical study BA058-05-003 considering anti-drug-antibody (ADA)-status and calculated amount of the impurity administered to the patients. The data show that ADA-positive and ADA-negative patients had received similar (not statistically significantly different) amounts (average as well as maximal amounts) of the impurity, suggesting that the impurity is not a primary driver of immunogenicity in patients.

The specification limit of ≤ 5% 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.

2.3.4. Ecotoxicity/environmental risk assessment

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.

2.3.5. 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

mobilisation at therapeutic doses of abaloparatide compared to hPTH1-34 *in vivo*, whereas hypercalcaemia was in fact observed at clinically relevant exposure levels of abaloparatide in repeat-dose toxicity studies. Furthermore, both compounds were similar 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 is expected to be observed clinically (see that section), 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 absolutely 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 mineralisation, 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 mineralisation can occur even without persistent hypercalcaemia, as evidenced by the transient or (in 26-weeks rats) non-detectable changes in serum calcium levels. Furthermore, mineralisation 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-weeks study. Hypercalcaemia has been observed in the clinical setting as well (see the Clinical Assessment Report); therefore, due to a request the applicant included hypercalcaemia as an important identified risk and organ calcification as an important potential risk in the summary of safety concerns of the proposed RMP.

In a two year bioassay in rats, 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 an 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) –for which appropriate risk mitigation and follow up measures would be necessary.

2.3.6. Conclusion on non-clinical aspects

Overall, in the non-clinical documentation all concerns have been addressed adequately.

2.4. Clinical aspects

2.4.1. Introduction

Abaloparatide is intended for the treatment of osteoporosis in postmenopausal women at increased risk of fracture to reduce the risk of osteoporotic fractures. In contrast to the primarily prescribed antiresorptive anti-osteoporotic drugs, e.g. bisphosphonates, which act by decreasing the bone loss, abaloparatide stimulates the production and activity of osteoblasts, increasing BMD by building new bone. Teriparatide is at time of this report the only bone anabolic drug licensed in the EU. The finished product abaloparatide is proposed to be supplied as a 1.5 mL multi-dose cartridge installed in a multi-use pen for subcutaneous (sc) injection enabling self-dosing.

Besides pharmacokinetic (PK) and pharmacodynamic (PD) studies abaloparatide has been investigated in 1 phase 2, dose-ranging, 24 weeks study in postmenopausal women with osteoporosis (BA058-05-002) and a 24 weeks extension (amendment 5) and 1 phase 3, pivotal clinical trial in postmenopausal women with osteoporosis to prevent the occurrence of vertebral and non-vertebral fractures (Study BA058-05-003) with an extension (BA058-05-005) for which the final analysis has been submitted during the procedure.

GCP

According to the applicant all clinical studies were performed in full compliance with Good Clinical Practice (GCP) and all other applicable local regulatory and ethical requirements and all clinical studies, including those conducted outside the European Community (EC) met the ethical requirements of Directive 2001/20/EC.

Three inspection requests were adopted by the CHMP for this application, a routine (GCP/INS/2015/030) and two triggered requests (GCP/INS/2016/001; GCP/INS/2016/013).

Six sites have been inspected with regard to this application. The routine request covered three investigator sites, one in Vilnius, Lithuania, one in Hong Kong, and the site of the contract research organisation in Denmark. In addition, two triggered, unannounced GCP inspections were requested and performed at three sites: an investigator site in Czech Republic and two investigator sites in Denmark.

These inspections were conducted between February and April 2016 in connection with the conduct of the single pivotal trial BA058-05-003 supporting the Marketing Authorisation Application (MAA) for abaloparatide.

In parallel and at the same time of the triggered inspections requested by the CHMP, the Czech competent authority conducted GCP inspections at three investigator sites in Czech Republic.

It should be noted that the triggered inspections have been focused to address specific concerns on the conduct of the clinical trial and thus the number of deviations in some facilities cannot be taken as a reflection of the compliance status in study BA058-05-003 in general.

During the inspections conducted by the Czech competent authority, critical findings were identified relating to patient's inclusion in the clinical trial, the quality system of the sites and the availability of documents requested during the inspection. Due to the critical findings observed at two sites in Czech Republic, the inspectors concluded that the data from these sites cannot be reliable, and recommended to exclude them when assessing the marketing authorisation application.
As a consequence, the CHMP has requested the applicant to exclude the data from these sites in the Czech Republic during the review of the marketing authorisation application for the purpose of the evaluation of the efficacy and safety of abaloparatide. The exclusion of these two study sites in the single pivotal study resulted in a reduction of the total study population by 16% from 2463 to 2070 participants.

- **Tabular overview of clinical studies**

Table 3 Clinical Pharmacology 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. randomi-sed	N° batch ABL-SC
127-001 Phase 1 1 in Germany	Part A: Randomized, Double-blind, Dose escalation, Placebo-controlled Single dose Part B: Randomized, Open-label, Two-period Cross-over Single dose	-PK analysis ABL-SC (dose escalation and bioavailability) -Change in serum total and ionized calcium, phosphorus, cAMP, creatinine -change in urine calcium, phosphorus, cAMP	Part A Healthy subjects 43 M/37 F Median age: 61 Range: 55-73 yr Part B Healthy subjects 8 M/8 F Median age: 60 Age range: 55-69 yr	Part A: ABL (lyo)-SC 2, 5, 7.5, 10, 15, 20, 40, 60, 80, and 100 µg Placebo Part B: IV & SC administration sequence randomized. ABL (lyophilisat)-IV 2.5 µg ABL (lyophilisat)-SC 15 µg	Part A (total 80): 6 /dose group (ABL-SC) 2 (Placebo) Part B (total 16): Randomised/ dosed 16	MBPY, NBLC, NBNC, NBNB
001 Phase 1 1 in Canada 1 in USA	Randomized, Double blind, Placebo-controlled, Parallel group, Dose escalating 7 days	- PK profile ABL-SC -Change in serum total and ionized calcium, phosphorus, PTH(1-84), 1-25 dihydroxy VitD -change in urine calcium, phosphorus, cAMP and creatinine -Change in serum bone markers (s-P1NP and s-CTX)	Healthy PMW Median age: 59 Range: 50-73 yr	ABL (lyo)-SC 5 µg QD ABL (lyo)-SC 20 µg QD ABL (lyo.)-SC 40 µg QD ABL (lyo)-SC 80 µg QD Placebo: matching SC QD	8 8 8 8 7	PBQZ

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. randomi-sed	N° batch ABL-SC
001B Phase 1 1 in Canada	Randomized, Double blind, Placebo-controlled, Parallel group, Dose escalating 7 days	- PK profile ABL-SC -Change in serum total and ionized calcium, phosphorus, PTH(1-84), 1-25 dihydroxy VitD -Change in urine calcium, phosphorus, cAMP and creatinine -Change in serum bone markers (s-P1NP, P1CP, BSAP, osteocalcin and s-CTX)	Healthy PMW Median age: 60 Range: 52-74 yr	ABL-SC 80 µg QD ABL-SC 100 µg QD ABL-SC 120 µg QD ABL-SC 160 µg QD Placebo: matching SC QD	8 8 8 Not enrolled 6	643004
010 Phase 1 1 in USA	Cohort 1 (bioavailability): randomized, open-label, single-dose, 2-treatment (SC and IV abaloparatide), 2-sequence crossover study. Cohorts 2-5 (MTD): randomized, double-blind, placebo-controlled, single ascending dose of abaloparatide-SC in healthy subjects (MTD determined for the QTc study).	-PK analysis of ABL-SC (Bioavailability and MTD)	Healthy subjects Cohort 1 Healthy subjects 19 total 11M/8F Median age: 34 Range: 20-54 yr Part B Healthy subjects 40 18M/22 F Median age: 32 Age range: 20 53yr	Cohort 1: ABL-SC80 µg and ABL -IV 40 µg over a 2-hour continuous infusion. Cohort 2: ABL-SC 120 µg placebo Cohort 3: ABL -SC 240 µg placebo Cohort 4: ABL -SC 320 µg and placebo Cohort 5: ABL -SC 400 µg and placebo	19 8 2 8 2 8 2 8 2	D28382/BEK L05 (for both ABL-SC and ABL-IV)
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-SC in subjects with varying degrees of renal function Single dose	- PK profile ABL-SC -Change in serum total and ionized 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 Age range: 26 77yr	ABL-SC 80 µg Group 1-mild ClCr≥60 to <90 ml/min Group 2-moderate ClCr≥30 to <60 ml/min Group 3-severe ClCr≥15 to <30 ml/min Group 4-normal ClCr≥90 ml/min	 8 8 8 8	20871004-01B - E07274; 20871004-02B - E07274; 20871004-03B – VVNJ24; 20871004-04B - E07274; and 20871004-05B
012 Phase 1 1 in USA	Randomized, partially double-blind (to ABL-SC and placebo), single dose, positive controlled and placebo-controlled, 4-way cross-over study to evaluate the effects of abaloparatide-SC 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 Range: 18-54 yr	ABL-SC 80 µg ABL-SC 240 µg Moxifloxacin PO 400 mg Placebo-SC	4-way cross-over, n=55	E07274
002 Phase 2 10 in USA, 10 in Argentina 6 in India, 4 in UK	Randomized Double-blind (for abaloparatide-SC /Placebo) Placebo- control led Parallel group Dose finding 6 months of treatment	-Change in BMD of the spine, hip and wrist - Change in serum levels of s-P1NP, P1CP, BSAP, osteocalcin, s-CTX and (urine) levels of NTX	PMW with osteoporosis 222F Median age: 64 yr (range: 54 – 84)	ABL-SC 20 µg QD ABL-SC 40 µg QD ABL-SC 80 µg QD Placebo Teriparatide 20 µg SC QD	43 43 45 46 45	6430004, 644006, 65007

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. randomi-sed	N° batch ABL-SC
002-Extension Phase 2 1 in US, 7 in Argentina 3 in India	Extension of Study 002 to provide longer term safety & efficacy data 6 months of treatment	-Change in BMD of the spine, hip and wrist - Change in serum levels of s-P1NP, P1CP, BSAP, osteocalcin, s-CTX and (urine) levels of NTX	PMW with osteoporosis 55F Median age: 66 yr (range 55-83)	ABL-SC 20 µg QD ABL-SC 40 µg QD ABL-SC 80 µg QD Placebo SC Teriparatide 20 µg SC QD	13 10 7 11 14	6430004, 644006, 65007
007 Phase 2 3 in US, 3 in Denmark 1 in Estonia 2 in Poland	Randomized 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, BSAP, osteocalcin, s-CTX)	PMW with osteoporosis 51 F (ABL-SC) Median age: 66 Age range: 56-84 50 F (PBO-TD) Median age: 66 Age range: 44-84	ABL-SC 80µg QD Placebo-TD ABL-TD: not presented in this submission	51 50 ---	D28382
003 Phase 3 16 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-P1NP, BSAP, osteocalcin, s-CTX)	PMW with osteoporosis 2469 F Median Age: 68 Age range: 49-86	ABL-SC: 80 µg QD Teriparatide 20 µg SC QD Placebo SC	824 818 821	BEJH08, BEJH09, BEJJ12, BEKF02, BEKL05, BELD06
005 Extension of Phase 3 study 003 15 in EU, 5 in Brazil 1 in Argentina 1 in Hong Kong, 3 in USA	Open-label extension of Study 003 to provide longer term safety & efficacy data after alendronate treatment (integrated analysis for 003/005 with 24 months of treatment) Controlled Comparative Safety and Efficacy – Extension Phase 3 study	Same as 003	Same as 003 1139 F Median Age: 68 Age range: 49-86	Alendronate 70 mg oral once per week	581(ex-ABL-SC) 558 (ex-Pbo) All subjects randomised to ABL-SC /PBO in Study 003 and who are candidates for alendronate treatment	Not applicable

Table 4 Description of Clinical Efficacy Studies

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 003 Phase 3 1376 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 non-vertebral fractures	PMW with osteoporosis 2463 F Median Age: 68 Age range: 49-86	Placebo-SC ABL-SC 80 µg QD Teriparatide 20 µg SC QD	821 824 818
Study 005 Extension of Phase 3 study 003 617 in EU, 204 in Asia, 302 in South America, 16 in North America	Open-label, 24-month extension of Study 003 to provide longer term safety & efficacy data after alendronate treatment 24 months of treatment	Incidence of new vertebral fracture and non-vertebral fractures	Same as 003 1139 F Median Age: 68 Age range: 49-86	Alendronate 70 mg oral once per week	581 (prior-abaloparatide-SC) 558 (prior-Pbo)
Study 002 Phase 2 14 in USA, 147 in Argentina, 49 in India, 12 in UK	Randomised Double-blind (for abaloparatide-SC/Placebo) Placebo- controlled Parallel group Dose finding 6 months of treatment	Change in BMD-spine Change in serum bone markers (s-P1NP, P1CP, s-BALP, s-OC)	PMW with osteoporosis 221 F Median age: 64 yr (range: 54 – 84)	ABL-SC 20 µg QD ABL-SC 40 µg QD ABL-SC 80 µg QD Placebo Teriparatide 20 µg SC QD	43 43 45 45 45
Extension Study 002 (Amendment 5) Phase 2 1 in US, 43 in Argentina, 11 in India	Extension of Study 002 to provide longer term safety & efficacy data 6 months of treatment	Change in BMD-spine Change in serum bone markers (s-P1NP, P1CP, s-BALP, s-OC)	PMW with osteoporosis 55 F Median age: 66 yr (range 55-83)	ABL-SC 20 µg QD ABL-SC 40 µg QD ABL-SC 80 µg QD Placebo SC Teriparatide 20 µg SC QD	13 10 7 11 14
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

Abbreviations: BALP=bone alkaline phosphatase; BMD=bone mineral density; F=female; M=male; No.=number; SC=subcutaneous; TD=transdermal; Pbo=placebo; P1NP=N-terminal propeptide of type I procollagen; PMW=postmenopausal women; QD=once daily; s-BALP=serum bone alkaline phosphatase; s-CTX1=serum C-telopeptide of type 1 collagen; s-OC=serum osteocalcin; s-P1NP=serum N-terminal propeptide of type I procollagen; UK=United Kingdom; US=United States; yr=years

2.4.2. Pharmacokinetics

The PK properties of abaloparatide were evaluated in healthy subjects, subjects with renal impairment, and postmenopausal women with osteoporosis. Six (6) phase 1 safety, PK, and PK/PD studies (single dose, multiple ascending dose, bioavailability), as well as 1 dose-finding phase 2, 1 supportive phase 2, and 1 pivotal phase 3 study (with an extension finalised during the MAA procedure) including a population PK analysis were conducted [studies 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 (population PK analysis)].

The first 2 phase 1 studies (2-52-52127-001, BA058-05-001) were conducted with an initial lyophilised formulation of abaloparatide. 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.

The applicant has provided an overview of analytical methods and details have been given in each relevant section. The analytical methods are considered appropriate. Conventional pharmacokinetic methods were used. In addition, a population PK analysis using data from the pivotal phase 3 trial was performed. The statistical methods used for PK analyses are acceptable.

Bioavailability of the to be marketed formulation of abaloparatide was determined following a single SC and IV administration in 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 $t_{½}$ were 1.9 h and 0.9 h, respectively. Following SC injection C_{max} reached 467.3 ± 143.83 ng/ml. Thereafter abaloparatide plasma concentrations declined in a multiphasic manner until 3 h for SC administration, the last time point with results 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%).

The applicant provided a new Pop PK model. The revised model assumed an empirical time varying IV infusion rate in study BA058-05-010 but it is clear that a constant infusion rate was used. The new model better described the data; a plausible mechanistic explanation for the modelled infusion rate has been provided.

According to the applicant except for the first two 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. All relevant PK and PD data have been generated with this formulation. Thus no bioequivalence data are required.

Abaloparatide is to be administered SC and therefore no studies to evaluate the effect of food on PK have been conducted.

Human plasma protein binding of abaloparatide is about 70% and the apparent volume of distribution around 170 L after SC administration. Data indicate that abaloparatide has fast elimination and 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 probably excreted renally.

Systemic exposure of abaloparatide appears to be approximately proportional to dose from 80 µg to 240 µg without further increase at doses of 280 µg and 320 µg; the lack of further increases in systemic exposure beyond 240 µg of abaloparatide is consistent with a saturation of absorption from the SC injection site.

Abaloparatide does not seem to exhibit time dependent pharmacokinetics; mean pharmacokinetic parameters were in general comparable between day 1 and day 7.

The pharmacokinetics of abaloparatide in subjects with impaired renal function has specifically been investigated. Abaloparatide is primarily excreted in urine and systemic exposure increases with decreasing renal function but the available data so far do not indicate the need for a dose adjustment for patients with mild to moderate renal impairment.
However, efficacy and safety of abaloparatide have been established in the phase 3 study BA058-05-003; the typical abaloparatide exposure in this study should be considered the ”normal” exposure. Therefore, in the renal impairment study, the exposure comparison and any recommendations should be made against subjects with renal function that is typical of the pivotal efficacy / safety trial patient population in study BA058-05-003. The data from the phase 3 study indicate that patient with moderate and mild renal impairment had higher exposure compared to the renal impairment study in healthy subjects.
Abaloparatide systemic exposure increases with decreasing renal function and in study BA-058-05-001B a planned 160 µg dose group was abandoned due to increasing nausea events in participants receiving 120 µg of abaloparatide, indicating that increased exposure to abaloparatide is associated with an increase in adverse events. The applicant has provided results of the additional Study 17RAD102 investigating the potential of abaloparatide as a substrate of renal transporters. The study seems adequate for all transporters except OAT3; based on these results, abaloparatide appears not to be a substrate of renal transporters OAT1, OCT2, MATE1, or MATE2K. The applicant is asked to further investigate whether abaloparatide is a substrate for OAT3 using a sensitive method with adequate uptake and positive controls as a PAM.

No specific pharmacokinetic studies in subjects with hepatic impairment were performed which is acceptable. As a compound comparable to an endogenous protein, abaloparatide is not expected to be considerably eliminated via hepatic metabolic mechanisms. Results of the population pharmacokinetic analysis in the pivotal phase 3 trial showed no evidence for a correlation with hepatic function.

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

Pharmacokinetics of abaloparatide in children have not been studied; the applicant received a product-specific waiver for conducting paediatric studies for all subsets of the paediatric population.

No in vivo drug-drug interaction studies have been conducted for this program. The applicant considered the potential for drug-drug interactions 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 also rapidly degraded by proteases in serum with a short halt-life, has no known inhibiting or inducing effects on metabolising enzymes from the CYP family, and is not a substrate or inhibitor of the P-gp and BCRP drug transporters. This is agreed.

As regards interactions the abaloparatide cut-offs 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) are listed in the Table 5 below.

Table 5 EMA DDI guideline cut-offs for relevance of in vitro data of abaloparatide

$50\times C_{max(u)}$ (nM)	$25\times$Inlet $C_{max(u)}$ (nM)
2,27	4,92

Abaloparatide has been investigated as a competitive and mechanism based 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. No inhibition was observed.

The in vitro induction study in hepatocyte showed no risk for CYP induction of abaloparatide on CYP1A2, 2B6, and 3A. However a decrease of the CYP mRNA levels compared to the vehicle control was observed.

Exposure safety margins were calculated between maximally dosages used in toxicity studies and the intended dose in humans. This is of little value for calculations of margins between animal and human exposure. Far more relevant are the margins between systemic exposure at NOAELs determined in long-term animal toxicity studies and the systemic exposure in humans at the proposed dose. Organ mineralisation occurred at low dosages after long-term administration in animal studies and thus these safety margins are extremely small if present at all.

2.4.3. Pharmacodynamics

Pharmacodynamic evaluations of the effect of abaloparatide on bone metabolism markers and bone mineral density (BMD) were carried out in studies 2-52-52127-001, BA058-05-001, BA058-05-001B, BA058-05-002, BA058-05-007, BA058-05-011, BA058-05-012, and the pivotal phase 3 Study BA058-05-003 with the initial 6 month of its ongoing extension BA058-05-005. Studies 2-52-52127-001 and BA-058-05-001 used the discontinued lyophilised formulation 1 of abaloparatide while all other studies used the to be marketed formulation.

As regards primary pharmacology abaloparatide induced a linear increase with dose in BMD at the spine and differences to placebo were statistically significant after 24 weeks of treatment. Femoral neck BMD increased compared to placebo but only the difference for 80 µg abaloparatide was statistically significant compared to placebo and also at the hip the increase in BMD was highest with 80 µg abaloparatide. At the ultra-distal wrist changes in BMD were not significantly different from placebo. The effects were also seen at the end of the extension period at 48 weeks.

PTH levels decreased slightly and not-dose dependant with abaloparatide and this effect was sustained with 80 µg of abaloparatide.

Treatment with abaloparatide led to a mobilisation of calcium and a transient decrease in serum phosphorus levels; both calcium and phosphorus levels remained within normal ranges and urine excretion remained unchanged.

Mean s-P1NP levels fluctuated around predose levels with lower doses of abaloparatide while mean s-P1NP and s-P1CP levels increased following 80 µg up to 8 days and then declined slightly; s-OC and s-BALP followed an opposite trend with a slight decrease in concentrations throughout the first 3 days of dosing, before increasing up to day 14. Mean serum s-CTX concentrations remained at or near predose levels. When administered for 24 weeks P1NP, BALP, and s-OC showed a statistically significant linear trend in dose response and differences from placebo were statistically significant for

abaloparatide 40 µg and 80 µg. P1CP initially increased then declined toward baseline levels. CTX and NTX both showed an apparent dose-dependent rise across 24-week treatment; differences of CTX levels were statistically significant from placebo for abaloparatide 40 µg and 80 µg, while results for NTX were only statistically significant for 40 µg. Changes in bone markers P1NP, BALP, and s-OC were also seen after 48 weeks of treatment at the end of the extension period while CTX values tended to plateau or decrease after week 24; results for NTX were more variable and continued to increase for abaloparatide 80 µg.

With lower doses of abaloparatide 1,25-dihydroxyvitamin D concentrations remained unchanged while they increased steadily reaching a plateau above normal range at 24 h with 40 µg and 80 µg abaloparatide.

As regards study BA058-05-007 investigating the transdermal application of abaloparatide only data from subjects who received abaloparatide 80 µg SC or placebo transdermal have been provided; the transdermal route of administration has not been applied for in the current procedure and according to the applicant is still under development. The provided data for abaloparatide 80 µg SC in this trial are in line with findings in study BA058-05-002 for abaloparatide 80 µg SC and thus the omission of the full CSR of study BA058-05-007 is considered acceptable within this application.

The investigation of pharmacodynamic effects of abaloparatide in subjects with renal impairment showed slight differences in calcium, phosphate, and cAMP levels in serum and urine in subjects with different degrees of renal function, but no relationship with severity of renal impairment could be identified due to high variability and overlapping values. Thus although abaloparatide systemic exposure increases with decreasing renal function, no clear relationship could be confirmed for pharmacodynamic parameters.

In the QT study 80 µg and 240 µg abaloparatide had no clinically meaningful or concerning impact on cardiac electrophysiology but caused a clear increase in heart rate.

Secondary pharmacology has not been specifically investigated. Possible secondary pharmacodynamic effects of abaloparatide might be mediated via increased calcium levels in serum or urine. The effect of abaloparatide on calcium homeostasis has been investigated and the results do not indicate significant effects that would trigger a concern in this regard. There were, however, higher incidences of adverse events such as palpitations, nausea, dizziness, and headache for abaloparatide compared to teriparatide. A higher percentage of subjects discontinued treatment due to orthostatic hypotension defined as a composite adverse event of special interest (AESI) 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 and that the primary pharmacology following abaloparatide treatment in nonclinical models was consistent with bone anabolic effects and secondary pharmacological effects including increases in urine and serum calcium levels, hypotension, and transient and reversible increases in heart rate. Changes observed in the cardiovascular system included positive chronotropic and inotropic effects. Abaloparatide did not bind to or activate the PTH2 receptor.

Median peak levels of abaloparatide increased in an approximate dose-proportional manner with 20 µg, 40 µg, and 80 µg SC and these doses induced a dose dependent increase in percent change in BMD at the lumbar spine, total hip, and femoral neck, while no differences were seen at the ultra-distal wrist; the largest increase in BMD was noted for abaloparatide 80 µg SC. This dose-response relationship was also confirmed for serum markers s-P1NP, s-BALP, and s-OC.

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.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics of abaloparatide were 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 is about 70% and the apparent volume of distribution around 170 L after subcutaneous administration. Data indicate fast elimination primarily via 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 probably excreted renally. Abaloparatide appears to show dose-proportionality between 80 and 240 µg without further increase in exposure at doses of 280 µg and 320 µg indicating a saturation of absorption from the subcutaneous injection site. The available data do not indicate time dependent pharmacokinetics. Abaloparatide systemic exposure increases with decreasing renal function; no dose adjustment is required for patients with mild to moderate renal impairment. No specific pharmacokinetic studies in subjects with hepatic impairment were performed which is acceptable. From the scarce data available no significant influence of gender on PK parameters has been identified. No analysis of the influence of ethnicity, weight, or age on pharmacokinetic parameters has been identified. Exposure safety margins were calculated between maximally dosages used in toxicity studies and the intended dose in humans which is of little value for calculations of margins between animal and human exposure; organ mineralisation occurred at low dosages after long-term administration in animal studies and thus these safety margins are extremely small if present at all. Evaluation of the population pharmacokinetic analysis revealed that the model does not describe the data very well; inter-individual variability and maximal and minimal concentrations seem to be underestimated.

As regards primary pharmacology abaloparatide induced increases with dose in bone mineral density at the spine, femoral neck, and hip; at the ultra-distal wrist changes in bone mineral density were not significantly different from placebo. PTH levels decreased slightly and not-dose dependant with abaloparatide, while calcium was mobilised and serum phosphorus levels decreased transiently. 1,25-dihydroxyvitamin D concentrations increased steadily reaching a plateau above normal range at 24 h. As regards bone serum markers s-P1NP and s-P1CP levels increased with 80 µg abaloparatide and s-osteocalcin and s-BALP slightly decreased throughout the first days of dosing before increasing; s-CTX concentrations remained at or near predose levels.
In the QT study abaloparatide had no clinically meaningful or concerning impact on cardiac electrophysiology but caused a relevant increase in heart rate (see also 'Thorough QTC study' in the safety section below).
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 defined as a composite AESI 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.

2.4.5. Conclusions on clinical pharmacology

Overall the available pharmacokinetic and pharmacodynamic data are adequate for this application.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

The application is based on 1 phase 2, dose-ranging, 24 weeks study in postmenopausal women with osteoporosis (BA058-05-002) and 1 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). In previous CHMP scientific advice, the applicant was not recommended to perform only one pivotal trial, instead two separate studies for vertebral fractures and for non-vertebral fractures were recommended.

Dose response study

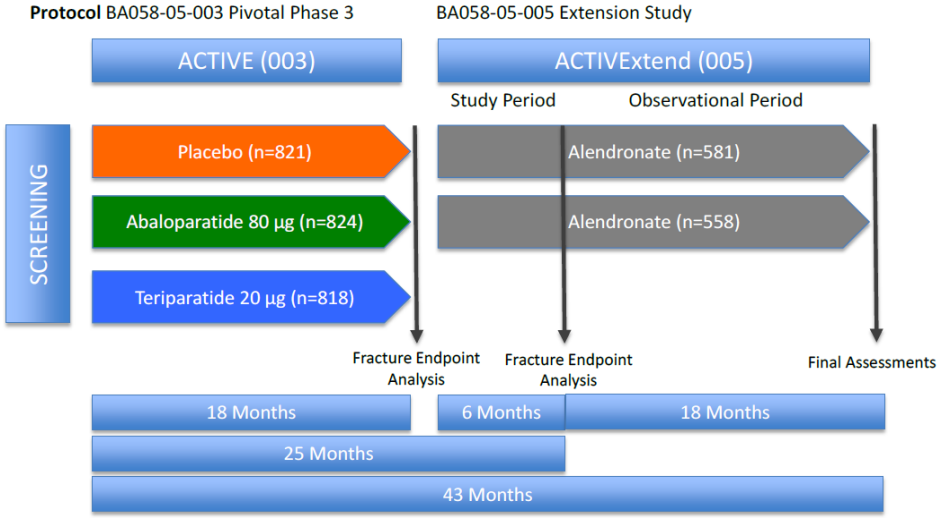
In the phase 2 dose response study BA058-05-002 postmenopausal patients with osteoporosis applied daily SC injections of either placebo, abaloparatide 20 µg, 40 µg, 80 µg, or teriparatide 20 µg; the initial treatment period was 24 weeks, but with protocol amendment 5, a 24 weeks extension was introduced for patients who had not had serious adverse events (SAE) considered treatment related, who were within 14 days of their last study drug administration, and who had not shown deterioration in BMD during the initial 24 weeks of treatment. Effects were assessed in terms of change in BMD from baseline to the end of the 24 weeks treatment period and the co-primary endpoints were changes in serum bone markers. An extension of care for a further 6 months was offered to patients.

The data indicate that doses of 20 µg, 40 µg, and 80 µg abaloparatide SC induced a dose dependent increase in percent change in BMD at lumbar spine, total hip, and femoral neck, while no differences were seen at ultra-distal wrist; the largest increase in BMD was noted for abaloparatide 80 µg SC. This dose-response relationship was also confirmed for serum markers s-P1NP, s-BALP, and s-OC. Thus the available data support the dose of 80 µg abaloparatide selected for the pivotal phase 3 trial.

Main study

The only pivotal phase 3 study BA058-05-003 was a randomised, double-blind, placebo- and comparator-controlled, multicentre international study (EudraCT Number: 2010-022576-30). The study design is depicted below.

Figure 2 Design of Study BA058-05-003 and extension BA058-05-005



In line with the 'Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis' (CPMP/EWP/552/95, rev. 2) the duration of treatment in the pivotal phase 3 trial for a new osteoporotic medicinal product should in general at least be 24 months in order to provide clear fracture and bone safety data; a total duration of 18 months of treatment in the phase 3 study is thus of concern. The applicant argues that the combined study BA058-05-003 (18 months abaloparatide) and its extension BA058-05-005 (interim data first 6 months alendronate) satisfy the requirement for 24-months of fracture assessment data. Patients treated either with abaloparatide or placebo but not those on teriparatide and who finalised study BA058-05-003 were offered participation in the extension study BA058-05-005 with additional 24 months of alendronate, from which the first 6 months were added to the original 18 month trial data for a total of 24 months of data. Although this design will allow for accruing 24 month of data the design has several deficiencies, among them patients on teriparatide have not been offered to participate in the extension study and the continuation in the extension study might introduce a selection bias to the data beyond 18 month of treatment.

Methods

Eligible for this trial were otherwise healthy, ambulatory, postmenopausal (≥5 years) women aged 50 to 85 years with osteoporosis. Women were to have a BMD T-score ≤-2.5 and >-5.0 at the lumbar spine 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 fracture criteria but had a T-score ≤-2.0 and >-5.0 could be enrolled. Additionally, women older than 65 who did not meet the fracture criteria could also be enrolled if their T-score was ≤-3.0 and >-5.0.

Further inclusion criteria were a body mass index (BMI) of ≥18.5 to ≤33 kg/m^2, albumin-adjusted serum calcium, PTH (1-84), serum phosphorus, and alkaline phosphatase values within normal range during screening; patients with an elevated alkaline phosphatase (AP) value, who met all other entry criteria needed a normal bone-specific AP result to be enrolled. Serum 25-hydroxyvitamin D values needed to be above 15 ng/mL and within 3 times the upper normal (ULN) range. Resting 12-lead electrocardiogram (ECG) during screening should not show clinically significant abnormality and a QTc ≤470 msec (Bazett's correction). Systolic blood pressure was to be ≥100 and ≤155 mmHg, diastolic

blood pressure ≥40 and ≤95 mmHg, and the heart rate ≥45 and ≤100 beats per minute (bpm) (sitting or supine). Concomitant medications could be continued if not listed as exclusion criteria.

Exclusion criteria were continuing significant deterioration of BMD at lumbar spine or hip from baseline (>7%, after confirmation), hypercalcaemia or hypercalciuria, treatment-related serious adverse events (SAEs), severe hypersensitivity to abaloparatide or teriparatide, refusal of treatment, inability to complete study procedures, loss to follow-up, and significant abnormality of serum haemoglobin (Hgb), haematocrit (Hct), white blood cells (WBC), platelets, or usual serum biochemistry (electrolytes, renal function, liver function, serum proteins). Investigators could also withdraw patients from the study for Eastern Cooperative Oncology Group (ECOG) Common Toxicity Criteria Grade 3 or 4 AEs, a complex of AEs which justified treatment cessation, serious intercurrent illness, non-compliance, protocol violations, administrative reasons, and for evidence of clinically significant abnormality in the opinion of the investigator.

Patients received either abaloparatide self-administered as an 80 µg daily subcutaneous (SC) injection, matching placebo, or teriparatide 20 µg for 18 months, randomised in a 1:1:1 scheme.

According to the statistical analysis plan and the CSR the endpoints were defined as follows.
The primary efficacy endpoint of this trial was the percent of patients with one or more incident new vertebral fracture according to Genant's method (Genant HK, et al, J Bone Miner Res. 1993:1137-48) from the baseline spine X-rays until post-baseline spine X-rays over the study treatment period of 18 month with abaloparatide 80 µg SC compared to placebo.

The key secondary efficacy endpoint was the time to the first incident non-vertebral fracture (NVF) by the follow-up visit 10 which equals 19 months. The applicant argues that NVF may occur and become clinically apparent at any time in the study and that it was expected that abaloparatide might reduce the incidence of NVF and also delay their onset. To evaluate both the incidence and the time-to-event, the statistical method to analyse NVF had been changed from the planned analysis in the protocol to using (a) the log-rank test for the inferential statistic and (b) the Kaplan-Meier method for estimates of event rates and to use all data up to the end of the follow-up visit 10 (19 months). Furthermore, the endpoint was changed from the incidence of NVF up to end of treatment (18 month) to time to first incidence of NVF by the end of the follow-up visit 10 (19 month). NVF was source-document verified and adjudicated and included fractures of the hip, wrist, forearm, shoulder, collar bone, upper arm, ribs, upper leg (not hip), knee, lower leg (not knee or ankle), foot, ankle, hand, pelvis (not hip), tailbone, and other, those associated with low trauma defined as a fall from standing height or less, or a fall on stairs, steps or curbs, and those associated with minimal or moderate trauma other than a fall. NVF excluded those of the spine, of the breast bone, knee cap, toes, fingers, skull, facial bones, pathologic fractures, fractures associated with high trauma, and those associated with severe trauma other than a fall.

Additional key secondary efficacy endpoints were the percent change from baseline in lumbar spine BMD, the percent change from baseline in total hip BMD, and the percent change from baseline in femoral neck BMD through end of 18-month treatment.
Other efficacy endpoints defined in the statistical analysis plan were the change and the percent change in vertical (standing) height from baseline to end of 18-month, severity of incident new or worsening vertebral fractures with abaloparatide versus placebo over the study treatment period up to 18 months, the percent change in distal 1/3 radius BMD from baseline through end of 18-month in a subset of patients, the percent change in serum P1NP, BALP, s-OC, and CTX in a subset of patients, and the incidence of patients with one or more incident new vertebral fractures with teriparatide compared to placebo over 18 months.

Safety related endpoints were incidence and severity of adverse events (AEs) through the 30-day follow-up period, frequency of hypercalcaemia versus teriparatide, changes in clinical laboratory parameters, determination of serum calcium, creatinine clearance, and the urine calcium / creatinine ratio, post-dose electrocardiogram (ECG) assessments, assessments of postural hypotension (60 min post dose), bone biopsy of the iliac crest in a subset of patients receiving abaloparatide, placebo, and teriparatide for assessment of quantitative bone histomorphometry, local injection site tolerance, anti-abaloparatide antibody assessment, assessment of renal parenchyma and collecting system for renal calcification via renal computed tomography (CT) scan in subset of patients.

Radiographs were to be viewed and assessed centrally according to the 'Charter for Independent Imaging Assessment' by a blinded, independent radiologist and confirmed by a second blinded radiologist for all patients for whom an incident fracture had been identified. In case of disagreement a third consensus assessment was made to adjudicate the incident fracture. A standardised graded scale of severity of the vertebral deformity was provided for this assessment.

NVFs were to be source-document verified and adjudicated according to the 'BA058-05-003 Clinical and Non-vertebral Fracture Verification and Adjudication Process'.

BMD scan for patient eligibility was to be determined at the study site; acceptability of each DXA scan was subsequently to be confirmed with the study sites by the Central Imaging CRO. According to the 'Charter for Independent Imaging Assessment' all BMD measurements were centrally read by BioClinica-Synarc. The Synarc corrected BMD was used to derive percent (%) change from baseline in BMD. Investigators were blinded to results of all follow-up DXA scans throughout the study unless a safety issue was identified by the independent radiologist.

The choice of incidence of new vertebral fractures as the primary endpoint is acceptable. As regards the key secondary efficacy endpoint and the additional key secondary and other efficacy endpoints, the description in the statistical analysis plan and the CSR is contradictory even within the documents; for further details see assessment of statistics below.

The study was blinded for all three treatment groups up to the time of randomisation when the study medication kit was assigned to eligible patients; abaloparatide and placebo remained double-blind, while it was not possible to blind the positive control teriparatide as it was delivered in its commercial form. The blind for abaloparatide and placebo was maintained throughout Study 003, the 6-month extension on alendronate and during data analysis.

Imaging data including spine X-ray images and DXA for BMD were centrally read as objective endpoints in a blinded fashion. All clinical fractures were also confirmed using source data without knowledge of treatment assignment. The overall safety of the study patients was monitored independently by a DSMB.

Although the active comparator has not been blinded due to commercial availability of teriparatide, the blind has been adequately maintained between abaloparatide and placebo throughout the study and randomised distribution to study arms was double-blind. Thus blinding is acceptable as regards the comparisons of abaloparatide versus placebo. However, 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.

In general, the methods of study BA058-05-003 are acceptable and teriparatide is an adequate comparator, although for the interpretation of the results it has to be considered that teriparatide treatment was not blinded.

The statistical analysis plan (SAP) was finalised two days prior to database lock with change of the analysis of key secondary endpoint NVFs from comparison of NVF incidence to time to first NVF. Additionally, post-hoc modifications to the definition of NVF were introduced following FDA advice. A hierarchical approach was employed to properly control the overall type-I error rate at the 2-sided significance level of 5% for testing the multiple hypotheses on the primary and the secondary efficacy endpoints for the efficacy.

The comparison of percentage with vertebral fractures between treatment groups (primary analysis) was based on the mITT population excluding patients without post-baseline radiologic assessment. As a substantial proportion of randomised patients was excluded from the mITT population and differential, treatment-related drop-out between treatment arms was observed, bias cannot be excluded. The main reasons why patients had no post-baseline radiological assessment were early termination within 3 months from post-baseline X-ray and patient refusal. In line with the overall missing data patterns, more patients in the abaloparatide group had their last spine x-ray taken at an earlier time point than in the control groups. However, the requested sensitivity analyses address the influence of missing data on the results. The ITT-based sensitivity analysis for the primary endpoint using multiple imputation provided by the applicant is acknowledged. Additional sensitivity analyses were requested, in particular analyses aiming to estimate the treatment effect taking loss of benefit after drop-out from active treatment. These sensitivity analyses were provided and supported the results of the primary analysis, including sensitivity analyses excluding the two sites from the Czech Republic. The analysis of time to first NVF was based on log-rank test, and the treatment effect was estimated as hazard ratio using Cox regression. The analysis of covariance (ANCOVA) model was used as the primary analysis method to compare treatment groups for the percent change from baseline in BMD with missing imputation based on last observation carried forward (LOCF). For time to first NVF and BMD, analyses aiming to estimate the treatment effect taking loss of benefit after drop-out from active treatment were provided as well and the results supported the pre-specified analyses.

The protocol amendments and the protocol deviations are not considered to have affected the outcome of this trial in a negative way. No unscheduled unblinding has been reported. However, it is of concern that the method for analysis of the key secondary endpoint NVFs was changed in the statistical analysis plan two days before database lock and that the definition of NVF events was modified in an amendment to the SAP after database lock which was explained in the study report by following a recommendation from the FDA. However, from a clinical point of view, the change of NVF definition (exclusion of knee cap) can be accepted.

Baseline data

All patients were postmenopausal women between the ages of 49 and 86 years, inclusive. The median age was 68 years (mean [SD] 68.8 [6.52]); 19% of the women were ≥75 years of age and only 4 patients were ≥85 years of age (0.2%). The median number of years since menopause was 20. Approximately 80% of the patients were white. The mean BMI was approximately 25 kg/m^2. Demographic and baseline characteristics are detailed below.

The treatment groups were adequately balanced in terms of their centrally assessed BMD T-scores and prevalent vertebral fractures at baseline. About 25% had BMD T-scores >-2.5 and about 18% had severe osteoporosis (at least 1 BMD T-score ≤-2.5 at any anatomical site and prevalent vertebral fracture).

Fracture history was locally assessed and reported in the eCRF by site investigators. There were no meaningful differences in the number of prior fractures, prior vertebral fractures, or prior NVFs between groups.

Demographic and baseline disease characteristics were adequately balanced between groups including baseline fracture status, BMD T-score, and fracture history. Calculation on the 10 year fracture probability has also been provided; results of the assessment of the 10 year fracture probability are considered to apply with recommendations set out in the CHMP guideline on osteoporosis (see assessment of FRAX report below).

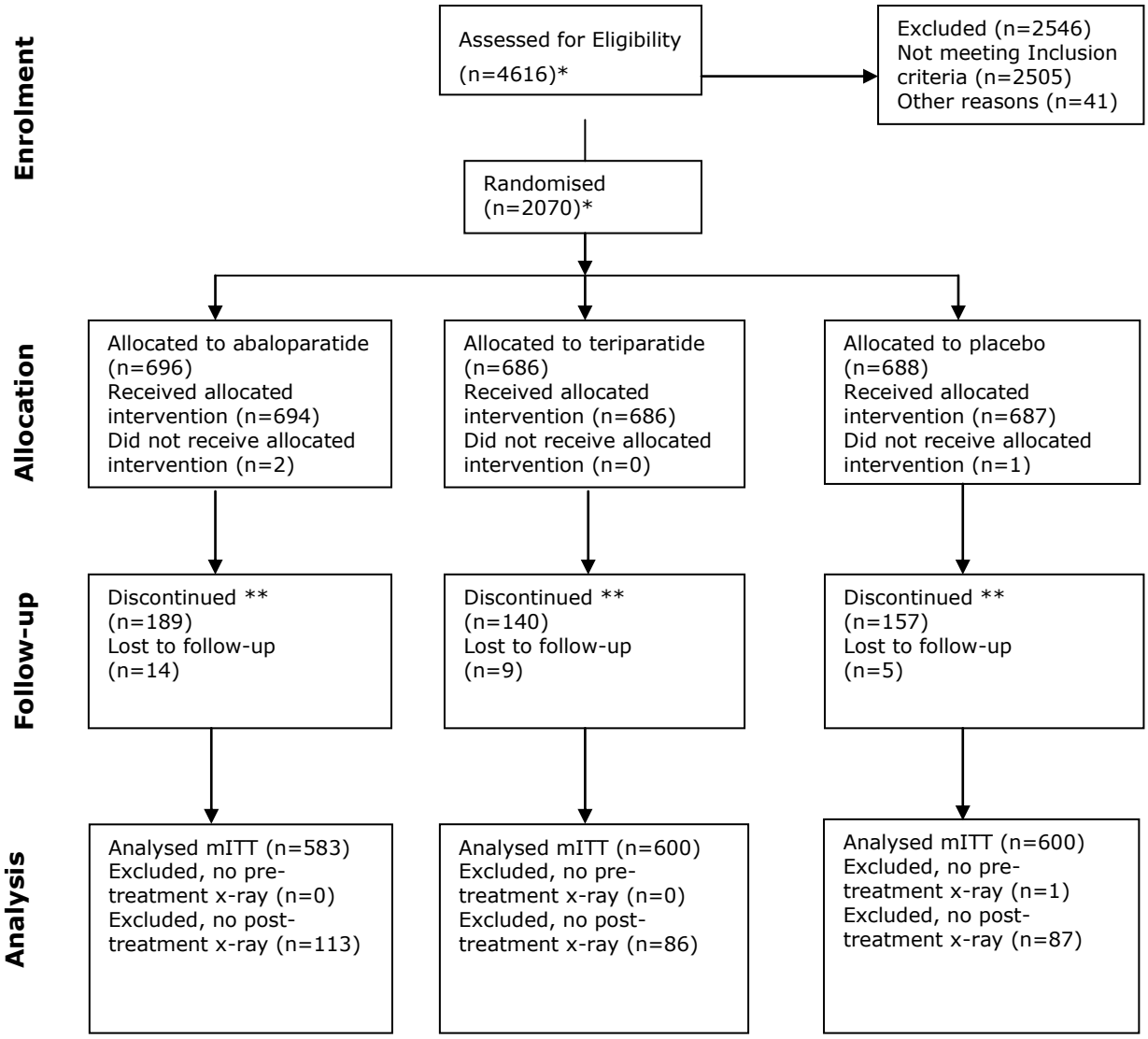
Numbers analysed

The percentage of discontinuation was different between groups; it was lowest in the teriparatide group where patients were aware of the assigned medication and highest in patients on abaloparatide. In addition, the highest percentage of discontinuation due to AEs occurred with abaloparatide. These differences were also apparent in comparison to placebo which was adequately blinded throughout the study.

Of the 2070 patients enrolled, 73% (507/696), 80% (546/686), and 77% (531/688) in the abaloparatide, teriparatide, and placebo groups, respectively, completed the 18-month study. Of the patients who discontinued 72 (38.1%) in the abaloparatide, 44 (31.4%) in the teriparatide, and 41 (26.1%) in the placebo group discontinued because of an adverse event (AE).

There was also a significant difference in the percentage of patients with no post-treatment x-ray between groups; the percentage of patients with no post-treatment x-ray was higher in patients on abaloparatide compared to both placebo and teriparatide. The participant flow is detailed below.

Figure 3



*Patients from the 2 sites from Czech Republic are excluded
**Includes the patients lost to follow-up

Primary efficacy endpoint new vertebral fractures after 18 months abaloparatide versus placebo

The predefined primary endpoint of the pivotal study BA058-05-003 was met and the reduction in the incidence of new vertebral fractures is considered clinically relevant. The analysis of the PP population as well as the sensitivity analysis supports the assumption that after 18 month of treatment abaloparatide is superior to placebo as regards the incidence of vertebral fractures. However, interpretation of the results is limited by the difference in discontinuation and the percentage of patients having a post-treatment x-ray. A potential bias cannot be excluded.

Table 6 Incidence of ≥1 New Vertebral Fracture (Study 003 mITT Population, excluding the two sites from the Czech Republic)

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]		<.0001	<.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 from Fisher's exact test comparing Abaloparatide-SC with Placebo and Teriparatide with 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.

Key secondary efficacy endpoint non-vertebral fractures after 18 months

The assessment of the key secondary efficacy endpoint non-vertebral fracture for abaloparatide versus placebo is considered a confirmatory approach.

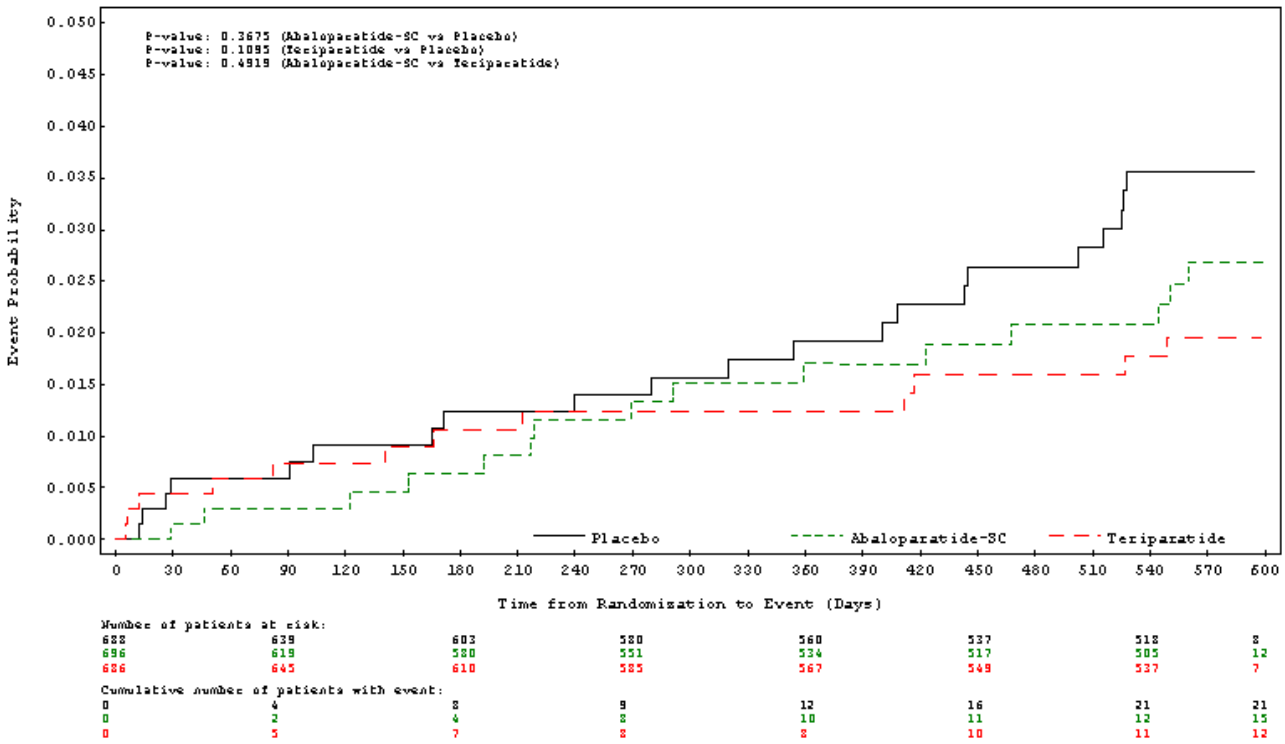
The analysis of the effect of abaloparatide versus placebo on the time to first incidence non-vertebral fracture was not statistically significant; the available data indicate a trend in favour of abaloparatide.

Table 7 Time to First Incidence of Non-vertebral Fractures - Time-to-Event Variables (Study 003 ITT Population, excluding the two sites from the Czech Republic)

Time-to-Event Variable	Parameter	Statistic	Placebo (N = 688)	Abaloparatide-SC (N = 696)	Teriparatide (N = 686)
Nonvertebral Fractures	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	

Source: Section 6.2, Table14.2.4.1A
[1] 95% CI for K-M estimates used a log-log transformation.
[2] 95% CI for ARR used standard error obtained by Greenwood's formula with the normal approximation.
[3] Cox proportional hazard model was used to calculate the hazard ratio with Placebo or Teriparatide as reference.
[4] P-values were from the logrank test.

Figure 4 Kaplan-Meier Curve of Time to First Incidence of Non-vertebral Fracture (NVF) by Treatment Group (Study 003 ITT Population, excluding the two sites from the Czech Republic)



P values from the log rank test
Source: Day180 Response 003 Figure B-14.2.4.1

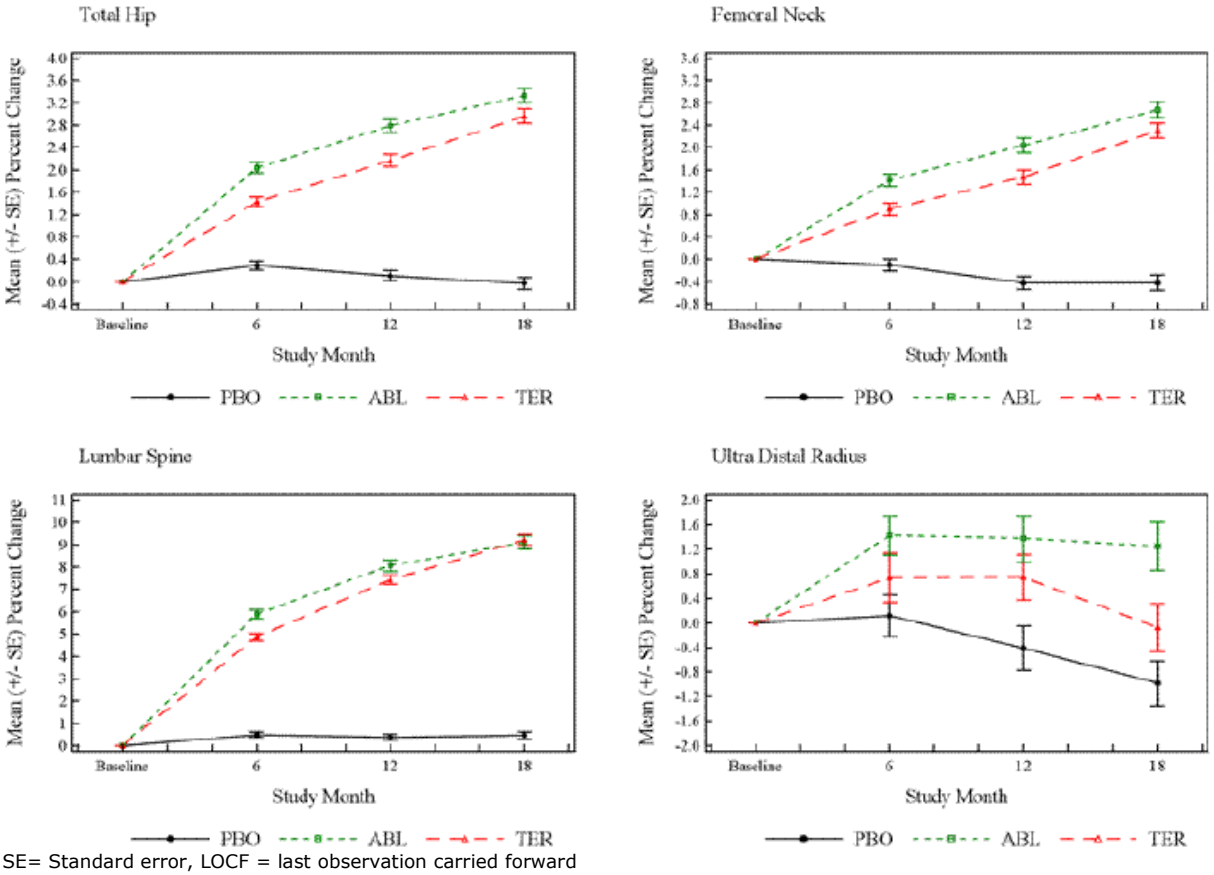
The comparison of non-vertebral fractures for abaloparatide versus teriparatide was not statistically significant (p=0.4919) and the reduction in the hazard ratio was accompanied by wide confidence intervals. . Furthermore, the scale of the y-axis leads to the visual impression of relatively large differences 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.

Additional key secondary efficacy endpoints bone mineral density at total hip, femoral neck, and lumbar spine at 18 months

According to the documents provided it appears that only comparisons of change in BMD from baseline to 18 months were prespecified for the analyses of 'key secondary' and 'other key secondary efficacy endpoint'. Therefore, this assessment presents 18 months comparisons in this section, while comparisons of changes in BMD from baseline to 6 and 12 months are presented below in the section on ancillary analyses.

Percentage change in total hip, femoral neck, and lumbar spine BMD from baseline to 18-month was statistically significantly higher with abaloparatide compared to placebo and results demonstrate a relevant increase in BMD at these sides in patients on abaloparatide. Increases in BMD were comparable between abaloparatide and teriparatide except for ultra-distal radius.

Figure 5 18 Month Mean (± SE) Percent Change from Baseline in BMD Using LOCF (Study 003 ITT Population, excluding the two sites from the Czech Republic)



SE= Standard error, LOCF = last observation carried forward
Source: Day180 Response 003 Figure B-14.2.10.1A, B-14.2.10.2A, B-14.2.10.3A, B-14.2.10.5A

Ancillary analyses

There were minimal numerical differences in change and percent change in vertical height between groups; these differences were neither statistically significant nor clinically relevant.

The percentage of patients with severe incident new or worsening vertebral fractures was lower with abaloparatide and teriparatide than 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.

The increase in the anabolic serum bone marker s-P1NP was 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-OC were higher with abaloparatide versus placebo and highest in participants using teriparatide.

Teriparatide showed a significant reduction in the incidence of new vertebral fractures compared to placebo.

Both abaloparatide and teriparatide reduced the incidence of new or worsening vertebral fractures versus placebo after 18 months of therapy.

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 prolonged with abaloparatide compared to placebo and patients on abaloparatide had fewer non-vertebral fractures including all trauma levels and were fracture-free longer, and the time to first clinical spine fracture was prolonged and the incidence lower with abaloparatide versus placebo. Time to first incidence of other fractures was also numerically increased for abaloparatide compared to teriparatide but differences were mostly not statistically significant and are not considered clinically relevant.

The percentage of patients with BMD changes >0%, >3%, and >6% at lumbar spine, femoral neck, and total hip combined was significantly higher with abaloparatide than with placebo and also higher than in patients on teriparatide.

The data indicate that at least the lumbar spine and probably the femoral neck increases in BMD with abaloparatide were higher in patients with reduced creatinine clearance compared to patients with normal creatinine clearance. The effect might be due to an increase in abaloparatide exposure due to reduced renal elimination (see 'Impaired renal function' above).

Analyses of new vertebral fracture, non-vertebral fracture, and BMD by subgroups including age, ethnicity, region, and risk at baseline did not indicate an interaction between treatment and the majority of subgroups investigated and Forest plots showed effects to be in the same direction for these analyses.

Divergent results were seen for non-vertebral fracture in the subgroups Asian race and Asia region, for BMD at the total hip in the subgroup North America, and for BMD at the femoral neck in subgroups Black race, North America, and 'prevalence of vertebral fracture at baseline ≥2 fracture' but confidence intervals overlapped, the number of events was small, and there were too few patients in these subgroups to draw any conclusions.

FRAX-report

Aims of the FRAX analysis were to evaluate the distribution of fracture risk assessed at baseline using the FRAX® tool and to determine the efficacy of abaloparatide and teriparatide in study BA058-05-003 as a function of baseline fracture risk.

Baseline fracture probabilities estimated by FRAX® were low compared to several other phase 3 studies in patients with osteoporosis but for example similar to that seen in clinical trials of bazedoxifene. Fracture probabilities increased with age. Baseline characteristics of fracture probabilities for patients recruited to the extension study BA058-05-005 did not differ from the population of study BA058-05-003 and there were no relevant differences between those who continued and those who did not.

Table 8 Ten-year probability (%) for Hip Fracture and Major Osteoporotic Fracture with and without BMD Overall (Study 003, excluding the two sites from the Czech Republic)

Ten-year probability	N	Median	Mean	SD	Range
hip fracture calculated with BMD	2067	3.44	4.96	4.97	0.1-50.0
hip fracture calculated without BMD	2070	3.73	5.24	5.03	0.2-59.0
osteoporotic fracture calculated with BMD	2067	10.95	13.10	8.35	2.3-57.5
osteoporotic fracture calculated without BMD	2070	10.90	13.14	8.38	2.2-67.2

Abaloparatide significantly reduced the incidence of all three clinical fracture outcomes in patients with probabilities at baseline that fell above the thresholds given in the CHMP guideline on osteoporosis (10-year probability for spine fracture 15% to 20%, for hip fracture 5% to 7.5%, for major non-vertebral fracture 10% to 15%).

Hazard ratios for the effect of abaloparatide on the various fracture outcomes did not change significantly across the range of baseline fracture probabilities, suggesting significant efficacy over the whole range. There was, however, a trend for the efficacy to increase with higher baseline major osteoporotic fracture probability; significant anti-fracture efficacy was demonstrated in patients deemed at high risk according to CHMP guideline on osteoporosis.

At equivalent fracture probability percentiles, the treatment effect of abaloparatide was greater on vertebral fracture risk than on the risk of clinical fractures at other sites; findings were robust to several sensitivity analyses.

There were no statistically significant interactions between treatment and the continuous or categorical baseline variables included in the FRAX analysis.

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 9 Summary of efficacy for study BA058-05-003c, excluding the two sites from the Czech Republic

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	
Design	Phase 3, comparative, randomised, partially double-blind, placebo-controlled, multi-centre, international study to assess 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: Duration of Run-in phase: Duration of Extension phase:	19 months not applicable Extension Study BA058-05-005 (24 months)

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.		
Treatments groups	Abaloparatide-SC		Double-blind abaloparatide-SC: 18 Months, 696 randomised
	Placebo		Double-blind placebo: 18 months, 688 randomised
	Teriparatide		Open-label teriparatide: 18 months, 686 randomised
Endpoints and definitions	Primary endpoint	Incidence of new vertebral fracture (VF) abaloparatide vs placebo	Percentage of patients with one or more incident new VF according to Genant's method (Genant et al, 1993) from baseline to 18 months abaloparatide vs placebo
	Key secondary endpoint	Time to first incident non-vertebral fracture (NVF)	Time to the first incident NVF by follow-up visit 10 (19 months)
	Additional key secondary endpoint	Percent change in total hip BMD	Percent change from baseline in total hip BMD at 18 months assessed by dual X-ray absorptiometry (DXA) using last observation carried forward (LOCF)
	Additional key secondary endpoint	Percent change in femoral neck BMD	Percent change from baseline in femoral neck BMD at 18 months assessed by DXA using LOCF
	Additional key secondary endpoint	Percent change in lumbar spine BMD	Percent change from baseline in lumbar spine BMD at 18 months assessed by DXA using LOCF
	Other endpoint	Change in bone turnover marker s-P1NP	Geometric mean ratio of post-baseline value over baseline value in bone turnover marker s-P1NP at 1, 3, 6, 12 and 18 months
	Other endpoint	Change in bone turnover marker s-CTX at 1, 3, 6, 12 and 18 months	Geometric mean ratio of post-baseline value over baseline value in bone turnover marker s-CTX at 1, 3, 6, 12 and 18 months
	Other endpoint	Incidence of new VF teriparatide vs placebo	Percentage of patients with one or more incident new VF from baseline to 18 months teriparatide vs placebo
	Other endpoint	Percent of responders BMD	Percent of subjects with >3% increase in BMD at all three sites (lumbar spine, femoral neck, total hip) at 6, 12, and 18 months
Database lock	10 December 2014		

Results and Analysis				
Analysis description	**Primary Analysis** **Incidence of new vertebral fracture abaloparatide vs placebo at 18 months**			
Analysis population and time point description	mITT Population, all randomised patients who had both pre-treatment and post-baseline evaluable radiologic assessment (lumbar and thoracic spine X-rays) Analysis at 18 months, excluding the two sites from the Czech Republic			
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	
Analysis description	**Key Secondary analysis** **Time to the first incident non-vertebral fracture (NVF) over 19 months**			
Analysis population and time point description	ITT Population, all patients who were randomised Analysis by follow-up visit 10 at 19 months, excluding the two sites from the Czech Republic			
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	
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	
Effect estimate per comparison		Comparison groups	Teriparatide vs Placebo	
		Hazard Ratio	0.56	
		95% CI	(0.28, 1.15)	
		P-value (Log-rank test)	0.1095	

Analysis description	**Additional key secondary analysis** **Percent change from baseline in total hip BMD at 18 months using LOCF**			
Analysis population and time point description	Intent-to-Treat (ITT) Population Analysis at 18 months, excluding the two sites from the Czech Republic			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=687	N=694	N=686
	Mean percent change from baseline	-0.029	3.328	2.961
	95% CI	(-0.239, 0.182)	(3.074, 3.581)	(2.712, 3.211)
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Teriparatide vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Teriparatide	
		P-value	0.0211	
Analysis description	**Additional key secondary** **Percent change from baseline in femoral neck BMD at 18 months using LOCF**			
Analysis population and time point description	Intent-to-Treat (ITT) Population Analysis at 18 months, excluding the two sites from the Czech Republic			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=687	N=694	N=686
	Mean percent change from baseline	-0.417	2.676	2.304
	95% CI	(-0.682, -0.151)	(2.380, 2.972)	(2.044, 2.563)
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Teriparatide vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Teriparatide	
		P-value	0.0389	
Analysis description	**Additional key secondary** **Percent change from baseline in lumbar spine BMD at 18 months using LOCF**			
Analysis population and time point description	Intent-to-Treat (ITT) Population Analysis at 18 months, excluding the two sites from the Czech Republic			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=688	N=695	N=686
	Mean percent change from baseline	0.470	9.092	9.202

	95% CI	(0.182, 0.758)	(8.527, 9.657)	(8.731, 9.673)
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Teriparatide vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Teriparatide	
		P-value	0.7861	
Analysis description	**Exploratory analysis** **Change in bone turnover marker s-P1NP at 1 month**			
Analysis population and time point description	Bone Metabolism Population included patients who received at least one dose of study medication, had baseline and at least one post-baseline biochemical marker of bone turnover assessment Analysis at 1 month			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=155	N=162	N=180
	Geometric mean	48.618	96.459	92.463
	Geometric mean (SE) of ratio (visit / baseline)	0.901 (0.0137)	1.899 (0.0690)	1.852 (0.0458)
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Placebo	
		Relative treatment effect (95% CI)	2.067 (1.921, 2.226)	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Teriparatide vs Placebo	
		Relative treatment effect (95% CI)	2.000 (1.861, 2.150)	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Teriparatide	
		Relative treatment effect (95% CI)	1.034 (0.963, 1.110)	
		P-value	0.3616	
Analysis description	**Exploratory analysis** **Change in bone turnover marker s-P1NP at 3 months**			
Analysis population and time point description	Bone Metabolism Population Analysis at 3 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=154	N=162	N=180
	Geometric mean	43.224	88.909	98.568
	Geometric mean (SE) of ratio (visit/baseline)	0.805 (0.0178)	1.732 (0.0900)	1.974 (0.0683)
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Placebo	
		Relative treatment effect (95% CI)	2.106 (1.893, 2.342)	

		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Teriparatide vs Placebo
		Relative treatment effect (95% CI)		2.390 (2.154, 2.652)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Teriparatide
		Relative treatment effect (95% CI)		0.881 (0.795, 0.976)
		P-value		0.0158
Analysis description	**Exploratory analysis Change in bone turnover marker s-P1NP at 6 months**			
Analysis population and time point description	Bone Metabolism Population Analysis at 6 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=156	N=164	N=180
	Geometric mean	41.387	92.135	124.332
	Geometric mean (SE) of ratio (visit/baseline)	0.769 (0.0246)	1.803 (0.1099)	2.490 (0.1099)
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Placebo
		Relative treatment effect (95% CI)		2.305 (2.025, 2.623)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Teriparatide vs Placebo
		Relative treatment effect (95% CI)		3.159 (2.783, 3.585)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Teriparatide
		Relative treatment effect (95% CI)		0.730 (0.644, 0.826)
		P-value		<0.0001
Analysis description	**Exploratory analysis Change in bone turnover marker s-P1NP at 12 months**			
Analysis population and time point description	Bone Metabolism Population Analysis at 12 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=156	N=164	N=180
	Geometric mean	44.280	85.463	126.119
	Geometric mean (SE) of ratio (visit/baseline)	0.823 (0.0231)	1.672 (0.1041)	2.526 (0.1156)
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Placebo
		Relative treatment effect (95% CI)		1.998 (1.756, 2.273)

		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Teriparatide vs Placebo
		Relative treatment effect (95% CI)		2.995 (2.639, 3.398)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Teriparatide
		Relative treatment effect (95% CI)		0.667 (0.589, 0.756)
		P-value		<0.0001
Analysis description	**Exploratory analysis Change in bone turnover marker s-P1NP at 18 months**			
Analysis population and time point description	Bone Metabolism Population Analysis at 18 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=156	N=164	N=180
	Geometric mean	49.207	71.805	102.144
	Geometric mean (SE) of ratio (visit/baseline)	0.914 (0.0277)	1.405 (0.0784)	2.046 (0.0880)
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Placebo
		Relative treatment effect (95% CI)		1.511 (1.342, 1.700)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Teriparatide vs Placebo
		Relative treatment effect (95% CI)		2.183 (1.944, 2.451)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Teriparatide
		Relative treatment effect (95% CI)		0.692 (0.617, 0.776)
		P-value		<0.0001
Analysis description	**Exploratory analyses Change in bone turnover marker s-CTX at 1 month**			
Analysis population and time point description	Bone Metabolism Population Analysis at 1 month			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=155	N=162	N=180
	Geometric mean	0.432	0.426	0.453
	Geometric mean (SE) of ratio (visit/baseline)	0.925 (0.0169)	0.946 (0.0251)	1.038 (0.0255)
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Placebo
		Relative treatment effect (95% CI)		1.019 (0.952, 1.090)

		P-value		0.5852
Effect estimate per comparison		Comparison groups		Teriparatide vs Placebo
		Relative treatment effect (95% CI)		1.113 (1.042, 1.189)
		P-value		0.0015
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Teriparatide
		Relative treatment effect (95% CI)		0.915 (0.857, 0.977)
		P-value		0.0078
Analysis description	**Exploratory analyses Change in bone turnover marker s-CTX at 3 months**			
Analysis population and time point description	Bone Metabolism Population Analysis at 3 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=154	N=162	N=180
	Geometric mean	0.426	0.554	0.657
	Geometric mean (SE) of ratio (visit/baseline)	0.920 (0.0188)	1.222 (0.0498)	1.505 (0.0461)
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Placebo
		Relative treatment effect (95% CI)		1.326 (1.212, 1.452)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Teriparatide vs Placebo
		Relative treatment effect (95% CI)		1.629 (1.491, 1.779)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Teriparatide
		Relative treatment effect (95% CI)		0.814 (0.746, 0.888)
		P-value		<0.0001
Analysis description	**Exploratory analyses Change in bone turnover marker s-CTX at 6 months**			
Analysis population and time point description	Bone Metabolism Population Analysis at 6 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=156	N=164	N=180
	Geometric mean	0.351	0.502	0.695
	Geometric mean (SE) of ratio (visit/baseline)	0.754 (0.0225)	1.108 (0.0582)	1.593 (0.0667)
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Placebo
		Relative treatment effect (95% CI)		1.467 (1.301, 1.653)

		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Teriparatide vs Placebo
		Relative treatment effect (95% CI)		2.100 (1.868, 2.361)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Teriparatide
		Relative treatment effect (95% CI)		0.698 (0.622, 0.784)
		P-value		<0.0001
Analysis description	**Exploratory analyses Change in bone turnover marker s-CTX at 12 months**			
Analysis population and time point description	Bone Metabolism Population Analysis at 12 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=156	N=164	N=180
	Geometric mean	0.388	0.486	0.695
	Geometric mean (SE) of ratio (visit/baseline)	0.832 (0.0276)	1.074 (0.0554)	1.593 (0.0662)
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Placebo
		Relative treatment effect (95% CI)		1.287 (1.142, 1.450)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Teriparatide vs Placebo
		Relative treatment effect (95% CI)		1.902 (1.692, 2.138)
		P-value		<0.0001
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Teriparatide
		Relative treatment effect (95% CI)		0.677 (0.603, 0.759)
		P-value		<0.0001
Analysis description	**Exploratory analyses Change in bone turnover marker s-CTX at 18 months**			
Analysis population and time point description	Bone Metabolism Population Analysis at 18 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects	N=156	N=164	N=180
	Geometric mean	0.426	0.440	0.626
	Geometric mean (SE) of ratio (visit/baseline)	0.915 (0.0294)	0.972 (0.0462)	1.434 (0.0581)
Effect estimate per comparison		Comparison groups		Abaloparatide-SC vs Placebo
		Relative treatment effect (95% CI)		1.059 (0.946, 1.186)

		P-value	0.3173	
Effect estimate per comparison		Comparison groups	Teriparatide vs Placebo	
		Relative treatment effect (95% CI)	1.557 (1.395, 1.739)	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Teriparatide	
		Relative treatment effect (95% CI)	0.680 (0.610, 0.758)	
		P-value	<0.0001	
Analysis description	**Exploratory Analysis** **Incidence of new vertebral fracture teriparatide vs placebo at 18 months**			
Analysis population and time point description	mITT Population, all randomised patients who had both pre-treatment and post-baseline evaluable radiologic assessment (lumbar and thoracic spine X-rays) Analysis at 18 months, excluding the two sites from the Czech Republic			
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	Teriparatide-SC 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	**Exploratory analysis** **Percent of responders at 6 months (>3% increase in BMD at lumbar spine, femoral neck, total hip)**			
Analysis population and time point description	Intent-to-Treat (ITT) Population Analysis at 6 months, excluding the two sites from the Czech Republic			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects with data at baseline and 6 months	N=542	N=511	N=547
	Number (%) of subjects with BMD Increase >3% at all sites	5 (0.92)	97 (18.98)	38 (6.95)
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Teriparatide vs Placebo	
		P-value	<0.0001	
Effect estimate per		Comparison groups	Abaloparatide-SC vs Teriparatide	

comparison		P-value	<0.0001	
Analysis description	**Exploratory analysis Percent of responders at 12 months (>3% increase in BMD at lumbar spine, femoral neck, total hip)**			
Analysis population and time point description	Intent-to-Treat (ITT) Population Analysis at 12 months, excluding the two sites from the Czech Republic			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects with data at baseline and 12 months	N=542	N=513	N=547
	Number of subjects with BMD Increase >3% at all sites	8 (1.48)	163 (31.77)	109 (19.93)
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Teriparatide vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Teriparatide	
		P-value	<0.0001	
Analysis description	**Exploratory analysis Percent of responders at 18 months (>3% increase in BMD at lumbar spine, femoral neck, total hip)**			
Analysis population and time point description	Intent-to-Treat (ITT) Population Analysis at 18 months, excluding the two sites from the Czech Republic			
Descriptive statistics and estimate variability	Treatment group	Placebo	Abaloparatide-SC	Teriparatide
	Number of subjects with data at baseline and 18 months	N=542	N=514	N=548
	Number of subjects with BMD Increase >3% at all sites	12 (2.21)	217 (42.22)	180 (32.85)
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Teriparatide vs Placebo	
		P-value	<0.0001	
Effect estimate per comparison		Comparison groups	Abaloparatide-SC vs Teriparatide	
		P-value	0.0016	

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 10 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 Trial 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)

The majority of patients in the pivotal trial BA058-05-003 were in the age range of 65 to 74 years of age; about 18% to 20% percent of the treated population was 75 years of age or older at baseline. 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)

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.

Supportive study

The applicant has provided data from the supportive clinical trial BA058-05-005. In the extension study BA058-05-005 patients who were either on abaloparatide or placebo, but not those on teriparatide, in the base study BA058-05-003 and who finished the base study were offered to participate and received open-label alendronate 70 mg once weekly. The first patient was enrolled on 20 November 2012 and the last patient completed on 03 October 2016; the final report is dated 19 October 2017. Even if not explicitly mentioned at every instance in this assessment report, the data for this supportive study are presented without data from the two sites in Czech Republic that cannot be used for the evaluation of the efficacy and safety of abaloparatide (see GCP section above).

Study BA058-05-003 was completed by 1038 patients on abaloparatide or placebo and 963 entered study BA058-05-005 (ITT population); of these 863 (89.6%) completed study BA058-05-005, the primary reason for non-completion were adverse events. Eight (8) patients did not complete the study due to continuing significant deterioration of >7% of BMD at spine or hip from the BA058-05-005 baseline. For further details see Table 11 below.

Table 11 Patient Enrolment and Disposition (Study 005, excluding the two sites from the Czech Republic)

Parameter	Placebo /Alendronate n (%)	Abaloparatide-SC /Alendronate n (%)	Overall n (%)
Study BA058-05-003 Randomized (Intent-to-Treat (ITT) Population) [1]	688 (100.0)	696 (100.0)	1384 (100.0)
Study BA058-05-003 Safety Population [2,3]	687 (99.9)	694 (99.7)	1381 (99.8)
Completed Study 003 [3,4]			
Yes	531 (77.2)	507 (72.8)	1038 (75.0)
No	157 (22.8)	189 (27.2)	346 (25.0)
Entered Study BA058-05-005 [5]			
Yes	494 (93.0)	469 (92.5)	963 (92.8)
Reason for Not Entered Study BA058-05-005 [5]			
Subject is more than 33 days from last study drug administration	4 (10.8)	3 (7.9)	7 (9.3)
Subject is not willing to continue in the study	21 (56.8)	20 (52.6)	41 (54.7)
Subject was withdrawn from BA058-05-003 for any reason	1 (2.7)	0	1 (1.3)
Subject is not a candidate for further osteoporosis treatment	0	3 (7.9)	3 (4.0)
Other	11 (29.7)	12 (31.6)	23 (30.7)
Study BA058-05-005 Intent-to-Treat (ITT) Population [6,7]	494 (93.0)	469 (92.5)	963 (92.8)
Study BA058-05-005 Safety Population [8,9]	493 (99.8)	465 (99.1)	958 (99.5)
Study BA058-05-005 Modified Intent-to-Treat (mITT) Population [9,10]	489 (99.0)	457 (97.4)	946 (98.2)
Reasons for Exclusion from Study BA058-05-005 mITT Population [9]			
Not included in Study BA058-05-003 mITT population	1 (0.2)	1 (0.2)	2 (0.2)
Did not have radiologic assessment at Visit 3 in Study BA058-05-005	4 (0.8)	11 (2.3)	15 (1.6)
Completed Study 005 [9,11]			
Yes	440 (89.1)	423 (90.2)	863 (89.6)
No	54 (10.9)	46 (9.8)	100 (10.4)
Primary Reason for Non-Completion of Study BA058-05-005 [12, 13]			
Adverse Event	26 (48.1)	20 (43.5)	46 (46.0)
Refusal of treatment	6 (11.1)	3 (6.5)	9 (9.0)
Continuing significant deterioration from baseline (> 7%) of BMD at spine or hip (after confirmation of the findings)[14]	2 (3.7)	6 (13.0)	8 (8.0)
Inability to complete study procedures	4 (7.4)	1 (2.2)	5 (5.0)
Lost to follow up	3 (5.6)	2 (4.3)	5 (5.0)
Protocol violation	0	1 (2.2)	1 (1.0)
Patient died during the study	1 (1.9)	2 (4.3)	3 (3.0)
Withdrew Consent	11 (20.4)	11 (23.9)	22 (22.0)
Other	1 (1.9)	0	1 (1.0)

Source: Appendix 5.1.1,Table 14.1.1A and Appendix 5.2.1, Table 14.1.1A
[1] Included all patients who were randomized into Study BA058-05-003 by the assigned randomized study medication kit on Study BA058-05-003 Day 1; [2] Includes all Study BA058-05-003 randomized patients who received 1 or more doses of Study BA058-05-003 medication; [3] Percentages based on Study BA058-05-003 number of patients randomized; [4] Study completion as indicated by the investigator on the Study BA058-05-003 End of Study CRF; [5] Summarized only for patients who completed Study BA058-05-003; [6] Included all Study BA058-05-003 ITT patients who enrolled in Study BA058-05-005; [7] Percentages based on Study BA058-05-003 number completed study; [8] Included all Study BA058-05-005 ITT patients who received 1 or more doses of Study BA058-05-005 medication, alendronate; [9] Percentages based on the number of Study BA058-05-005 ITT patients; [10] Included all Study BA058-05-003 mITT patients who had a BA058-05-005 post baseline evaluable radiologic assessment (spine x-ray); [11] Study completion as indicated by the investigator on the Study BA058-05-005 End of Study CRF. Patient 1010064 completed the study at 6 months under the original protocol dated 23 July 2012; [12] Primary reasons were exclusive; i.e., each patient had only one primary reason; [13] Percentages based on the number of patients who did not complete Study BA058-05-005; [14] Represents baseline from the start of the BA058-05-005 study.

Demographic and baseline characteristics were adequately balanced between groups. When based on investigator's locally evaluated DXA and X-rays recorded on the electronic case report form, 99.5% of patients in study BA058-05-005 met the study BA058-05-003 BMD and fracture inclusion criteria No 3. When centrally read and adjudicated by BioClinica-Synarc the percentage of women meeting this inclusion criteria dropped to 80.6%, therefore the assessments of inclusion criterion No. 3 were discrepant in the study. Imbalances between the abaloparatide/alendronate and the placebo/alendronate group were seen for baseline BMD values in line with the abaloparatide treatment effect in study BA085-05-003; fewer patients on abaloparatide/alendronate (9.4%), than on placebo/alendronate (19.6%) had severe osteoporosis at study BA058-05-005 baseline.

For the primary endpoint incidence of new vertebral fractures (mITT) from study BA058-05-003 baseline to Month 25 of study BA058-05-005 (18 months double-blind abaloparatide or placebo study BA058-05-003, 1 month follow-up, 24 months alendronate study BA058-05-005) 4/457 patients (0.88%) in the abaloparatide / alendronate group and 26/489 (5.32%) in the placebo / alendronate experienced new vertebral fractures; the risk reduction versus placebo (95% CI) was -4.44 (-6.86, -2.30; p<0.0001).

In the placebo/alendronate group, there were 16 patients with new vertebral fracture at Month 18, and an additional 10 patients from Month 18 to Month 43, while in the abaloparatide group there were 2 patients with new vertebral fracture at Month 18, and an additional 2 patients from Month 18 to Month 43.

The incidence of new vertebral fracture in the PP population was in line the analysis of the mITT population.

In the analysis of new vertebral fracture in study BA058-05-005 from BA058-05-005 baseline, 0/457 patients (0%) in the abaloparatide / alendronate group and 6/489 (1.23%) in the placebo / alendronate experienced new vertebral fractures at Month 6; the risk reduction versus placebo (95% CI) was -1.23 (-2.65, -0.16; p=0.0313). At Month 24 these values were 2/457 (0.44%) and 13/489 (2.66%), respectively, a risk reduction versus placebo (95% CI) of -2.22 (-4.08, -0.64; p=0.0074).

Table 12 New Vertebral Fracture Through Month 43 (Visit 6 in BA058-05-005) Compared to Baseline (Visit 1 in BA058-05-003) (BA058-05-005 mITT Population, excluding the two sites from the Czech Republic)

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 (%)	25/489 (4.29)	2/457 (0.44)
	95% CI [1]	2.83, 6.48	0.12, 1.58
	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)

Source: Appendix 5.1.2, Table 14.2.1A and Appendix5.2.2, Table 14.2.1A
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.

As regards non-vertebral fractures the incidence from the BA058-05-003 baseline to end of study BA058-05-005 was 19/469 patients (4.05%) in the abaloparatide / alendronate and 32/494 (6.48%) in the placebo / alendronate group; the risk reduction versus placebo (95% CI) was -2.43 (-5.33, 0.44; p=0.0928).

The incidence non-vertebral fractures from the BA058-05-005 baseline to end of study BA058-05-005 was 10/469 patients (2.13%) in the abaloparatide / alendronate and 15/494 (3.04%) in the placebo / alendronate group; the risk reduction versus placebo (95% CI) was -0.90 (-3.05, 1.21; p=0.3778).

In study BA058-05-005 all patients were switched from abaloparatide or placebo to alendronate after the 30-day period following Month 18 (Day 540) in study BA058-05-003. After transition to alendronate at Month 19, further increases in BMD from the BA058-05-003 baseline were observed in

both the abaloparatide / alendronate and the placebo / alendronate group, at Months 25, 31, 37 and 43 with statistically significant differences favouring abaloparatide / alendronate ($p<0.0001$) at the total hip, femoral neck, and lumbar spine for all time-points. 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 were not statistically significant except at Month 24 for total hip ($p=0.0025$) and the lumbar spine at all time-points ($p<0.0001$).

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

According to the applicant all clinical trials were conducted in compliance with GCP principles. Three inspection requests were adopted by the CHMP concerning the conduct of the single pivotal trial BA058-05-003, a routine (GCP/INS/2015/030) and two triggered requests (GCP/INS/2016/001 - GCP/INS/2016/013). The routine request covered three sites, while two triggered, unannounced GCP inspections were also requested and performed at three sites.

In parallel and at the same time of the CHMP triggered inspections, the Czech competent authority conducted national GCP inspections at three sites.

Due to the critical findings observed at two sites in Czech Republic, the inspectors concluded that the data from these sites cannot be reliable, and recommended to exclude them when assessing the marketing authorisation application. As a consequence, the CHMP has requested the applicant to exclude the data from these sites in the Czech Republic during the review of the marketing authorisation application for the purpose of the evaluation of the efficacy and safety of abaloparatide. The GCP related serious findings, leading to the exclusion of two study sites, reduced the total study population by 16% from 2463 to 2070 participants.

The applicant has provided only one pivotal study powered to assess superiority of abaloparatide versus placebo in reducing the risk of occurrence of new vertebral fractures in postmenopausal women. The effect of abaloparatide on the occurrence of new non-vertebral fracture was included as a secondary endpoint and no data from a separate study to assess the efficacy of abaloparatide on non-vertebral fractures are available.

In general the 'Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis' (CPMP/EWP/552/95, rev. 2) requests that the efficacy of an anti-osteoporotic drug should be tested for both the effect on vertebral as well as on non-vertebral fractures in separate studies. Although one pivotal study might be acceptable if the effect on the secondary endpoint non-vertebral fractures is undisputable, adherence to requirements set out in the guideline on one pivotal study is essential (e.g. statistical evidence considerably stronger than $p<0.05$, narrow confidence intervals, pre-specified alternative analyses for demonstration of consistency). Furthermore, in line with the CHMP guideline on osteoporosis the duration of treatment in the pivotal phase 3 trial for a new osteoporotic medicinal product should in general be at least 24 months in order to provide clear fracture and bone safety data; a total duration of 18 months of treatment in the provided phase 3 study is thus limiting the extrapolation of the results. The applicant argues that the combined study BA058-05-003 (18 months abaloparatide versus teriparatide and placebo) and the interim data of its extension BA058-05-005 covering 6 months of alendronate treatment in patients on either abaloparatide or placebo but not those on teriparatide in the base study satisfies the requirement for

24-months of fracture assessment data. It is further stated that abaloparatide is a rapid acting anabolic agent with an early onset of fracture prevention and that the 18-month duration of study BA058-05-003 is consistent with the final study designs and results of overall treatment exposures in the pivotal phase 3 studies for EU approved teriparatide and rhPTH(1-84). The chosen design will allow for accruing 24 months of data, but has several deficiencies, among them that patients on teriparatide have not been offered to participate in the extension study and that the continuation in the extension study might introduce a selection bias to the data beyond 18 month of treatment.

In general, the primary efficacy endpoint of vertebral fractures is acceptable. However, the analysis of the primary endpoint was based on the mITT population excluding patients without post-baseline radiologic assessment. A substantial proportion of randomised patients were excluded from the mITT population. Although radiologic assessment was planned according to protocol when a patient discontinued treatment, post-baseline radiologic assessment was not available for 344 patients, which is mainly explained by non-repetition of scan for early drop-outs to limit radiation exposure, and by patient's refusal. Differential, treatment-related drop-out was observed and drop-out was probably the most important reason for missing radiologic data. Consequently, differences between treatment groups with regard to observed and unobserved baseline characteristics were not attributable to chance alone and resulting bias cannot be excluded.

Furthermore, the mITT population includes drop-outs whose post-baseline radiological assessment was probably performed at time of dropout. This implies that the time in study and at risk of vertebral fracture differed between patients in the mITT population, and 18 month incidence of vertebral fracture may have been underestimated. The proportion of patients included in the primary mITT analysis with a spine x-ray taken at early termination / prior to month 18 was similar between abaloparatide and placebo groups, 11.9% and 11.0%, respectively, but smaller in the teriparatide group, 8.2%. The time-point for early termination / last post-baseline assessment did however differ between abaloparatide and both control groups; more patients in the abaloparatide group had the last spine x-ray taken at an earlier time-point. This is in line with the overall pattern of time to withdrawal, which shows that discontinuations occurred earlier in the abaloparatide group compared to placebo or teriparatide groups. More patients having last spine x-ray at an earlier time point in the mITT population slightly favours abaloparatide but additional sensitivity analyses requested by the CHMP address this issue.

Additionally, as the mITT analysis includes only on-treatment data it aims at estimation of the treatment effect if all patients had been fully adherent to randomised treatment until end of month 18; however, the treatment effect assuming loss of benefit after discontinuation of treatment is also relevant for the B/R evaluation in this context.

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 two sites from the Czech Republic.

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.

As regards the analyses of the key secondary endpoint non-vertebral fractures it has to be taken into account that this should have preferably been tested in a separate study (see above) and that since instead only one pivotal study has been provided, the effect of abaloparatide on the secondary endpoint non-vertebral fractures should be undisputable (statistical evidence considerably stronger than $p<0.05$; precise estimates of the treatment effects, i.e. narrow confidence intervals; pre-specified alternative analyses for demonstration of consistency). The CHMP recommendation to define vertebral fractures and non-vertebral fracture in this one pivotal study as co-primary endpoints was not followed, but for the key secondary endpoint confirmatory testing was performed within a hierarchical testing procedure to control the family-wise type 1 error (see also section on benefit/risk regarding the conclusions from the secondary endpoint analysis).

The analysis of this key secondary endpoint non-vertebral fracture was changed from comparison of event rates to an analysis of time to non-vertebral fracture in the statistical analysis plan that was finalised two days prior to database lock; usually, it is expected that changes to principle features of the analysis are documented in a protocol amendment rather than only in the statistical analysis plan. Furthermore, changes to analyses were introduced after database lock, including changes of the definitions of the primary and the key secondary endpoints and change of analysis from MMRM to ANCOVA for continuous secondary endpoints, which according to the applicant was done following US FDA advice. In the analysis of non-vertebral fracture applying time to event analysis (i.e. time to first non-vertebral fracture was analysed) non-informative censoring is assumed, which implies the assumption that the risk of non-vertebral fracture for a patient after drop-out is the same as the risk of a patient who continues the study. This means that the analysis addresses the treatment effect that would be observed when all patients would be adherent to study treatment until end of month 19.

However, the treatment effect assuming loss of benefit after active treatment discontinuation is more relevant for the benefit-risk evaluation in this context. Therefore, a sensitivity analysis with imputation of patients censored before month 19 based on the time to event distribution in placebo patients was requested and showed smaller differences between abaloparatide and placebo as expected; the same sensitivity analysis was also performed excluding the GCP non-compliant study sites.

As regards the hierarchical approach for testing the multiple hypotheses on the primary and the secondary efficacy endpoints different information can be found for the endpoints 6, 7, and 9 concerning effects of abaloparatide versus teriparatide on BMD at the total hip, femoral neck, and

lumbar spine; while the statistical analysis plan 'Fixed-sequence Tests of the Primary and the Secondary Efficacy Endpoints for Multiple Comparisons' defines the comparison at 6 months as confirmatory and comparisons at 12 and 18 months as exploratory, other sections of the statistical analysis report, the final clinical study report, and the study protocol refer only to the 18 months comparison while the 6 and 12 months comparisons are not mentioned at all. In this assessment the effects after 18 months of treatment are described and discussed first and the effect after 6 and 12 months are included in the ancillary analyses. BMD was analysed by ANCOVA (LOCF) and MMRM. However, the treatment effect that is targeted by ANCOVA (LOCF) is not clear; it is neither the effect that would be observed if all patients would be fully adherent to treatment, nor the effect that would be observed if loss of benefit from active treatment after treatment drop-out is taken into account. MMRM analysis addresses the treatment effect if all patients would have been fully adherent. Additional analyses assuming loss of treatment benefit after drop-out were requested; a placebo multiple imputation analysis supported the results of the original analysis. In a responder analysis considering missing data as non-response, statistically significant superiority of abaloparatide over placebo was observed but the difference was smaller than for observed cases due to higher drop-out in the abaloparatide group.

Radiographs were viewed and assessed centrally by a blinded, independent radiologist and confirmed by a second blinded radiologist for all patients for whom an incident fracture had been identified. In case of disagreement a third consensus assessment was made to adjudicate the incident fracture.

BMD scans for patient eligibility were determined at the study site; acceptability of each DXA scan was subsequently confirmed with the study sites by the Central Imaging CRO. Investigators were blinded to results of all follow-up DXA scans throughout the study unless a safety issue was identified by the independent radiologist.

The active comparator teriparatide was not blinded due to commercial availability of teriparatide, but the blind has been adequately maintained between abaloparatide and placebo throughout the study and randomised distribution to study arms was double-blind. Thus blinding is acceptable as regards the comparisons of abaloparatide versus placebo. However, 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 significantly 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.

Efficacy data and additional analyses

Data from the dose-finding study BA058-05-002 indicate that doses of 20 µg, 40 µg, and 80 µg abaloparatide SC induced a dose dependent increase in percent change in BMD at lumbar spine, total hip, and femoral neck, while no differences were seen at ultra-distal wrist; the largest increase in BMD was noted for abaloparatide 80 µg SC. This dose-response relationship was also confirmed for serum markers s-P1NP, s-BALP, and s-OC. Thus the available data support the dose of 80 µg abaloparatide selected for the pivotal phase 3 trial.

In the pivotal study BA058-05-003 demographic and baseline disease characteristics were adequately balanced between groups. Calculation of the 10 year fracture probability has also been provided and the results are considered to apply with recommendations set out in the CHMP guideline on osteoporosis.

The percentage of discontinuation was different between groups; it was lowest in the teriparatide group were patients were aware of the assigned medication and highest in patients on abaloparatide. In addition the highest percentage of discontinuation due to AEs occurred with abaloparatide and the percentage of patients with no post-treatment x-ray was higher in patients on abaloparatide compared to both placebo and teriparatide.

The predefined primary endpoint, new vertebral fractures after 18 months of abaloparatide versus placebo, was met and the reduction in the incidence of new vertebral fractures (abaloparatide 0.51% vs placebo 4.2%) is considered clinically relevant. The analysis of the PP population as well as the sensitivity analysis support the assumption that after 18 month of treatment abaloparatide is superior to placebo as regards the incidence of new vertebral fractures but interpretation of the results is limited by the difference in discontinuation and the percentage of patients having a post-treatment x-ray; a potential bias cannot be excluded. Additional sensitivity analyses have been provided.

As regards the key secondary efficacy endpoint non-vertebral fractures after 18 months the prolongation of the time to first incident non-vertebral fracture with abaloparatide versus placebo was not statistically significant (p=0.3675) and confidence intervals were wide.
Considering that study BA058-05-003 was the only pivotal trial in this application these results are not able to establish an advantage of abaloparatide versus placebo on non-vertebral fractures after 18 months of treatment although the available data indicate a trend in favour of abaloparatide. The study did not show statistical evidence considerably stronger than $p<0.05$ nor did it demonstrate the required narrow confidence intervals.

The comparison of non-vertebral fractures after 18 months for abaloparatide versus teriparatide was not statistically significant (p=0.4919) and the reduction in the hazard ratio was accompanied by wide confidence intervals. Non-vertebral fractures occurred in 15/696 (2.2%) patients on abaloparatide vs 12/686 (1.7%) patients on teriparatide. Any differences may well be attributable to chance. Furthermore, 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.

As regards the additional key secondary efficacy endpoints BMD the percent changes at total hip, femoral neck, and lumbar spine from baseline to 18-month were statistically significantly higher with abaloparatide compared to placebo and results demonstrate a relevant increase in BMD in patients on abaloparatide. Increases in BMD after 18 months of treatment were also greater for abaloparatide compared to teriparatide at the total hip and femoral neck but not at the lumbar spine; teriparatide increased BMD from baseline to 18 months at all three sites. BMD decreased with placebo at all three sites.

After 6 months of treatment patients on abaloparatide showed higher increases in BMD at the total hip, femoral neck, and lumbar spine than those on teriparatide, but these numerical differences are not considered clinically relevant and it has not been shown that they relate to a clinically relevant reduction in fracture risks.

The responder analysis of change in BMD showed that the percentage of patients with BMD changes >0%, >3%, and >6% at lumbar spine, femoral neck, and total hip combined was significantly higher with abaloparatide than with placebo and also higher than in patients on teriparatide.
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 BMD was lowest in participants receiving placebo and highest in those receiving teriparatide. At the ultra-distal radius bone mineral density 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.

The data on change in BMD by baseline renal status indicate that at least the lumbar spine and probably the femoral neck increases in BMD with abaloparatide were higher in patients with reduced creatinine clearance compared to patients with normal creatinine clearance. This effect might be due to an increase in abaloparatide exposure following reduced renal elimination of abaloparatide.

There were minimal numerical differences in change and percent change in vertical height between groups but differences were neither statistically significant nor clinically relevant.

The percentage of patients with severe incident new or worsening vertebral fractures was lower with abaloparatide and teriparatide than with placebo.

Teriparatide also showed a significant reduction in the incidence of new vertebral fractures compared to placebo and both abaloparatide and teriparatide reduced the incidence of new or worsening vertebral fractures versus placebo after 18 months of therapy.

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 prolonged with abaloparatide compared to placebo and patients on abaloparatide had fewer non-vertebral fractures including all trauma levels and were fracture-free longer, and the time to first clinical spine fracture was prolonged and the incidence lower with abaloparatide versus placebo. Time to first incidence of other fractures was also numerically increased for abaloparatide compared to teriparatide but differences were mostly not statistically significant and are not considered clinically relevant.

As regards the percent changes in biochemical markers of bone turnover the increase in the anabolic serum bone marker s-P1NP was 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-OC were higher with abaloparatide versus placebo and highest in participants using teriparatide.

Analyses of new vertebral fracture, non-vertebral fracture, and BMD by subgroups including age, ethnicity, region, and risk at baseline did not indicate an interaction between treatment and the majority of subgroups investigated and Forest plots showed effects to be in the same direction for these analyses. Divergent results were seen for non-vertebral fracture in the subgroups Asian race and Asia region, for BMD at the total hip in the subgroup North America, and for BMD at the femoral neck in subgroups Black race, North America, and 'prevalence of vertebral fracture at baseline ≥2 fracture' but confidence intervals overlapped, the number of events was small, and there were too few patients in these subgroups to draw any conclusions.

The FRAX analysis of the data from study BA058-05-003 indicates that the estimated baseline fracture probabilities were low compared to several other phase 3 studies in patients with osteoporosis but for example similar to that seen in clinical trials of bazedoxifene, a selective oestrogen receptor modulator approved in 2009 in the EU for the treatment of postmenopausal osteoporosis. Fracture probabilities increased with age. Baseline characteristics of fracture probabilities for patients recruited to the extension study BA058-05-005 did not differ from the population of study BA058-05-003 and there were no relevant differences between those who continued and those who did not.

Abaloparatide significantly reduced the incidence of all three clinical fracture outcomes in patients with probabilities at baseline that fell above the thresholds given in the CHMP guideline on osteoporosis (10-year probability for spine fracture 15% to 20%, for hip fracture 5% to 7.5%, for major non-vertebral fracture 10% to 15%) and hazard ratios for the effect of abaloparatide on the various fracture outcomes did not change significantly across the range of baseline fracture probability, suggesting significant efficacy over the whole range. There was, however, a trend for the efficacy to increase with higher baseline major osteoporotic fracture probability; significant anti-fracture efficacy was demonstrated in patients deemed at high risk according to the CHMP guideline on osteoporosis. At equivalent fracture probability percentiles, the treatment effect of abaloparatide was greater on vertebral fracture risk than on the risk of clinical fractures at other sites; findings were robust to several sensitivity analyses.

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. The majority of patients in the pivotal trial BA058-05-003 were in the age range of 65 to 74 years of age; about 18% to 20% percent of the treated population was ≥75 years of age at baseline and only 4 patients were ≥85 years of age (0.2%).

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

The data from the supportive extension trial BA058-05-005 in general support the findings of the pivotal trial; patients who were either on abaloparatide or placebo, but not those on teriparatide, in the base study BA058-05-003 and who finished the base study were offered to participate and received open-label alendronate 70 mg once weekly.

For the primary endpoint incidence of new vertebral fractures (mITT) from study BA058-05-003 baseline to Month 25 of study BA058-05-005 (18 months double-blind abaloparatide or placebo study BA058-05-003, 1 month follow-up, 24 months alendronate study BA058-05-005) 4/457 patients (0.88%) in the abaloparatide / alendronate group and 26/489 (5.32%) in the placebo / alendronate experienced new vertebral fractures; the risk reduction versus placebo (95% CI) was -4.44 (-6.86, -2.30; p<0.0001). New vertebral fractures from BA058-05-005 baseline occurred in 0/457 patients (0%) on abaloparatide / alendronate and 6/489 (1.23%) on placebo / alendronate at Month 6 [risk reduction versus placebo (95% CI) -1.23 (-2.65, -0.16; p=0.0313)] and 2/457 (0.44%) and 13/489 (2.66%), respectively, at Month 24 [risk reduction versus placebo (95% CI) -2.22 (-4.08, -0.64; p=0.0074)].

As regards non-vertebral fractures the incidence from the BA058-05-003 baseline to end of study BA058-05-005 was 19/469 patients (4.05%) on abaloparatide / alendronate and 32/494 (6.48%) on placebo / alendronate [risk reduction versus placebo (95% CI) -2.43 (-5.33, 0.44; p=0.0928)] and from BA058-05-005 baseline incidences were 10/469 patients (2.13%) on abaloparatide / alendronate and 15/494 (3.04%) on placebo / alendronate [risk reduction versus placebo (95% CI) -0.90 (-3.05, 1.21; p=0.3778)].

Further increases in BMD from the BA058-05-003 baseline were observed in both the abaloparatide / alendronate and the placebo / alendronate group, at Months 25, 31, 37 and 43 with statistically significant differences favouring abaloparatide / alendronate (p<0.0001) at the total hip, femoral neck, and lumbar spine for all time-points. 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 were not statistically significant except at Month 24 for total hip (p=0.0025) and the lumbar spine at all time-points (p<0.0001).

2.5.3. Conclusions on clinical efficacy

In the pivotal trial, 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. Teriparatide as comparator also showed a significant reduction in the incidence of new vertebral fractures compared to placebo.

A significant and clinically relevant efficacy of abaloparatide compared to placebo on non-vertebral fractures has not been established and there was no significant difference between abaloparatide and teriparatide on the time to first incidence of non-vertebral fracture. Only one hip fracture (on placebo) occurred in the study.

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 results demonstrate a relevant increase in BMD in patients on abaloparatide. There were no relevant differences in BMD after 18 months of treatment between abaloparatide and teriparatide except for ultra-distal radius. BMD decreased with placebo at all sites.

Data on change in BMD by baseline renal status indicate that increases in BMD with abaloparatide are higher in patients with reduced creatinine clearance compared to patients with normal creatinine clearance; this effect might be due to an increase in abaloparatide exposure due to reduced renal elimination.

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.

Analyses of new vertebral fracture, non-vertebral fracture, and BMD by subgroups including age, ethnicity, region, and risk at baseline did not indicate a clinically relevant interaction between treatment and these subgroups.

The FRAX analysis of the data from study BA058-05-003 indicate that the estimated baseline fracture probabilities were low compared to several other phase 3 studies in patients with osteoporosis but for example similar to that seen in clinical trials of bazedoxifene. Fracture probabilities increased with age. Baseline characteristics of fracture probabilities for patients recruited to the extension study BA058-05-005 did not differ from the population of study BA058-05-003 and there were no relevant differences between those who continued and those who did not. Hazard ratios for the effect of abaloparatide on the various fracture outcomes did not change significantly across the range of baseline fracture probability, suggesting significant efficacy over the whole range. There was however a trend for the efficacy to increase with higher baseline major osteoporotic fracture probability and at equivalent fracture probability percentiles, the treatment effect of abaloparatide was greater on vertebral fracture risk than on the risk of clinical fractures at other sites.

Patients who were either on abaloparatide or placebo, but not those on teriparatide, in the base study BA058-05-003 and who finished the base study were offered to participate and received open-label

alendronate 70 mg once weekly in the supportive extension trial BA058-05-005; the data from this trial in general support the findings of the pivotal trial.

Overall, efficacy regarding radiological new vertebral fractures was demonstrated, however, the pivotal study failed to demonstrate a statistically significant efficacy on non-vertebral fractures vs placebo.

2.6. Clinical safety

Patient exposure

Safety data are primarily derived from up to 18 month 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.

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 studies BA058-05-003, BA058-05-002, and BA058-05-007 together 876 subjects received 80 µg abaloparatide daily.

The difference in patients completing trial BA058-05-003 is also evident 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.

Table 13 Subjects on Abaloparatide, Teriparatide, or Placebo by Study and Group of Studies (Safety Population)

Phase	Study	ABL-SC	Teriparatide	Placebo	Total
Studies in postmenopausal women with osteoporosis					
Phase 3	Study 003	694	686	687	2067
Phase 2	Study 002	131	45	45	221
Phase 2	Study 007	51	0	50	101
Total		**876**	**731**	**782**	**2389**
Phase 1 studies in healthy postmenopausal women, healthy volunteers and subjects with renal impairment					
Phase 1	Study 127-001	75	0	20	95
Phase 1	Study 001	32	0	7	39
Phase 1	Study 001B	24	0	6	30
Phase 1	Study 010	51	0	8	59
Phase 1	Study 011	32	0	0	32
Phase 1	Study 012	52	0	51	53
Total Phase I studies		**266**	**0**	**92**	**308**
TOTAL ALL STUDIES		**1142**	**731**	**874**	**2697**

Table 14 Summary of Drug Exposure to Abaloparatide in Postmenopausal Women with Osteoporosis

	Daily dose (µg)					
	20	40	80			Total
Study number	002	002	003	002	007	
Duration of exposure (months)						
n	43	43	655	45	51	837
Mean (SD)	6.31 (3.52)	6.26 (3.69)	14.97 (6.000)	5.43 (3.23)	5.41 (1.61)	12.98 (6.666)
Median (Min, Max)	5.60 (0.40, 12.40)	5.60 (0.03, 18.17)	17.87 (0.03, 19.27)	5.60 (0.03, 12.43)	5.97 (0.07, 6.17)	17.73 (0.03, 19.27)
Duration of exposure by category, n (%)						
≤ 1 month	5 (11.6)	4 (9.3)	52 (7.9)	5 (11.1)	4 (7.8)	70 (8.4)
> 1 to 3 months	2 (4.7)	3 (7.0)	25 (3.8)	6 (13.3)	1 (2.0)	37 (4.4)
> 3 to 6 months	23 (53.5)	26 (60.5)	24 (3.7)	27 (60.0)	26 (51.0)	126 (15.1)
> 6 to 12 months	12 (27.9)	6 (14.0)	24 (3.7)	5 (11.1)	20 (39.2)	67 (8.0)
> 12 to 18 months	1 (2.3)	3 (7.0)	395 (60.3)	2 (4.4)	0	401 (47.9)
> 18 months	0	1 (2.3)	135 (20.6)	0	0	136 (16.2)
Total person months	271.5	269.1	9805.7	244.5	276.1	10866.9
Number of injections[1]						
n			655			
Mean (SD)			439.4 (178.07)			
Median (Min, Max)			527.0 (1, 575)			
Total dose received[1] (µg)						
n			655			
Mean (SD)			35149.1 (14245.56)			
Median (Min, Max)			42160.0 (80, 46000)			

In study 003, 40 subjects with unknown stop dates were excluded from calculation of drug exposure.
1 Study 002 did not collect data on missing injections and Study 007 only collected data on missing injections at two visits, therefore they are excluded from the summary of number of injections and total dose received.

Table 15 Summary of Drug Exposure to Placebo and Teriparatide in Postmenopausal Women with Osteoporosis

Study number	Placebo				Teriparatide		
	003	002	007	Total	003	002	Total
Duration of exposure (months)							
n	660	45	50	755	659	45	704
Mean (SD)	15.55 (5.306)	6.82 (2.81)	5.45 (1.59)	14.36 (5.927)	15.75 (5.050)	7.11 (3.32)	15.20 (5.388)
Median (Min, Max)	17.87 (0.03, 19.07)	5.60 (1.23, 12.43)	5.98 (0.03, 6.30)	17.77 (0.03, 19.07)	17.77 (0.03, 19.83)	5.60 (0.03, 12.43)	17.77 (0.03, 19.83)
Duration of exposure by category, n (%)							
≤ 1 month	34 (5.2)	0	4 (8.0)	38 (5.0)	26 (3.9)	2 (4.4)	28 (4.0)
> 1 to 3 months	20 (3.0)	2 (4.4)	0	22 (2.9)	24 (3.6)	1 (2.2)	25 (3.6)
> 3 to 6 months	21 (3.2)	31 (68.9)	31 (62.0)	83 (11.0)	11 (1.7)	28 (62.2)	39 (5.5)
> 6 to 12 months	28 (4.2)	11 (24.4)	15 (30.0)	54 (7.2)	38 (5.8)	11 (24.4)	49 (7.0)
> 12 to 18 months	432 (65.5)	1 (2.2)	0	433 (57.4)	451 (68.4)	3 (6.7)	454 (64.5)
> 18 months	125 (18.9)	0	0	125 (16.6)	109 (16.5)	0	109 (15.5)
Total person months	10262.9	306.7	272.5	10842.1	10381.4	320.0	10701.4
Number of injections[1]							
n	660				659		
Mean (SD)	459.5 (158.89)				464.7 (151.18)		
Median (Min, Max)	530.0 (1, 570)				528.0 (1, 595)		
Total dose received[1] (µg)							
n					659		
Mean (SD)					9293.8 (3023.50)		
Median (Min, Max)					10560.0 (20, 11900)		

In study 003, 27 Placebo subjects and 27 Teriparatide subjects with unknown stop dates were excluded from calculation of drug exposure.
1 Study 002 did not collect data on missing injections and Study 007 only collected data on missing injections at two visits, therefore they are excluded from the summary of number of injections and total dose received.

Overall, the extent and duration of exposure is adequate to assess the safety of abaloparatide, but for rare events, as well as for the assessment of carcinogenicity, adequate post-licensing safety data is needed (see risk management plan section).

Adverse events

In the analysis by system organ class relevant differences were seen for 'cardiac disorders' with 12%, 6%, and 5%, respectively on abaloparatide, teriparatide, and placebo, and 'nervous system disorders' with 25%, 20%, and 20%, respectively.

The adverse events palpitations (abaloparatide, teriparatide, placebo: 5.6%, 1.7%, 0.4%), nausea (8.5%, 5.4%, 3.1%), and dizziness (11.1%, 8.2%, 7.1%) occurred with a higher frequency in patients treated with abaloparatide compared with those receiving teriparatide or placebo; no long term clinical sequelae were reported in association with palpitations, nausea, or dizziness and no reports of falls in association with dizziness. 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. The higher frequency of abaloparatide in the SOC 'cardiac disorders' was mainly driven by the increased rate of palpitations.

Hypercalcaemia and hypercalciuria occurred less frequently in patients on abaloparatide than on teriparatide but more often than on placebo.

Table 16 Adverse Events by System Organ Class in Placebo and Active Controlled Trials; number of subjects (%) - Postmenopausal women with osteoporosis

	Study 003			Study 002					Study 007	
	Placebo	ABL-SC 80 µg	Teripa-ratide SC	Placebo	ABL-SC 20 µg	ABL-SC 40 µg	ABL-SC 80 µg	Teripa-ratide SC	Placebo	ABL-SC 80 µg
	0-18 mo	0-18 mo	0-18 mo	0-28 wks N = 45	0-28 wks N = 43	0-28 wks N = 43	0-28 wks N = 45	0-28 wks N = 45	0-24 wks	0-24 wks
	N = 687	N = 694	N = 686	*0-52 wks N = 11*	*0-52 wks N = 13*	*0-52 wks N = 10*	*0-52 wks N =7*	*0-52 wks N = 14*	N = 50	N = 51
System Organ Class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	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)
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)
Congenital, familial and genetic disorders	1 (0.1)	1 (0.1)	0	1 (2.2) *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)
Endocrine disorders	10 (1.5)	11 (1.6)	10 (1.5)	1 (2.2) *0*	0	0	0	0	1 (2.0)	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)
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)
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)
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)
Immune system disorders	8 (1.2)	2 (0.3)	4 (0.6)	0	0	1 (2.3) *1 (10)*	0	0	0	0
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)
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)
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)
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)
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)
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)
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)
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)
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)
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)
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)

	Study 003			Study 002					Study 007	
	Placebo	ABL-SC 80 µg	Teripa-ratide SC	Placebo	ABL-SC 20 µg	ABL-SC 40 µg	ABL-SC 80 µg	Teripa-ratide SC	Placebo	ABL-SC 80 µg
	0-18 mo	0-18 mo	0-18 mo	0-28 wks N = 45	0-28 wks N = 43	0-28 wks N = 43	0-28 wks N = 45	0-28 wks N = 45	0-24 wks	0-24 wks
	N = 687	N = 694	N = 686	*0-52 wks N = 11*	*0-52 wks N = 13*	*0-52 wks N = 10*	*0-52 wks N =7*	*0-52 wks N = 14*	N = 50	N = 51
System Organ Class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
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)
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
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)

Note that if there is no subject reporting AEs during the initial 6 months treatment period (0-24 weeks) and the extension period (0-52 weeks) in Study 002, "0" is noted only once.

Table 17 Summary of Most Common Adverse Events (≥5% of Subjects in Any Treatment Group in Studies 003, 002 [0-24 weeks] and 007) in Placebo and Active Controlled Trials; number of subjects (%) - Postmenopausal women with osteoporosis

	Study 003			Study 002					Study 007	
AE Category	Placebo 0-18 mo N = 687 n (%)	Abalo-paratide-SC 80 µg 0-18 mo N = 694 n (%)	Teripa-ratide SC 0-18 mo N = 686 n (%)	Placebo 0-28 wks N = 45 *0-52 wks N = 11* n (%)	Abalo-paratide-SC 20 µg 0-28 wks N = 43 *0-52 wks N = 13* n (%)	Abalo-paratide-SC 40 µg 0-28 wks N = 43 *0-52 wks N = 10* n (%)	Abalo-paratide-SC 80 µg 0-28 wks N = 45 *0-52 wks N=7* n (%)	Teripa-ratide SC 0-28 wks N = 45 *0-52 wks N = 14* n (%)	Placebo[a] 0-24 wks N = 50 n (%)	Abalo-paratide-SC 80 µg 0-24 wks N = 51 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)
Gastrointestinal disorders										
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)
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
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)
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)
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)
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)
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
Injection site haemorrhage	0	4 (0.6)	0	0	0	0	1 (2.2) *0*	3 (6.7) *0*	0	0
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)
Gastroenteritis	14 (2.0)	12 (1.7)	12 (1.7)	0	1 (2.3) *1 (7.7)*	3 (7.0) *2 (20.0)*	3 (6.7) *0*	0	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)
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)

AE Category	Study 003			Study 002					Study 007	
	Placebo 0-18 mo N = 687 n (%)	Abalo-paratide-SC 80 µg 0-18 mo N = 694 n (%)	Teripa-ratide SC 0-18 mo N = 686 n (%)	Placebo 0-28 wks N = 45 *0-52 wks* *N = 11* n (%)	Abalo-paratide-SC 20 µg 0-28 wks N = 43 *0-52 wks* *N = 13* n (%)	Abalo-paratide-SC 40 µg 0-28 wks N = 43 *0-52 wks* *N = 10* n (%)	Abalo-paratide-SC 80 µg 0-28 wks N = 45 *0-52 wks* *N=7* n (%)	Teripa-ratide SC 0-28 wks N = 45 *0-52 wks* *N = 14* n (%)	Placebo[a] 0-24 wks N = 50 n (%)	Abalo-paratide-SC 80 µg 0-24 wks N = 51 n (%)
Upper respiratory tract infection	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)
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
Metabolism and nutrition disorders										
Hypercalcaemia	2 (0.3)	11 (1.6)	28 (4.1)	1 (2.2) *1 (9.1)*	1 (2.3) *1 (7.7)*	3 (7.0) *0*	2 (4.4) *0*	4 (8.9) *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
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)
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)
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)
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)
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)
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
Renal and urinary disorders										
Hypercalciuria	73 (10.6)	93 (13.4)	101 (14.7)	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)
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)
Vascular disorders										
Hypertension	37 (5.4)	47 (6.8)	36 (5.2)	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

Note that if there is no subject reporting AEs during the initial 6 months treatment period (0-24 weeks) and the extension period (0-52 weeks) in Study 002, "0" is noted only once.
a) A transdermal placebo was administered.

In general the highest incidence of adverse events by system organ class occurred with an onset between 0 to <2 months; in the system organ classes 'cardiac disorders', 'gastrointestinal disorders', 'nervous system disorders', and 'renal and urinary disorders' the incidence of adverse events was higher in patients on abaloparatide compared to teriparatide and placebo, but decreased during the 18 months study duration and differences were no longer apparent from 6 months onwards. In the system organ class 'cardiac disorders' the difference was primarily driven by palpitations, in the system organ class 'gastrointestinal disorders' by nausea, and in the system organ class 'nervous system disorders' by dizziness and headache. Frequencies in the system organ class 'renal and urinary disorders' were driven by hypercalciuria but the frequency of this adverse event was heterogeneous over the 18 months study duration.

The diminishing differences in frequency of adverse events in the system organ classes 'cardiac disorders', 'gastrointestinal disorders', and 'nervous system disorders' might 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

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 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 lower on abaloparatide (14.3%) than on teriparatide (17.6%); it was higher than in the placebo group (11.1%). 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. The number of patients who discontinued treatment due to hypercalciuria AEs was higher in the teriparatide than in the abaloparatide group (0.6% vs. 0.1%); no patient on placebo discontinued due to a hypercalciuria AE.

The analyses of adverse events of renal impairment did not reveal significant differences between abaloparatide, teriparatide, and placebo groups.

The incidences of 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, as well as palpitations, nausea, and dizziness were higher on abaloparatide, than teriparatide or placebo and the percentage of subjects who discontinued treatment due to orthostatic hypotension defined as a composite AESI was higher on abaloparatide compared to teriparatide and placebo. Orthostatic hypotension 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). The percentage of subjects who discontinued treatment due to orthostatic hypotension defined as a AESI was 3.6%, 1.7%, and 0.9% on abaloparatide, teriparatide, and placebo, respectively. The applicant argues that the increased incidence in orthostatic hypotension is due to an increase in heart rate post injection versus placebo

leading to an increased incidence of palpitations, dizziness, and nausea. This mechanistic consideration seems unconvincing; moreover, a comparable increase in heart rate was seen in patients treated with teriparatide.

Table 18 Incidence of Adverse Events Associated With Orthostatic Hypotension in Studies 002 and 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 002, AEs leading to discontinuation were reported.
Each patient was counted once for the same MedDRA grouping level.

Table 19 Incidence of Adverse Events Potentially Associated with Palpitation in Study 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.

Table 20 Patients with Increases in Heart Rate from Pre-dose to Post-dose at Any Visit (Study 003 Safety Population, excluding the two sites from the Czech Republic)

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 sites 131 and 132.
*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.

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 questioning the sensitivity of the analysis.

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.

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.

Serious adverse events and deaths

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. 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, 5 events (brain neoplasm, colon cancer, intestinal adenocarcinoma, leiomyosarcoma, 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 this difference was not seen at later points during the trial.

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 in Study 003 and thorough QTC study

In study BA058-05-003, ECGs were performed pre-dose and 1 hour post-dose at regular intervals during the first year of the study (over 6 visits). The baseline heart rate was measured at rest and the change in HR was determined relative to any of the 1-hour post-dose measurements when subjects were active during the 6 visits.

Table 21 below summarises the heart rate data at baseline and post-injection assessments.

Table 21 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	 Change from Baseline	Abaloparatide-SC (N=694) Value	 Change from Baseline	Teriparatide (N=686) Value	 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 1.0 to 1.9 bpm. Pre-injection heart rate values were similar to baseline values for all time points in all three groups. Overall, 7.9%, 3.6%, and 0.7% of patients on abaloparatide, teriparatide, and placebo, respectively, had an increase in heart rate >25 bpm at any visit.

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 male and female 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) for abaloparatide and placebo, including the mean difference in heart rate, up to 24 hours. Subjects were requested to stay in a supine position. Meal and moderate activity were allowed after the first 4 hours.

Table 22 Thorough QTC study (012). Changes and mean difference in heart rate for abaloparatide 80 mcg and placebo

Timepoint (post dose)	Statistic	Abaloparatide 80 µg N=52	Placebo N=51	Mean Difference (ABL-Placebo)
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)	14.5
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)	13.1
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)	10.3
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)	8.6
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)	7.2
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)	5.2
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)	5.0
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)	3.7
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)	2.3
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)	4.0
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)	2.2
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)	-0.1

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 maximal 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 abaloparatide 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 abaloparatide 80 µg group was somewhat higher than in study BA058-05-003. Significant increases in heart rate persisted at least 12 hours (mean 9.5 bpm) in the QT study. However, elevations were seen also in the placebo group after 6 hours 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.

The marked mean post-dose increase in heart rate observed in the thorough QT study and in study BA058-05-003 is of major concern. In addition, the pivotal study had extensive exclusion criteria based on ECG findings and medical history of cardiovascular disease. Adequate wording in the PI is needed to mitigate the risks of cardiovascular events associated with the marked increased heart rate in the general osteoporosis population where concomitant cardiovascular diseases are expected to be more common than in the pivotal study.

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.

Safety in special populations

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 analysis of ethnic subgroups 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.

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.

The incidence of hypercalcaemia adverse events increased with decreasing renal function in the teriparatide group (1.3%, 3.6% and 7.7% for the normal, mild and moderate renal impairment). In patients on abaloparatide with impaired renal function, i.e. subgroups with creatinine clearance <60

ml/min (moderate renal impairment) and 60 to <90 ml/min (mild impairment), the incidence of hypercalcaemia adverse events was higher (1.9% for both groups of mild and moderate renal impairment) compared to patients with normal renal function (0.6%). The incidence of hypercalcaemia as a laboratory assessment was similar between the subgroups with creatinine clearance <60 ml/min (moderate renal impairment) and 60 to <90 ml/min (mild renal impairment). 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 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.

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. 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 still antibody positive after 6 months into the extension.

Whether development of anti-abaloparatide antibodies results in a decrease in pharmacokinetics of abaloparatide is unclear due to deficiencies in the bioanalytical method.

The limited data available did not indicate an influence of the development of anti-abaloparatide antibodies as well as neutralising antibodies on the efficacy or safety of abaloparatide. However, the high amount of patients developing anti-abaloparatide antibodies and neutralising antibodies is of concern since the limited data do not allow assessing the long-term effect of these antibodies on parathyroid hormone activity in humans.

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.

Discontinuation due to AES

The number of patients who discontinued treatment and the incidence of adverse events leading to study discontinuation was 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; 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. There were no relevant differences between these groups in the occurrence of serious adverse events leading to discontinuation. During the follow-up trial BA058-05-005 there were 1 severe adverse event of nausea in a patient previously on placebo and 4 severe adverse events in patients previously on abaloparatide including intestinal

adenocarcinoma (subsequently revised to ovarian epithelial cancer) and brain tumour, leading to discontinuation.

Table 23 Summary of Adverse Events Leading to Study Drug Discontinuation (≥0.5% of Subject in Any Treatment Group in Study 003) by SOC and PTs in Placebo and Active Controlled Trials; number of subjects (%) - Postmenopausal women with osteoporosis

	Study 003			Study 002					Study 007	
	Placebo	ABL-SC 80 µg	Teripa-ratide SC	Placebo	ABL-SC 20 µg	ABL-SC 40 µg	ABL-SC 80 µg	Teripa-ratide SC	Placebo	ABL-SC 80 µg
	0-18 mo	0-18 mo	0-18 mo	0-28 wks N = 45	0-28 wks N = 43	0-28 wks N = 43	0-28 wks N = 45	0-28 wks N = 45	0-24 wks	0-24 wks
AE Category	N = 687 n (%)	N = 694 n (%)	N = 686 n (%)	*0-52 wks N = 11* n (%)	*0-52 wks N = 13* n (%)	*0-52 wks N = 10* n (%)	*0-52 wks N =7* n (%)	*0-52 wks N = 14* n (%)	N = 50 n (%)	N = 51 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)
Cardiac disorders	3 (0.4)	12 (1.7)	1 (0.1)	0	0	0	0	0	0	1 (2.0)
Palpitations	1 (0.1)	6 (0.9)	0	0	0	0	0	0	0	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)
Nausea	2 (0.3)	11 (1.6)	3 (0.4)	0	0	1 (2.3)	0	0	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)
Malaise	4 (0.6)	1 (0.1)	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
Metabolism and nutrition disorders	0	1 (0.1)	4 (0.6)	0	0	0	0	0	0	0
Hypercalcaemia	0	1 (0.1)	4 (0.6)	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
Osteoporosis	8 (1.2)	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
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)
Dizziness	3 (0.4)	10 (1.4)	8 (1.2)	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)
Psychiatric disorders	3 (0.4)	4 (0.6)	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	3 (0.4)	4 (0.6)	5 (0.7)	0	0	0	0	1 (2.2) *0*	0	2 (3.9)
Vascular disorders	1 (0.1)	6 (0.9)	3 (0.4)	0	0	0	0	0	0	0

Note that if there is no subject reporting AEs during the initial 6 months treatment period (0-24 weeks) and the extension period (0-52 weeks) in Study 002, "0" is noted only once.

Post marketing experience

According to the applicant abaloparatide has been licensed in the USA since April 2017, but post marketing data is very limited.

2.6.1. Discussion on clinical safety

Safety data for abaloparatide were derived from 10 clinical trials, but are primarily based on the single 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.

Overall, the extent and duration of exposure is adequate to assess the safety of abaloparatide, but for rare events, as well as for the assessment of carcinogenicity, adequate post-licensing safety data would be needed.

In the analysis of adverse events by system organ class relevant differences were seen for 'blood and lymphatic disorders', '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.

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 a increase in HR by >20 bpm at any time point vs. 11% of patients treated with teriparatide and 3% of placebo patients. Patients that experienced highest increases in HR by >40 bpm (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 of study drug due to adverse events (10% vs 7%) were also reported more frequently in patients treated with abaloparatide compared to teriparatide. There were more early (≤1 month) drop-outs in the abaloparatide arm (7.9%) compared to teriparatide (3.9%).

There were a considerable number of adverse events in the system organ class 'neoplasms benign, malignant and unspecified (17 (2.4%), 27 (3.9%), and 24 (3.5%) for abaloparatide, teriparatide, and placebo, respectively); further analysis did not reveal any significant findings.

The adverse event dizziness appeared to show a dose-response effect in patients treated with abaloparatide. Hypercalcaemia and hypercalciuria occurred less frequently in patients on abaloparatide than on teriparatide but more often than on placebo.

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 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 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 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.

Adverse events of hypercalcaemia and hypercalciuria occurred less frequently in patients treated with abaloparatide than those treated with teriparatide but more often than those treated with placebo. The limited data available did not indicate an increase in the incidence of adverse events of hypercalcaemia with increasing doses of abaloparatide.

The analyses of adverse events of renal impairment did not reveal significant differences between abaloparatide, teriparatide, and placebo groups, but the incidence of hypercalcaemia adverse events was higher in the patients with impaired renal function in the abaloparatide and teriparatide groups.

The percentage of subjects who discontinued treatment due to orthostatic hypotension defined as a composite adverse event of special interest was higher on abaloparatide compared to teriparatide and placebo.

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.

The bone biopsy analysis did not indicate a pathological effect of abaloparatide on bone parameters; histomorphometry also did not show evidence of bone anabolic effects by abaloparatide or teriparatide.

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.

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.

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. However, numbers are too small for a final assessment of differences in the incidence of death and serious adverse events. 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, 5 serious adverse events (brain neoplasm, colon cancer, intestinal adenocarcinoma, leiomyosarcoma, renal cancer) were reported in the system organ class ‘neoplasms benign, malignant and unspecified (incl. cysts and polyps)’ in patients

previously on abaloparatide versus none in patients previously on placebo; however this difference was not seen at later points during the extension trial.

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.

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 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 ethnic 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 at least partially explain the slightly higher incidence of adverse events 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 the 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.

As regards weight groups <54 kg, 54 to <68 kg, ≥68 kg the percentage of subjects with adverse events considered related across these subgroups decreased with increasing weight.

The incidence of hypercalcaemia adverse events increased with decreasing baseline renal function in the teriparatide group (1.3%, 3.6% and 7.7% for the normal, mild and moderate renal impairment). In patients on abaloparatide with impaired renal function, i.e. subgroups with creatinine clearance <60 mL/min (moderate renal impairment) and 60 to <90 mL/min (mild renal impairment), the incidence of hypercalcaemia was higher (1.9% for both groups of mild and moderate renal impairment) compared to patients with normal renal function (0.6%). The incidence of hypercalcaemia as a laboratory assessment was similar between the subgroups with creatinine clearance <60 mL/min (moderate renal impairment) and 60 to <90 mL/min (mild renal impairment). 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 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.

The incidence of hypersensitivity adverse events was comparable between abaloparatide and teriparatide treated patients.

During 18 months in study BA058-05-003 about half of the patients developed anti-abaloparatide antibodies and about one third showed 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. Whether development of anti-abaloparatide antibodies results in a decrease in pharmacokinetics of abaloparatide is unclear due to deficiencies in the bioanalytical method. The limited data available did not indicate an influence of the development of anti-abaloparatide antibodies as well as neutralising antibodies on the efficacy or safety of abaloparatide. However, the rate of antibody development is high; about 50% of the women treated with abaloparatide developed anti-abaloparatide antibodies, including about 30% with neutralising antibodies.

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.

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 and patients on abaloparatide dropped out earlier than on teriparatide or placebo. 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 for these adverse events were lower than in the abaloparatide group. There were no relevant differences between these groups in the occurrence of serious adverse events leading to discontinuation. During the follow-up trial BA058-05-005 within the first 6 months there were 1 severe adverse event of nausea in a patient previously on placebo and 4 severe adverse events in patients previously on abaloparatide including intestinal adenocarcinoma (diagnosis subsequently changed to ovarian epithelial cancer) and brain tumour, led to discontinuation.

In the same trial, within 24 months trial period, 2 severe adverse events of nausea and peritoneal neoplasm in patients previously on placebo and 7 severe adverse events including 5 in the system organ class 'neoplasms benign, malignant and unspecified (incl. cysts and polyps)' in patients previously on abaloparatide, led to discontinuation.

Abaloparatide was authorised in the US in April 2017. From May 2017 through 26 January 2018 approximately 9200 pens were distributed to estimated number of 3600 patients (approximately 770 patient-years of therapy). As of 26 January 2018, there had been no unanticipated events. The post-marketing safety database received 1,308 total number of adverse events. These were classified as follows:

- Adverse events (serious & non-serious) (504 patients)
    - Highest frequency: headache (n=126), nausea (n=84), dizziness (n=76)
    - Highest frequency Cardiovascular events: palpitations (n=49), heart rate increased (n=25)
    - All other cardiovascular events ≤10 each preferred term
- Serious adverse events (n=39 patients)
    - Highest frequency SAEs: dizziness (n=5); headache, death (n=4 each); irregular heartrate, hospitalisation (n=3 each)

- Death cases - 1 not related to treatment, 1 with prior hospitalization for thrombosis and unknown cause of death, 2 with unknown cause of death
- Additional Cardiovascular SAEs: heart rate increased, palpitations, blood pressure increased (n=2 each); atrial fibrillation (pacemaker, medical history), intracardiac thrombus (medical history), angina pectoris/myocardial infarction, thrombosis (death case above) (n=1 each)

The limited post-marketing experience did not raise any additional safety concern (see further in the document).

Additional expert consultations

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 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 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 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 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 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.

2.6.2. Conclusions on clinical safety

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.

Extent and duration of exposure as well as the chosen comparator teriparatide are adequate except for rare events and the assessment of carcinogenicity; post-licensing safety data will be collected to further assess the safety of abaloparatide in this regard.

Relevant differences were seen in the incidences of the adverse events orthostatic hypotension, palpitations, nausea, dizziness, and headache, 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. 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. Besides the post-injection increase in heart rate evaluations of electrocardiograms did not indicate clinically relevant changes. However, an increase in heart rate of the magnitude seen in the clinical trials with abaloparatide may 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 was probably 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 these risks, the applicant proposed to monitor patients in clinical practice 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. If severe orthostatic hypotension or severe cardiovascular symptoms occur, treatment would have been discontinued.

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. Information provided through the SmPC sections 4.3, 4.4, 4.8, and 5.1, as well as the PL were proposed.

Hypercalcaemia and hypercalciuria occurred less frequently in patients on abaloparatide than on teriparatide but more often than on placebo; the incidence of hypercalcaemia adverse events increased with decreasing baseline renal function. 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. Organ calcification has been identified in preclinical trials; this has been addressed as an important potential risk in the Risk Management Plan. 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.

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.

There were no significant differences between abaloparatide, teriparatide, and placebo in adverse events leading to death and serious adverse events, but numbers are too small for a final assessment. It was of concern that in the first 6 months of the follow-up study BA058-05-005, 5 serious adverse

events (brain neoplasm, colon cancer, intestinal adenocarcinoma, leiomyosarcoma, renal cancer) were reported in the system organ class 'neoplasms benign, malignant and unspecified (incl. cysts and polyps)' in patients previously on abaloparatide versus none in patients previously on placebo; however this difference was not seen at later points during the trial.

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. The diminishing differences in frequency of adverse events might 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.

The bone biopsy analysis did not indicate a pathological effect of abaloparatide on bone parameters; histomorphometry also did not show evidence of bone anabolic effects by abaloparatide or teriparatide.

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 limited 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.

While no increase in major adverse cardiovascular events in patients treated with abaloparatide compared to the comparators was seen in the pivotal study, common adverse events, likely linked in part to heart rate increase, such as palpitations, tachycardia, dizziness, nausea and discontinuations, were reported more frequently in patients treated with abaloparatide. With respect to serious cardiovascular events, due to the size and the exclusion criteria, the pivotal study did not have power to detect such events and therefore was considered by CHMP not sufficient to assess risk for adverse cardiovascular outcomes associated with heart rate increase in a generally more vulnerable real-life osteoporosis population.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Hypercalcaemia Orthostatic hypotension Medication error

Important potential risks	Development of osteosarcoma Cardiovascular risks associated with a marked transient increase in heart rate following abaloparatide injection and long term cardiovascular risk in vulnerable (predisposed) patients Organ calcification potentially related to hypercalcaemia
Missing information	Patients with active or recent urolithiasis Patients with hepatic impairment Patients with severe renal impairment Patients ≥ 85 years Long-term use > 18 months Off-label use in children

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
1. PMC-TYM-002 (non-interventional, 3)	Evaluation of cardiovascular morbidity and mortality among adults with increased cardiovascular risk and treated with abaloparatide	Potential risk: - Cardiovascular risks associated with a marked transient increase in heart rate following abaloparatide injection and long term cardiovascular risk in vulnerable (predisposed) patients	Planned	Planned: Interim - To be determined Final - Dependent on results of the interim assessment; To be determined
2.Enhanced Pharmacovigilance Plan for Osteosarcoma (non-interventional, 3)	To assess cases of osteosarcoma reported in abaloparatide-treated patients, to submit cases as expedited 15-day reports and in periodic aggregate reports	Potential risks: - Development of osteosarcoma	Planned	Reports to be submitted as part of the PSUR/PBRER through 2032 (15 years of data)

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypercalcaemia	Text in SmPC Prescription only medicine	None
Orthostatic hypotension	Text in SmPC Prescription only medicine	None
Medication error	Packaging design UnoPen platform Easy-to-use pen Instructions for use The appropriate needle length will be provided in the pen Training. Text in SmPC Prescription only medicine.	None
Development of osteosarcoma	Text in SmPC Prescription only medicine	None
Cardiovascular risks associated with a marked transient increase in heart rate following abaloparatide injection and long term cardiovascular risk in vulnerable (predisposed) patients	Text in SmPC Prescription only medicine	
Organ calcification potentially related to hypercalcaemia	Text in SmPC Prescription only medicine	None
Patients with active or recent urolithiasis (Missing information)	Text in SmPC Prescription only medicine	None
Patients with hepatic impairment (Missing information)	Text in SmPC Prescription only medicine	None
Patients with severe renal impairment (Missing information)	Text in SmPC Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients ≥ 85 years (Missing information)	Text in SmPC Prescription only medicine	None
Long-term use > 18 months (Missing information)	Text in SmPC Prescription only medicine	None
Off-label use in children (Missing information)	Text in SmPC Prescription only medicine	None

Conclusion

The CHMP and PRAC, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

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.

2.9. New Active Substance

The applicant declared that abaloparatide has not been previously authorised in a medicinal product in the European Union.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

2.10. Product information

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.10.1. 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.*

However, due to the aforementioned concerns a satisfactory package leaflet cannot be agreed at this

stage.

2.10.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Abaloparatide subcutaneous daily injection is intended for treatment of postmenopausal osteoporosis in order to increase bone mineral density (BMD) and consequently reduce the risk of vertebral and non-vertebral fractures.

In Europe, 22 million women and 5.5 million men were estimated to have osteoporosis in 2010; and 3.5 million new osteoporotic fractures were sustained. 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.

As regards anti-osteoporotic treatment for the reduction of the risk of osteoporotic fractures the majority of options aim at antiresorptive properties while therapeutic options to increase new bone formation and BMD with a bone anabolic agent are limited. Abaloparatide is a synthetic, 34 amino acid analogue of PTHrP(1-34) and belongs to the same class as teriparatide (approved for osteoporosis approximately 10 years ago) and stimulates the production and activity of osteoblasts, increasing BMD by building new bone.

3.1.1. Disease or condition

A definition from 1993 states osteoporosis is a "disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk". A more recent definition from the NIH Consensus Development Panel on Osteoporosis defines osteoporosis as a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture (Szulc & Bouxsein, 2010).

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 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 in contrast stimulates the production and activity of osteoblasts, increasing BMD by building new bone.

3.1.3. Main clinical 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. 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.

Based on the deviations found during the GCP inspections at two sites in Czech Republic of study BA058-05-003, data from these two sites cannot be used when assessing the marketing authorisation application and, consequently only endpoints and information excluding data from those two sites are the basis for the benefit-risk evaluation. The applicant proposed to consider a post hoc defined population of "postmenopausal women at increased risk of fracture" (IROF population) to be the basis of the efficacy evaluation rather than the originally defined population excluding the two sites in Czech Republic; this was not considered acceptable.

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; the active comparator teriparatide also showed a significant reduction in the incidence of new vertebral fractures compared to placebo in this population. 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 previously on placebo experienced new vertebral fractures while after 24 months these 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.

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.

The FRAX analysis of the data from study BA058-05-003 indicate that the estimated baseline fracture probabilities were low compared to several other phase 3 studies in patients with osteoporosis but for example similar to that seen in clinical trials of bazedoxifene. Fracture probabilities increased with age. Baseline characteristics of fracture probabilities for patients recruited to the extension study BA058-05-005 did not differ from the population of study BA058-05-003 and there were no relevant differences

between those who continued and those who did not. Hazard ratios for the effect of abaloparatide on the various fracture outcomes did not change significantly across the range of baseline fracture probability, suggesting significant efficacy over the whole range.

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; mean percent BMD increases were generally greater in the placebo / alendronate group than in the abaloparatide / alendronate group.

3.3. Uncertainties and limitations about favourable effects

In contrast to the CHMP guideline on osteoporosis requiring in general a duration of treatment in the pivotal phase 3 trials for a new osteoporotic medicinal product of at least 24 months in order to provide clear fracture and bone safety data, the Applicant has provided only a total duration of 18 months of treatment in the single phase 3 study, with a separate extension study without abaloparatide treatment. The chosen design has several deficiencies, among them that patients on teriparatide have not been offered to participate in the extension study and that the continuation in the extension study might have introduced a selection bias to the data beyond 18 months of treatment.

The active comparator teriparatide was not blinded due to commercial availability of teriparatide and 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 significantly 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.

GCP related serious findings lead to exclusion of two study sites in the single pivotal study, reducing the 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 has not been established [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, including changes of the definition of the key secondary endpoint; usually, it is expected that changes to principle features of the analysis are documented in a protocol amendment rather than only in the statistical analysis plan.

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.

BMD in patients on abaloparatide appears to increase with diminishing creatinine clearance; this effect might be due to an increase in abaloparatide exposure due to reduced renal elimination.

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.

3.4. Unfavourable effects

Relevant differences were seen in the incidences of the adverse events such as 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 (mean (SD) maximum increases 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. Also the incidence of orthostatic hypotension, defined as a composite adverse event of special interest, was higher on abaloparatide than on teriparatide or placebo treatments (28.4%, 19.8%, and 14.4%, respectively). 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).

TEAEs associated with hypercalcaemia and hypercalciuria (AEs of special interest) occurred less frequently in patients on abaloparatide (2.2%, 14.3%) than on teriparatide (4.8%, 17.6%) but more often than on placebo (0.6%, 11.1%); the incidence of hypercalcaemia adverse events increased with decreasing baseline renal function (CrCl ≥90 ml/min, ≥60 <90 ml/min, <60 ml/min: 0.6%, 1.9% and 1.9% for abaloparatide and 1.3%, 3.6% and 7.7% for teriparatide).

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, 7.9%, 3.6%, and 0.7% of patients on abaloparatide, teriparatide, and placebo, respectively, had a maximal increase in heart rate >25 bpm at any time point. About 20% of abaloparatide patients experienced a maximal increase in HR by >20 bpm at any time point, compared to 11% of teriparatide patients and 3% of placebo patients; only patients on treatment with abaloparatide experienced HR increases by more than 40 bpm and there was even a single case where the maximal 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, primarily due to palpitations and tachycardia.

In line with the findings in the pivotal study BA058-05-003, marked post-injection increases in heart rate for abaloparatide were observed in male and female 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 in the abaloparatide group vs. 0.9 bpm in the placebo group were seen 1 h post-dose. Significant increases in heart rate seem to persist at least12 h (mean 9.5 bpm in the abaloparatide group vs 7.3 bpm in the placebo group). The mean 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.

There is substantial epidemiologic information concerning the relationship between heart rate and cardiovascular disease. Generally, these studies show that elevations of heart rate can be associated with the development or worsening of cardiovascular disorders but whether this is due to confounding or whether an increase in heart rate is a risk factor in itself is not clear. Furthermore, the epidemiological studies investigated the association of cardiovascular risk with overall mean heart rate and not with transitory, intermittent increases in heart rate due to an external intervention.

The population of the pivotal trial BA058-05-003 is not considered entirely representative of the expected general patient population due to relevant exclusion criteria for study participation and for the most vulnerable populations either no or very limited data are available.
AEs associated with the SOC cardiac disorders were reported more frequently in the abaloparatide group (12%) compared to placebo (5%) and teriparatide (6%). The difference between groups was driven by higher incidences of palpitations and tachycardia in the abaloparatide group.
Taken together, an increase in heart rate due to vasodilation and possibly coronary vasodilation leading to coronary steal effects may precipitate myocardial ischemia in vulnerable patients. Albeit based on low event rates, a higher rate of myocardial ischemia was observed with abaloparatide and with teriparatide compared to placebo.

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, 4 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, but remained high. For teriparatide an antibody rate of 2.8% is given in the SPC and of about 4% in the EPAR. The limited 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.

3.5. Uncertainties and limitations about unfavourable effects

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.

Extent and duration of exposure do not allow an assessment of rare adverse events or adverse events with late onset including carcinogenicity and long-term cardiovascular adverse effects; post-licensing safety data will be needed to further assess the safety of abaloparatide.

As regards the increase in the incidence of orthostatic hypotension the applicant argues that this is due to an increase in heart rate post injection, but an increase in heart rate was also seen in patients treated with teriparatide resulting in a lower frequency of orthostatic hypotension adverse events.

Regarding major adverse cardiac events (MACE), the number of events during 18 months was 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. Due to the size and the exclusion criteria, the pivotal study did not have power to sufficiently detect such MACE events and therefore was considered by CHMP not sufficient to assess risk for adverse cardiovascular outcomes associated with heart rate increase in a generally more vulnerable real-life osteoporosis population.

No studies in hypertensive women and in patients with stable heart failure were included in this MAA for abaloparatide.

The thorough QT study produced data which fulfilled, although borderline, the criterion for a negative QT study.

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; this was proposed to be addressed as an important potential risk in the Risk Management Plan.

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.

There were no significant differences between abaloparatide, teriparatide, and placebo in adverse events leading to death and serious adverse events, but numbers are too small for a final assessment. It was of concern that in the first 6 months of the follow-up study BA058-05-005, 5 serious adverse events (brain neoplasm, colon cancer, intestinal adenocarcinoma, leiomyosarcoma, renal cancer) were reported in the system organ class 'neoplasms benign, malignant and unspecified (incl. cysts and polyps)' in patients previously on abaloparatide versus none in patients previously on placebo; however this difference was not seen at later points during the trial.

The diminishing differences in frequency of adverse events might 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, most frequently during the first month of the study. The most frequently occurring TEAEs leading to study drug discontinuation by SOC were nervous system disorders (2.6%), gastrointestinal disorders (2.0%), cardiac disorders (1.7%), and investigation (1.1%) for abaloparatide, gastrointestinal disorders (1.3%) and nervous system disorders (1.9%) for teriparatide, and musculoskeletal and connective tissue disorders (1.7%) for placebo. The mean duration of exposure for abaloparatide in study BA058-05-003 was 15.0 months compared to 15.6 months in the placebo and 15.8 months in the teriparatide group. 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 regards the validity of the bone biopsy analysis sensitivity seems limited since histomorphometry did not show evidence of bone anabolic effects by abaloparatide or teriparatide.

Relatively marked differences in AE reporting were seen between Asian and Caucasian subpopulations with higher incidences of total AEs, related AEs, and serious AEs. The observed differences were mainly driven by preferred terms dizziness, headache, palpitations, and hypercalciuria.

3.6. Effects Table

Table 24 Effects Table for abaloparatide in the treatment of osteoporosis in postmenopausal women (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	(mITT for VF and ITT for NVF) 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 (Safety Population)						
Neutralising antibodies		%	~30	N/A	N/A	plb and comparator (teri) controlled study teri not blinded only 18 months of exposure to abalo number of patients not suitable to assess rare events long-term follow-up unclear comparison antibodies indirect only, different	see discussion on clinical safety
Orthostatic hypotension (AESI)		%	28.4	19.8	14.4		
Discon. due to orthostatic hypotension (AESI)		%	3.6	1.7	0.9		
Palpitation		%	5.6	1.7	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	assays	
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		%	38.1	31.4	26.1		

Abbreviations: n.s. – not significant; abalo – abaloparatide; teri – teriparatide; RR – absolute risk reduction; RRR – relative risk reduction; vs. – versus; plb – placebo; 95% CI – 95% confidence intervals; p – p-value; mITT – modified intent to treat (randomised patients with both pre-treatment and post-baseline evaluable radiologic assessments); ITT - intent to treat (all patients randomised); K-M – Kaplan-Meier; HR - Hazard Ratio; SOC – system organ class; N/A – not applicable; discon – discontinuation; n – number of patients

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 in particular, 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 1 pivotal trial with non-vertebral fractures as key secondary, but not as co-primary endpoint. In this pivotal trial no effect of abaloparatide on non-vertebral fractures has been established.

Other endpoints investigated, 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 nor on an advantage of abaloparatide over teriparatide as claimed by the Applicant.

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. The inclusion and exclusion criteria in study BA058-05-003 were relatively extensive which impacts the generalisability of the pivotal study, mainly regarding safety data, to the elderly osteoporosis population with concomitant chronic diseases and medications. The marked increase in heart rate is of

concern in the general osteoporosis population where concomitant cardiovascular diseases are expected to be more common than in the population included in the pivotal trial. The increase in heart rate was more pronounced in patients treated with abaloparatide compared with teriparatide.
An increase in heart rate of the magnitude seen in the clinical trials with abaloparatide may 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 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.
To mitigate these risks, the applicant proposed to monitor patients in clinical practice 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 in attendance 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. If severe orthostatic hypotension or severe cardiovascular symptoms occur, treatment would have been discontinued.

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. Information provided through the SmPC in sections 4.3, 4.4, 4.8, and 5.1, as well as the PL were proposed.

The frequency of the development of anti-abaloparatide antibodies and neutralising antibodies is very high. The limited available data do not show an effect of antibodies to abaloparatide on efficacy or safety.

There were a number of adverse events in the system organ class ‘neoplasms benign, malignant and unspecified´ and in the first 6 months of the follow-up study BA058-05-005, 5 events (brain neoplasm, colon cancer, intestinal adenocarcinoma, leiomyosarcoma, renal cancer) were reported in this system organ class in patients previously on abaloparatide versus none in patients previously on placebo; however this difference was not seen at later time-points during the trial.

The incidence of hypercalcaemia adverse events is lower in patients treated with abaloparatide than teriparatide, but organ calcification has been identified in preclinical trials. Thus, it can currently not be excluded that abaloparatide might induce organ calcification and e.g. impair renal function.

3.7.2. Balance of benefits and risks

Efficacy of treatment with abalaoparatide 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.

All available data indicate a dose related increase in heart rate that parallels exposure to abaloparatide. The marked increase in heart rate associated with abaloparatide is not solely related to peripheral vasodilation but there is a direct chronotropic effect on cardiomyocytes as indicated by non-clinical studies. The heart rate increase with abaloparatide cannot be considered comparable to physiological variations in heart rate and is therefore a safety concern.

Marked post-injection increases in heart rate 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 heart rate seemed to persist for several hours. This is of concern, particularly as abaloparatide was intended to be given once daily as a subcutaneous injection.

In the pivotal study, the 1 hour post-dose heart rate increased more in abaloparatide treated patients compared to teriparatide. Therefore, safety data from clinical studies and post-marketing experience from teriparatide cannot be extrapolated to abaloparatide. In the pivotal study, for example, 20% of patients treated with abaloparatide experienced an increase in heart rate by >20 bpm at any time point versus 11% of patients treated with teriparatide and 3% of placebo patients. Patients that experienced highest increases in HR by >40 bpm (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 more early (≤1 month) drop-outs in the abaloparatide-arm (7.9%) compared to teriparatide (3.9%).

Risk minimisation measures proposed by the applicant with contraindications in patients with pre-existing cardiac disease, if followed, may reduce the CV risk associated with heart rate increases. However, thorough screening for undiagnosed conditions with echocardiography for these conditions appears unlikely to be feasible in a general osteoporosis population. In light of overall increased heart rate related adverse events compared to teriparatide, a reasonable target population for abaloparatide in clinical practice could not be identified.

As a single pivotal trial of a new osteoporosis agent the size of the study was small. Only healthy ambulatory postmenopausal woman, screened for being free from any significant cardiac disturbances, were included and the overall number of serious cardiovascular events during the 18 month study period was low. Therefore, this study is not considered sufficient in order to assess the risk for adverse cardiovascular outcomes associated with heart rate increases in a real-life osteoporosis population generally more vulnerable regarding cardiovascular risk.

Overall, this application for a new osteoporosis agent is not considered to be in accordance with EMA points to consider on application with one pivotal study with "particularly compelling results with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency."

Considering the above mentioned limitations, the efficacy data are not considered sufficient to outweigh the risks associated with the increase in heart rate.

The benefit-risk balance for abaloparatide is therefore negative.

3.7.3. Additional considerations on the benefit-risk balance

n/a

3.8. Conclusions

The overall B/R of Eladynos is negative.

Divergent position(s) are appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Eladynos in the treatment of osteoporosis in postmenopausal women at increased risk of fracture (see Section 5.1), the CHMP considers by majority decision that the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product. The CHMP considers that:

Whereas the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated:

- The efficacy of Eladynos (abaloparatide), for the treatment of osteoporosis, was supported by one pivotal study only. This study failed to demonstrate a statistically significant effect on non-vertebral fractures vs. placebo which is a requirement outlined in the "Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis". In the pivotal study, there were serious GCP related findings and data from two sites had to be excluded which reduced the size of the study population.
- Marked post-injection increases in heart rate 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. In the pivotal phase III study, 1 hour post-dose heart rate increased more in abaloparatide treated patients compared to both placebo and teriparatide with 42% of patients treated with abaloparatide experiencing an increase in heart rate of >15 bpm at any time.
    - No increase in major adverse cardiovascular events in patients treated with abaloparatide was noted compared to comparators. However, more common adverse events such as palpitations, tachycardia, dizziness, nausea and discontinuations were reported more frequently in patients treated with abaloparatide compared to both teriparatide and placebo which may be related to the documented effect of abaloparatide on heart rate. Furthermore, the size of the study was small and the number of serious cardiovascular events during the 18 month study period was low and therefore the study did not have power to detect such events. In addition, patients with significant pre-existing cardiovascular disease, being at a higher risk of cardiovascular events, were excluded from the study. Therefore, this study is not considered sufficient in order to assess risk for adverse cardiovascular outcomes

associated with heart rate increase in a generally more vulnerable real-life osteoporosis population.

- Risk minimisation measures including contraindications in patients with pre-existing cardiac disease as well as monitoring of patients at risk were proposed by the Applicant. However, in light of an increased baseline risk of cardiovascular events in the postmenopausal osteoporosis patient population, a reasonable target population for abaloparatide in clinical practice could not be identified.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Eladynos.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, the CHMP, in light of the negative recommendation, was of the opinion that it is not appropriate to conclude on the new active substance status at this time.

Divergent positions to the majority recommendation are appended to this report.

5. Re-examination of the CHMP opinion of 22 March 2018

Following the CHMP conclusion that Eladynos was not approvable on the grounds outlined above, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc Expert Group meeting on 10 July 2018 to seek their views on the CHMP grounds for refusal, taking into account the applicant's response.

Detailed grounds for re-examination submitted by the applicant

The applicant presented detailed grounds for re-examination in writing and at an oral explanation.

A summary of the applicant's grounds for re-examination is presented as follows:

Efficacy (the efficacy of Eladynos was supported by one pivotal study only, which failed to demonstrate a statistically significant effect on non-vertebral fractures vs. placebo)

Ground #1: Failure to demonstrate a statistically significant effect on non-vertebral fractures as required by the osteoporosis guideline.

- In line with the requirements of the EMA guideline on osteoporosis, long-term 25 and 43-month abaloparatide/alendronate (ALN) sequential therapy data showed statistically significant and clinically relevant reductions in non-vertebral fractures (NVF) (25 months, p=0.0244 and at 43 months, p=0.0237) in the pre-specified Per Protocol (PP) population, which is a pre-planned analysis representative and supportive of the Intention-to-Treat (ITT) population. In the context of Annex 1 to Directive 2001/83, the 25 and 43-month results should be considered.

- The pre-specified ITT analysis at 25 and 43 months is a comparison vs an active agent (alendronate). To analyse the effect of the sequential abaloparatide/ALN therapy compared to a true placebo, alone, the K-M rate of NVF fractures at 19 months (3.6%) in the placebo arm using the 003 ITT population has been linearly extrapolated to 43 months with a slope of 0.19% per month (=3.6%/19). When comparing the 43-month Study 003/005 abaloparatide/alendronate ITT data to the 43-month extrapolated placebo, the K-M rate of NVF for the ITT analysis (excluding the two Czech sites), is 4.2% in the abaloparatide/ALN group at 43 months vs 8.15% in the placebo group, RRR 48%, p=0.0102 using a Chi-squared test. Similarly, at 25 months, the abaloparatide/alendronate data vs extrapolated placebo, the K-M rate is 4.74 vs 2.4%, RRR 49%, p=0.0334 using a Chi-squared test. These results support the superiority of abaloparatide/alendronate over placebo alone at 43 months.
- The long-term and sequential therapy of abaloparatide/alendronate represents how the product will be used in real-world settings in line with current clinical recommendations and supports the clinical relevance of these data. The pivotal study demonstrates clear and consistent long-term efficacy in all important and clinically relevant primary and secondary endpoints, thus supporting a high degree of internal consistency of all efficacy parameters.
- Conbriza (bazedoxifene) was approved in the EU in 2009 for use in treating postmenopausal women with osteoporosis at increased risk of fracture despite the absence of a statistically significant decrease of non-vertebral fractures at 3 years in the single pivotal study (the CHMP accepted non-statistically significant post hoc analyses in small subgroups of women at high risk of non-vertebral fracture as the demonstration of efficacy). As indicated above and in contrast to Conbriza, long-term abaloparatide/ALN data showed a statistically significant and clinically relevant reduction in NVF. In any event, the Applicant cannot identify any valid basis for the CHMP to apply a different (or higher) regulatory standard to the application for abaloparatide.
- The CHMP identified no Major Objections regarding efficacy in the 3rd D180LoOIs and it was verbally stated by the Rapporteurs on two separate occasions (debrief discussion after the first Oral Explanation (OE) and at the start of the Ad-hoc Expert Group meeting) that efficacy was no longer an issue. Therefore, the applicant has proceeded on this basis.

Ground #2: The reduction of the size of the studied population as result of the exclusion of the two Czech study sites negatively impacts the efficacy assessment.

- The exclusion of these two sites, as expected, led to a loss of statistical power for the ITT analyses of non-vertebral fractures. However, in line with the requirements of the EMA guideline on osteoporosis, long-term 25 and 43-month abaloparatide/alendronate (ALN) sequential therapy data showed statistically significant and clinically relevant reductions in non-vertebral fractures (NVF) (25 months, p=0.0244 and at 43 months, p=0.0237) in the pre-specified Per Protocol (PP) population. Similar point estimates and statistical significance of the relative risk reduction of non-vertebral fractures were observed, irrespective of whether the two sites were removed from the analyses or not.
- The loss of study power did not change the direction of the treatment effect which remains consistently in favour of abaloparatide as compared with the control arm. Overall, the study results were robust in that similar findings were still observed in all important and clinically relevant efficacy endpoints relating to assessment of vertebral, non-vertebral, major non-vertebral (as defined by the EMA), major osteoporotic and clinical fractures.

- While the applicant acknowledges it may be difficult for the CHMP to overcome an apparent continuing lack of confidence and trust in the trial data due to the GCP issues identified at sites 131 and 132 in the Czech Republic, no similar issues were identified at other study sites in inspections by EMA and other health authorities or in extensive audits by the applicant, and the applicant therefore believes there is no basis for not accepting the validity and objectivity of the study data from the remaining sites.

Ground #3: The submitted single pivotal study is not sufficient to demonstrate efficacy.

- The single abaloparatide study included 680 patients/arm, i.e. 20% more than the 550 patients/arm of the pivotal Phase 3 study of teriparatide (Forsteo) and was appropriately sized against the primary endpoint.
- When considering the longer-term treatment effect at Month 25 (p=0.0244) and at Month 43 (p=0.0237) based on abaloparatide/alendronate sequential therapy, highly statistically and clinically relevant reductions in non-vertebral fractures were observed in the pre-specified Per Protocol population.
- The study 003/005 met all 8 prerequisites for relying on one pivotal study according to the applicable EMA Guideline.
- As a matter of consistency in applying the regulatory standard in the same therapeutic indication, the clinical efficacy of the most recently approved medicinal products indicated for treating postmenopausal osteoporosis (including denosumab, bazedoxifene and teriparatide) was based on a single pivotal Phase 3 study. The Applicant cannot identify any valid basis for abaloparatide to be treated differently.

Safety (Marked post-injection increases in heart rate with abaloparatide were observed together with possibly related adverse events. The size of the pivotal trial, the applied exclusion criteria and the low number of serious cardiovascular events did not allow to assess sufficiently the risk for adverse cardiovascular outcomes and proposed risk minimisation measures could not identify a reasonable target population)

Ground #4: The study was too small, not powered to detect serious cardiovascular events and not considered sufficient to assess the risk for adverse cardiovascular outcomes in a real-world osteoporosis population.

- The CHMP recognized that "*no increase in major adverse cardiovascular events in patients treated with abaloparatide was noted compared to comparators*", as supported by extensive evaluation of the Study 003 (19-month) and Study 005 (long-term follow-up, 43-month) data.
- Despite the observed transient heart rate increases, no meaningful adverse events were experienced, indicating a potential risk and not an identified risk for serious cardiovascular events.
- The long-term and sequential therapy of abaloparatide/alendronate representing how the product will be used in the real-world setting in line with current clinical recommendations identifies no clinically relevant safety concern.
- Representative of the intended patient population in real-world settings, the pivotal Study 003/005 did include 69% of patients at risk of cardiovascular disease (16% of patients with cardiac disorders and 58% of patients with vascular disorders [e.g. hypertension]), pre-existing at baseline in the overall study population. These patients did not experience more cardiac adverse events during the 18 months of therapy with abaloparatide compared to those

treated with teriparatide. There was no bias in the comparative analysis as the majority of these patients (74% abaloparatide, 78% teriparatide and 76% of placebo patients) completed the initial 18-month treatment. Further, 90% of these prior abaloparatide-treated patients and 89% of the prior placebo patients completed the 24-month extension study.

- The similarity in the distributions of maximal heart rate increases at 1-hour post dose between abaloparatide and teriparatide (95% overlap; p=0.146 indicating no difference in the distributions) should be considered as relevant to support the safety of abaloparatide given their overall comparability and the 15 years of post-market clinical safety experience with teriparatide.
- Consistent with the pivotal study results, the cumulative 12-month US post-marketing safety results (7,267 patients treated with about 1,810 patient years of exposure to abaloparatide) demonstrate a safety profile consistent with the submitted safety data from the pivotal trial. The cumulative data support the conclusion that there are no new signals of cardiovascular (CV) risk associated with abaloparatide treatment.
- As initially endorsed by the CHMP and PRAC, any uncertainties on the potential risk associated with the transiently increased heart rate with abaloparatide can be appropriately and effectively studied in a prospective observational comparative PASS. This approach is also consistent with the adopted EU Good Pharmacovigilance Practices relating to risk management.
- The abaloparatide safety database included more than 1200 patients. Any requirement for a larger pre-approval safety study would be inconsistent with the established regulatory standard for managing an identified and/or potential risk identified in pre-authorisation scientific evaluation (Note for Guidance on Population Exposure to Assess Clinical Safety).

Ground #5: In light of an increased baseline risk of CV events in the postmenopausal osteoporosis patient population, a reasonable target population for abaloparatide could not be identified.

- To mitigate any possible risk, and consistent with the pivotal trial inclusion/exclusion criteria and the recommendations of the Ad Hoc Expert Group, the Applicant agreed that the most vulnerable patients (at highest risk of cardiovascular disease or with existing significant cardiac disorders) will be contraindicated in the SmPC. It follows that patients who are less susceptible to cardiovascular risk would thus be considered as the target patient population where abaloparatide can be used safely and effectively.
- An analysis of the risk of MACE, done in compliance with the EU guideline, found an upper limit of hazard ratio of 3.37 at 19 months and of 2.13 at 43 months, which, in both cases, are lower than 4.92, the upper limit for teriparatide, a drug with a well-established CV safety profile and which shares with abaloparatide the same mechanism of heart rate increase and possible risk of CV safety.
- Patients who are prescribed with abaloparatide will be closely monitored for symptoms according to the recommendations in the SmPC.
- During the oral explanation of March 2018, the applicant agreed to conduct a Drug Utilisation Study which will include measurement of the effectiveness of the above risk minimisation of CV risk.
- The Ad-hoc Expert Group meeting (14 March 2018) reported that, "*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."

Ground #6: The proposed PASS was not taken into account in the negative opinion and in the last assessment reports.

- As requested by the PRAC, the applicant agreed to conduct a PASS, PMC-TYM-002, to address the important potential 'cardiovascular risks associated with a marked transient increase in heart rate following abaloparatide injection and long-term cardiovascular risk in vulnerable (predisposed) patients'.
- The PASS was initially endorsed by the CHMP and the PRAC, and a protocol was to be submitted by the applicant within 6 months of the Marketing Approval.
- The proposed PASS approach is consistently applied by EU regulatory authorities to assess specific safety concerns in newly approved medications. This approach was similarly applied to the centrally approved medicinal products for treatment of osteoporosis (Conbriza and Prolia), in line with the EU pharmacovigilance regulatory framework established since 2010.
- The proposed PASS is appropriately designed to ensure that it can be practically implemented to provide valuable comparative data on the relative safety of abaloparatide and teriparatide.

Ground #7: The Benefit-Risk is therefore negative

- The pivotal study demonstrates clear and consistent, statistically significant and clinically relevant long-term (43-month) efficacy in all important primary and secondary endpoints, thus supporting a high degree of internal consistency of all efficacy parameters in the study.
- The observed effects on VF and NVF of abaloparatide and the sequential therapy of abaloparatide/ALN compare favourably to the alternative therapies, including denosumab, bazedoxifene, alendronate and other antiresorptive approved therapies.
- The safety of abaloparatide was demonstrated in a population that is representative of the real-world osteoporosis population in Europe, and is supported by the important, post-authorisation safety data collected in the US (7,267 patients treated with about 1,810 patient years of exposure to abaloparatide) showing no particular safety signals of concern.
- Collectively, the long-term efficacy and safety data shown in the sequential therapy of abaloparatide/alendronate represent how the product will be used according to current treatment recommendations, and support the statistically significant and clinically relevant efficacy that was maintained with no cardiovascular risks identified.
- The proposed risk minimisation measures and pharmacovigilance plan (PASS and drug utilization study) are appropriate to address the potential cardiovascular risk associated with a marked transient increase in heart rate.
- Taken together, the benefit-risk relationship should be considered positive.

Report from the 2nd Ad Hoc expert Group meeting held on 10 July 2018

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 (more healthy) 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).

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Ad Hoc Expert Group.

Efficacy

Ground #1: Failure to demonstrate a statistically significant effect on non-vertebral fractures as required by the osteoporosis guideline, and ground #3: The submitted single pivotal study is not sufficient to demonstrate efficacy.

After exclusion of the two CZ trial sites due to GCP non-compliance, corresponding to a reduction of the study population by 16%, results of the key secondary endpoint, NVF (time to fracture event, abaloparatide vs placebo), were not statistically significant. Although there is a clear trend supporting efficacy of abaloparatide on NVF, the pre-specified analysis of NVF did not reach statistical significance. The Applicant argued that for assessment of abaloparatide´s efficacy on NVF one should consider the results of the extension trial -005 at 25 and 43 months, and specifically results in the Per Protocol (PP) population (rather than the ITT population). These analyses suggested a significant difference in NVF rate between the abaloparatide/alendronate and the placebo/alendronate group and several arguments were provided by the Applicant why this would be most appropriate. However, using the PP population

for the primary analysis of NVFs, as well as the extrapolation model for the placebo arm of the studies, was found to be not acceptable to CHMP, for the following reasons:

ITT and Per Protocol (PP) Populations in Study 003/005: Considerations regarding the choice of the primary analysis population are described in ICH-E9 and pre-specified in the clinical study protocols and statistical analysis plans. The PP population in Study 005 included only 444/688 (64.5%) of the subjects in 003's placebo group, and 436/696 (62.6%) in the abaloparatide group. Therefore, important patient selection has likely occurred, both due to patients not entering Study 005 and due to patients with protocol deviations during Study 005. Although it can be said that "the PP approach provides an estimate of the true treatment efficacy", this is not an acceptable conservative method to analyse the treatment effect in a superiority trial. The PP analysis uses data of compliant and completing patients and usually overestimates the efficacy in comparison to the ITT analysis. Both according to the relevant guideline and according to the pre-specified analysis plans, the confirmatory analysis for the secondary endpoint of NVF should be based on the (m)ITT population. PP analyses were pre-specified, but as supportive analyses. The switch to the PP population is considered post-hoc and possibly data-driven and introduces significant selection of the population. As a consequence, the use of the PP population is not acceptable. Claims for superiority with regard to efficacy for NVFs were therefore not supported by CHMP. In addition, the lack of consistency between the ITT and PP analyses results reflects negatively upon the internal consistency of the trial results in the context of a single pivotal trial.

Extrapolation: The Applicant chose a design that included a control treatment that was a hybrid between placebo and active, even during the period up to 24 months where efficacy should be established according to the guideline. In such an analysis, there is no conservative approach to account for the effect of the active controlled phase in the study in the statistical analysis. This is considered an important weakness in the design of the pivotal trial. In the context of a single pivotal trial, e.g. by introducing the linear extrapolation, deviating from the predefined statistical analysis is also not acceptable.

Efficacy comparison with EU-approved products: The applicant submitted a cross-trial comparison of clinical efficacy (trial population, BMD, vertebral fractures and non-vertebral fractures) versus EU approved medicinal products of which the interpretation is challenging. The CHMP considered that such a comparison had severe limitations, such as changing clinical practice over the long time span covered, different baseline characteristics and different analysis populations (PP v ITT).

Length of study: The scientific advice for the product stated that treatment duration in the pivotal trial should be (at least) 24 months. While it is agreed with the applicant that a treatment strategy of 18 months for an anabolic agent followed by anti-resorptive treatment could be reasonable, and may be the usage scenario in clinical practice, the applicant designed the prolongation of the study beyond 18 months as an extension trial to obtain data at 25 months. Not all participants from trial 003 continued in trial 005 and in this way uncertainty is introduced regarding which of many analyses would be most important. The 25 months analysis is not described in the SAP as the main assessment to be used for the MAA. Moreover, data from the extension of the trial beyond 18 months has several other limitations outlined in various sections of this report.

Single trial: As mentioned in the CHMP points to consider guideline on clinical development, submission with only one pivotal study should be the exceptional case. A single pivotal study has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality and internal consistency. Moreover, scientific advice recommended that compelling results should be provided both for VF and NVF, preferably as co-primary endpoints, in line with the guideline on evaluation of products for the treatment of osteoporosis, considering the clinical importance of

NVF, in particular of the hip. By contrast, the pivotal trial was small, lacked compelling effect on NVF and only one event of hip fracture did occur, and did only include relatively healthy ambulatory postmenopausal woman.

Comparison with teriparatide: The applicant argued that abaloparatide and teriparatide have similar structures and mechanism of action, and that the totality of the comparison of abaloparatide and teriparatide provided support that both drugs reduce similarly the risks of new vertebral and nonvertebral fracture in women with postmenopausal osteoporosis and that these data also support the long-term efficacy of the sequential use of abaloparatide followed by alendronate in this population. In conclusion the applicant is of the opinion that the established benefit of teriparatide can be used to support the abaloparatide results. This reasoning can be accepted as hypothesis-generating only, as no formal equivalence or non-inferiority analysis was performed. Trial 003 was a trial in which two active agents were compared to placebo. There were no predefined confirmatory objectives for comparison of abaloparatide with teriparatide and no non-inferiority or equality margins were predefined, therefore the study was not designed to detect equality or differences. Moreover, unlike abaloparatide and placebo, teriparatide was used in a non-blinded fashion. Therefore, these data are considered of exploratory, but not of confirmatory quality. Specifically, the claim that efficacy with abaloparatide and teriparatide would be "similar" cannot be accepted based on these data.

BMD data were generally supportive of efficacy for both vertebral and non-vertebral fracture efficacy, but these data are considered of supportive nature only.

BMD data and fractures were analysed in multiple other ways (e.g. responder analyses) in the study reports and these additional analyses were considered of exploratory nature.

Reference is made by the applicant to previous marketing authorisations for products for the treatment of osteoporosis; however, data provided, the level of efficacy demonstrated, safety concerns identified etc. do not allow direct comparison and each application is assessed independently.

Based on the totality of the data, the majority of experts at the AHEG meeting on 10 July 2018 were of the view that an effect of abaloparatide on reduction of non-vertebral fractures could be expected; however, considering the deficiencies of the NVF data outlined above, and further considering the limited value of supporting evidence from surrogate endpoints such as changes in BMD and serum markers of bone metabolism, CHMP considered that a robust positive effect on reduction of non-vertebral fractures has not been established.

The CHMP's overall view on efficacy, taking into account the grounds for re-examination, is summarised in the B/R section on favourable effects (section 6.2).

Ground #2: The reduction of the size of the studied population as result of the exclusion of the two Czech study sites negatively impacts the efficacy assessment.

The CHMP has decided that the trial's data can be used for the purpose of the MAA, after exclusion of the two sites where serious GCP non-compliance was reported by SUKL, the Czech Health Authority, mainly related to inclusion/exclusion data. All scientific conclusions of the CHMP from the pivotal trial made therefore unrestricted use of the full data set after exclusion of those sites. The validity and objectivity of the study data from the remaining sites was not questioned in the initial opinion adopted by the CHMP and is not being questioned in the present re-examination opinion.

However, the fact remains that CHMP in its analyses and conclusions had to rely on a smaller sized data set from the pivotal trial compared to the data set initially submitted by the company, which may have negatively impacted on the demonstration of (statistically) significant effect of certain outcomes, namely efficacy with regard to NVFs.

Safety

Ground #4: The study was too small, not powered to detect serious cardiovascular events and not considered sufficient to assess the risk for adverse cardiovascular outcomes in a real-world osteoporosis population.

From a regulatory standards point of view, the total number of study participants exposed to abaloparatide in the pivotal study, after the exclusion of 2 study sites, was lower than expected by ICH standards of ca. 1500 (Note for Guidance on Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95).

Heart rate increase: In the QTc study the highest effect on pulse rate was seen at 15 minutes after the injection. As this was also the first time-point for which data are presented, the maximum increase in heart rate may not have been recorded.. With regard to the pivotal study, at 1 hour post dose the highest change in pulse rate has already passed and the 1-hour post dose data are not representative of the maximum change in heart rate, which remains uncertain. Moreover, the effect on HR remained appreciable over 12 hours.

Major adverse cardiac events in the pivotal study: The applicant was asked to present additional analyses of the study data to provide analyses for MACE and MACE + Heart Failure (regardless of hospitalisation) for study 003 and study 003/005. The included events were collected routinely as adverse events during the clinical trials but were not adjudicated. The number of events and the confidence intervals are summarised in the effects table (see below). This analysis did not indicate CV harm with abaloparatide treatment as compared to placebo with regard to MACE. The analysis of MACE + Heart Failure showed a decrease in MACE or heart failure events in the abaloparatide treated patients versus placebo in Study 003. However, the study was not designed to detect CV events other than those reported by the investigator in routine monitoring. Major limitations of these analyses are in particular the lack of adjudication and the different drop-out rates of the various strata prior to the possibility of a MACE, possibly due to symptoms linked to heart rate increase, thus potentially introducing bias favouring abaloparatide. Moreover, due to the size and the exclusion criteria regarding CV risk factors, the number of events in the pivotal study was too small to assess such MACE events adequately. Therefore, this study is not considered sufficient in order to assess the risk for adverse cardiovascular outcomes associated with HR increases in a real-life osteoporosis population generally more vulnerable regarding cardiovascular risk.

In comparison to teriparatide, based on results of study 003, AEs of palpitations (abaloparatide, 5.6%; teriparatide, 1.7%) and tachycardia (abaloparatide 1.3%; teriparatide, 0.4%) occurred more often with abaloparatide; both AEs occurred less frequently in the placebo group (palpitations, 0.4%; tachycardia, 0.3%). With regard to numerical increases of heart rate, results were also different. Only few serious cardiac-related events were observed, which seems to confirm that the population was not so frail.

Presented post-authorisation data from the use of abaloparatide in the US between May 2017 and January 2018 was acknowledged by CHMP, but was considered of very limited value to exclude CV harm (in line with the view of the AHEG convened on 1 March 2018), as from those observational data it is difficult to exclude an increase in MACE and differences with the EU population may also be important.

With regard to the proposed risk mitigation measures and the PASS proposed by the applicant, see assessment of ground #6.

The pivotal trial had several exclusion criteria to exclude CV risks: At inclusion for trial 003, resting 12-lead electrocardiogram (ECG) during screening should not show clinically significant abnormality and should have a QTc ≤470 msec (Bazett's correction). Systolic blood pressure was to be ≥100 and ≤155 mmHg, diastolic blood pressure ≥40 and ≤95 mmHg, and the heart rate ≥45 and ≤100 beats per minute (bpm) (sitting or supine). In this population no relations were found between (any remaining) cardiac history, serious adverse events and increase in pulse rate. As no risk factors for (potential) adverse consequences of heart rate increase were identified, it is difficult to assess the additional value of any proposed risk minimisation measures.

Overall, the patients enrolled in Study 003 were underrepresented with regard to pre-existing heart disease and were not fully representative of the European population of osteoporotic postmenopausal women receiving osteoporosis medications. The single pivotal trial was not considered sufficient in order to assess the risk for adverse cardiovascular outcomes associated with HR increases in a real-life osteoporosis population.

Ground #5: In light of an increased baseline risk of CV events in the postmenopausal osteoporosis patient population, a reasonable target population for abaloparatide could not be identified.

The population defined in the proposed SmPC section 4.1 was a general osteoporosis population ('treatment of osteoporosis in postmenopausal women at increased risk of fracture'). In clinical use, abaloparatide could have been expected to have a similar place as teriparatide, which is second line. However, the pivotal trial included almost no patients with bisphosphonate pre-treatment. Also, the second line positioning would likely be associated with extensive co-morbidities (including cardiovascular disease) which the applicant considered as exclusion criteria for their clinical trial, although contraindications in the SmPC were proposed to that regard. As osteoporosis is a risk factor for CV disease, a somewhat higher risk of MACE than in the general population might be expected. Overall, this means that the study population is not representing the proposed target population, questioning external validity of the trial results.

With regard to the significance of the MACE results, see assessment of ground #4.

With regard to the proposed risk mitigation measures and the PASS proposed by the applicant, see assessment of ground #6.

The majority of osteoporosis experts at the AHEG of 1 March 2018 considered indeed side effects manageable; however, this concerned the short term symptoms after injection.

Ground #6: The proposed PASS was not taken into account in the negative opinion and in the last assessment reports.

The proposed PASS was considered and taken into account by CHMP.

The choice of comparator was found to be problematic; for instance for teriparatide, while an approved indication might be similar in the US and the EU, its real world use could be different.

The applicant proposed a Post-Authorisation Safety Study (PASS) to further characterise the cardiovascular risk profile among new users of abaloparatide. The proposed PASS has limitations compared to a randomised, prospective trial: Full characterisation at baseline of the included patients is not possible as a consequence of its design; moreover, even propensity scores cannot fully address potential confounding by indication. The gold standard for post-authorisation assessment of CV risks has been set in the field of diabetes and includes a randomised, prospective trial. In this respect, the design of the proposed PASS would not match the standard set for the proposed aim albeit in a

different therapeutic area. As a consequence the interpretability of the results would likely have been very challenging.

The foreseen accrual of patients in the EU was considered low in comparison to US patients, considering likely differences in usage and population, with a rather long timeline to complete these studies.

No risk factors for adverse effects of the increased pulse rate were identified during the procedure. Therefore, no specific measures are or can be proposed to mitigate this risk.

The experts of the AHEG on 1 March 2018 welcomed in principle the conduct of such a PASS, would the product have been authorised, and were of the view that risk minimisation measures as proposed in the product information could address the potential safety risk associated with HR increase. CHMP has considered the AHEG advice and recommendations. However, the evidence confirming or excluding consequences for the patient of the pharmacologically induced temporary increases in pulse rate for potentially > 50% of the time during 1.5 years is scarce, and the AHEG did not eliminate uncertainties on the safety of the product sufficiently (see also assessment of ground #4).

The CHMP's overall view on safety is summarised in the B/R section on unfavourable effects (section 6.4).

Ground #7: The Benefit-Risk is therefore negative.

With regard to the individual points raised by the applicant in this section, please see the previous sections covering the assessment of the grounds presented by the applicant regarding efficacy and safety aspects.

CHMP's overall assessment of the benefit-risk of abaloparatide following re-examination is provided in section 6 of this report.

5.1. Risk Management Plan

The CHMP and PRAC, having considered the data submitted in the application for re-examination of the CHMP opinion of 22 March 2018, was of the opinion that due to the concerns identified with this application, the updated risk management plan version 1.5 cannot be agreed at this stage.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

Abaloparatide subcutaneous daily injection was intended for treatment of postmenopausal osteoporosis in order to increase bone mineral density (BMD) and consequently reduce the risk of vertebral and non-vertebral fractures.

In Europe, 22 million women and 5.5 million men were estimated to have osteoporosis in 2010; and 3.5 million new osteoporotic fractures were sustained. 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.

As regards anti-osteoporotic treatment for the reduction of the risk of osteoporotic fractures the majority of options aim at anti-resorptive properties while therapeutic options to increase new bone

formation and BMD with a bone anabolic agent are limited. Abaloparatide is a synthetic, 34 amino acid analogue of PTHrP(1-34) which belongs to the same class as teriparatide (approved for the treatment of postmenopausal osteoporosis in the EU in 2003) and stimulates the production and activity of osteoblasts, increasing BMD by building new bone.

Disease or condition

A definition from 1993 states osteoporosis is a "disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk". A more recent definition from the NIH Consensus Development Panel on Osteoporosis defines osteoporosis as a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture (Szulc & Bouxsein, 2010).

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 anti-resorptive drug and the other is to increase new bone formation and BMD with a bone anabolic therapy. Anti-resorptive 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 in contrast stimulates the production and activity of osteoblasts, increasing BMD by building new bone.

Main clinical 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. The clinical efficacy and safety of daily 80 µg abaloparatide SC 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 treatment 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.

Based on the deviations found during the GCP inspections at two sites in Czech Republic of study BA058-05-003, data from these two sites cannot be used when assessing the marketing authorisation application and, consequently only endpoints and information excluding data from those two sites were the basis for the benefit-risk evaluation.

6.2. 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; the active comparator teriparatide also showed a significant reduction in the incidence of new vertebral fractures compared to placebo in this population. 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. The absolute risk reduction in the abaloparatide treated group compared to placebo was 3.65, (95% CI: 2.00; 5.59) ($p<0.0001$).

In the extension study BA058-05-005, when both former abaloparatide and former placebo patients were treated with alendronate, benefit in the former abaloparatide group was preserved. At **25** months after the start of trial 003, new patients with vertebral fractures were for abaloparatide 2 (0.44%) versus placebo 21 (4.29%). The absolute risk reduction versus placebo (95% CI) was 3.86 (95% CI: 2.00; 6.06). At **43** months after the start of trial 003, new patients with vertebral fractures were for abaloparatide 4 (0.88%) versus placebo 26 (5.32%). The absolute risk reduction versus placebo (95% CI) was 4.44 (95% CI: 2.30; 6.86). A statistically significant reduction of major osteoporotic fractures was seen for abaloparatide vs placebo at all time points (19, 25 and 43 months).

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. The advantage for former abaloparatide-treated patients remained, when all patients were switched to alendronate in extension study BA058-05-005 up to 43 months. BMD increased earlier with abaloparatide compared to teriparatide, indicating earlier onset of effect.

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.

Fracture probabilities at baseline (FRAX analysis) calculated from the data from study BA058-05-003 were estimated to be low compared to several other phase 3 studies in patients with osteoporosis but for example similar to that seen in clinical trials of bazedoxifene. Fracture probabilities increased with age. Baseline characteristics of fracture probabilities for patients recruited to the extension study BA058-05-005 did not differ from the population of study BA058-05-003. Hazard ratios for the effect of abaloparatide on the various fracture outcomes did not change significantly across the range of baseline fracture probability, suggesting significant efficacy over the whole range.

6.3. Uncertainties and limitations about favourable effects

In contrast to the CHMP guideline on osteoporosis requiring in general a duration of treatment in the pivotal phase 3 trials for a new osteoporotic medicinal product of at least 24 months in order to provide clear fracture and bone safety data, the Applicant has provided only a total duration of 18 months of treatment in the single phase 3 study, with a separate extension study without abaloparatide treatment. The chosen design has several deficiencies, among them that patients on teriparatide have not been offered to participate in the extension study and that the continuation in the extension study might have introduced a selection bias to the data beyond 18 months of treatment.

In trial 003, the active comparator teriparatide was not blinded due to commercial availability of teriparatide. Discontinuation and the percentage of patients with no post-treatment x-ray were significantly 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.

GCP related serious findings lead to exclusion of two study sites in the single pivotal study, reducing the 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.

The efficacy of abaloparatide compared to placebo on **non-vertebral fractures** did not reach statistical significance (for the number of NVFs see effects table, below). During the re-examination, the Applicant presented data from the per protocol analysis of the non-vertebral fractures and from an analysis in which placebo data for non-vertebral fractures were extrapolated for the extension study over 18 months. While these analyses did provide statistically significant results, in line with the experts at the AHEG meeting on 10 July 2018 who expressed reservations to the use of the PP population and the use of the linear extrapolation model, these analyses were considered only as secondary analyses by CHMP.

Furthermore, the analysis of the 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, including changes of the definition of the key secondary endpoint (upon a request of the US FDA); usually, it is expected that changes to principle features of the analysis are documented in a protocol amendment rather than only in the statistical analysis plan.

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 considered to be of unclear relevance.

The relevance of differences in changes in serum bone markers and their relation to differences in the reduction of fracture risk between abaloparatide and teriparatide remain unclear.

Based on the totality of the data, the majority of experts at the AHEG meeting on 10 July 2018 were of the view that an effect of abaloparatide on reduction of non-vertebral fractures could be expected. However, concerns with the level of evidence were raised, in particular from a methodological point of view from the NVF data, and further considering the limited value of supporting evidence from surrogate endpoints such as changes in BMD and serum markers of bone metabolism, CHMP considers that a robust positive effect on reduction of non-vertebral fractures has not been established.

6.4. Unfavourable effects

Relevant differences were seen in the incidences of the adverse events such as palpitations (abaloparatide, teriparatide, placebo: 5.6%, 1.7%, and 0.4%, respectively), nausea (8.5%, 5.4%, and 3.1%, respectively) and dizziness (11.1%, 8.2%, and 7.1%, respectively). Also the incidence of orthostatic hypotension, defined as a composite adverse event of special interest, was higher on abaloparatide than on teriparatide or placebo treatments (28.4%, 19.8%, and 14.4%, respectively). 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 evaluated as composite Adverse Events of Special Interest occurred less frequently in patients on abaloparatide (2.2%, 14.3%) than on teriparatide (4.8%, 17.6%) but more often than on placebo (0.6%, 11.1%); the incidence of hypercalcaemia adverse events increased with decreasing baseline renal function (CrCl ≥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 highest increase in heart rate may have occurred earlier. The highest measured effect on pulse rate was at 15 minutes after the injection in male and female healthy volunteers in the QTc study. In study BA058-05-003, 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 1.0 to 1.9 bpm. Overall, 7.9%, 3.6%, and 0.7% of patients on abaloparatide, teriparatide, and placebo, respectively, had an increase (pre- to 1h post dose) in heart rate >25 bpm at any time. About 20% of patients on abaloparatide experienced an increase in HR by >20 bpm at any time point ; only patients on treatment with abaloparatide experienced maximal HR increases by more than 40 bpm and there was even a single case were the maximal 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, primarily due to palpitations and tachycardia.

In line with the findings in the pivotal study BA058-05-003, marked post-injection increases in heart rate for abaloparatide were observed in male and female healthy volunteers in the thorough QT-study BA058-05-012. A 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. Because the first post-dose measurement was also the highest, the maximum increase may have been missed. Mean increases of 9.5 bpm in the abaloparatide group were seen 1 h post-dose. Significant increases in heart rate seem to persist at least 12 h (mean 9.5 bpm in the abaloparatide group vs. 7.3 bpm in the placebo group). 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.

AEs associated with the SOC cardiac disorders were reported more frequently in the abaloparatide group (12%) compared to placebo (5%) and teriparatide (6%). The difference between groups was driven by higher incidences of palpitations and tachycardia in the abaloparatide group.

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, 4 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, but remained high. For teriparatide an antibody rate of 2.8% is given in the SPC and of about 4% in the EPAR. The limited 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.

The thorough QT study yielded data which fulfilled the criterion for a negative QT study.

6.5. Uncertainties and limitations about unfavourable effects

Safety data for abaloparatide are limited to an exposure of 18 months in comparison to open-label teriparatide and blinded 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.

Extent and duration of exposure do not allow an assessment of rare adverse events or adverse events with late onset including carcinogenicity and long-term cardiovascular adverse effects.

There is substantial epidemiologic information concerning the relationship between heart rate and cardiovascular disease. Generally, these studies show that chronic elevations of heart rate can be associated with the development or worsening of cardiovascular disorders but whether this is due to confounding or whether an increase in heart rate is a risk factor in itself is not clear. Furthermore, the epidemiological studies investigated the association of cardiovascular risk with overall mean heart rate and not with daily, pharmacologically induced transient increases in heart rate. Uncertainty remained regarding the clinical implications of the observed heart rate increases with abaloparatide. The applicant provided information pointing to both a positive chronotropic effect directly on the sinus node of the heart as well as a vasodilatory effect on smooth muscle to be relevant for the mechanism of action for the increase in heart rate caused by abaloparatide. While this was found to be reassuring, also by the experts of the AHEG meeting on 10 July 2018, the impact of such a periodic heart rate increase in the expected population to be treated with abaloparatide remains unknown.

The population of the pivotal trial BA058-05-003 is not considered entirely representative of the expected general patient population. Because of the presence of a placebo control arm, it was considered unethical to include subjects with severe osteoporosis. Indeed, only about 1% of subjects listed bisphosphonates as a prior medication whereas US real-world data show that 36% of teriparatide users used anti-osteoporosis medication beyond calcium/vitamin D before treatment. Due to relevant entry criteria for study participation, there are only limited data available for many subjects with chronic conditions including cardiovascular disease. Abaloparatide has not been evaluated in hypertensive women and in patients with stable heart failure.

Regarding major adverse cardiac events (MACE), the number of events was too limited for any conclusions on differences between groups. The applicant was asked to present additional analyses of the study data to provide analyses for MACE and MACE + Heart Failure (regardless of hospitalisation) for study 003 and study 003/005. The analysis of MACE + Heart Failure suggested a decrease in MACE or heart failure events in the abaloparatide treated patients versus placebo in Study 003. However, the included events were collected routinely as adverse events during the clinical trials and were not adjudicated. The number of MACE events and the confidence intervals are summarised in the effects table (see below). This analysis did not indicate CV harm with abaloparatide treatment as compared to placebo with regard to MACE. However, the study was not designed to detect CV events. While this might provide some reassurance, major concerns remained about the key limitations of these analyses, in particular the lack of adjudication and the different drop-out rates of the various strata prior to the possibility of a MACE,possibly due to symptoms linked to heart rate increase thus potentially introducing bias favouring abaloparatide. Moreover, due to the study size and the exclusion criteria regarding CV risk factors, the number of events in the pivotal study was too small to assess such MACE events adequately. Therefore, this study is not considered sufficient in order to assess the risk for adverse cardiovascular outcomes associated with HR increases in a real-life osteoporosis population generally more vulnerable regarding cardiovascular risk.

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; this was proposed to be addressed as an important potential risk in the Risk Management Plan.

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.

There were no significant differences between abaloparatide, teriparatide, and placebo in adverse events leading to death and serious adverse events, but numbers are too small for a final assessment. It was of concern that in the first 6 months of the follow-up study BA058-05-005, 5 serious adverse

events (brain neoplasm, colon cancer, intestinal adenocarcinoma, leiomyosarcoma, renal cancer) were reported in the system organ class 'neoplasms benign, malignant and unspecified (incl. cysts and polyps)' in patients previously on abaloparatide versus none in patients previously on placebo; however this difference was not seen at later points during the trial.

The diminishing differences in frequency of adverse events might 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, most frequently during the first month of the study. There were more early (≤1 month) drop-outs in the abaloparatide arm (7.9%) compared to teriparatide (3.9%) or placebo (5.2%). The mean duration of exposure for abaloparatide in study BA058-05-003 was 15.0 months compared to 15.6 months in the placebo and 15.8 months in the teriparatide group. 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.

The sensitivity of the bone biopsy analysis seems limited since histomorphometry did not show evidence of bone anabolic effects by abaloparatide or teriparatide.

Relatively marked differences in AE reporting were seen between Asian and Caucasian subpopulations with higher incidences of total AEs, related AEs, and serious AEs in Asians. The observed differences were mainly driven by preferred terms dizziness, headache, palpitations, and hypercalciuria.

6.6. Effects Table

Table 25 Effects Table for abaloparatide in the treatment of osteoporosis in postmenopausal women.

Effect	Short Description	Unit	Treat-ment	Control		Reference
Favourable effects						
Vertebral fracture						
			ABL	PBO	TER	003 mITT (ex sites 131/132)
	N		583	600	600	
18 months	fractures	n	3	25	4	
	pts with event	%	0.51	4.17	0.67	
		95% ci	0.18; 1.50	2.84; 6.08	0.26; 1.70	
	ARR v PBO	%	3.65		3.50	
		95% ci	2.00; 5.59		1.82; 5.45	
	RRR v PBO	%	88		84	
		95% ci	59; 96		54; 94	
		p	<.0001		<.0001	
			ABL/ALN	PBO/ALN		005 mITT (ex sites 131/132)
	N		457	489		
25 months	fractures	n	2	21		
	pts with event	%	0.44	4.29		
		95% ci	0.12; 1.58	2.83; 6.48		
	ARR	%	3.86			
		95% ci	2.00; 6.06			
	RRR	%	90			
		95% ci	57; 98			
		p	<.0001			

Effect	Short Description	Unit	Treat-ment	Control		Reference
Nonvertebral fracture						
			ABL	PBO	TER	003 ITT (ex sites 131/132)
	N		696	688	686	
18 months	n fractures		15	21	12	
	pts with event	%	2.2	3.1	1.7	
	K-M rate	%	2.7	3.6	2.0	
		95% ci	1.63; 4.44	2.33; 5.42	1.11; 3.43	
	ARR v PBO	%	0.87		1.61	
		95% ci	-1.15; 2.89		-0.26; 3.47	
	RRR v PBO	%	26		44	
		95% ci	-43; 62		-15; 72	
		p	0.37		0.11	
			ABL/ALN	PBO/ALN		005 ITT (ex sites 131/132)
	N		469	494		
25 months	n fractures		11	22		
	pts with event	%	2.3	4.5		
	K-M rate	%	2.4	4.5		
		95% ci	1.33; 4.27	3.00; 6.79		
	ARR	%	2.13			
		95% ci	-0.18; 4.45			
	RRR	%	48			
		95% ci	-8; 75			
		p	0.073			

BMD						
			ABL	PBO	TER	003 ITT LOCF (ex sites 131/132)
18 months	N		696	688	686	
Femoral neck	change from baseline	% (g/cm2)	2.7	-0.4	2.3	
		95% ci	2.4; 3.0	-0.7; -0.2	2.0; 2.6	
Total hip	change from baseline	% (g/cm2)	3.3	-0.0	3.0	
		95% ci	3.1; 3.6	-0.2; 0.2	2.7; 3.2	
Lumbar spine	change from baseline	% (g/cm2)	9.1	0.5	9.2	
		95% ci	8.5; 9.7	0.2; 0.8	8.7; 9.7	

Unfavourable Effects							
			ABL	PBO	TER		Trial 003 (Safety population ex sites 131/132), non-adjudicated
19 months	N		694	687	686		
MACE	KM analysis	N (KM%)	1 (0.2)	7 (1.2)	4 (0.6)		
		HR v PBO	0.15		0.57		
		95% ci	0.02; 1.21		0.17; 1.93		
			ABL	PBO	TER		Trial 003 (Safety population ex sites 131/132)
With TEAEs		%	90.3	88.4	89.5		
With Serious TEAE		%	8.9	9.5	9.3		
With AE	discontinuation	%	9.8	6.1	6.9		
Orthostatic hypotension	with AESI	%	28.4	14.4	19.8		
	discontinuation	%	3.6	0.9	1.7		
Palpitations		%	5.6	0.4	1.7		
Increase HR	>20 bpm	%	19.7	3.2	10.9		
Increase HR	>30 bpm	%	3.9	0	1.2		
Increase HR	>40 bpm	%	0.7	0	0		
Nausea		%	8.5	3.1	5.4		
Dizziness		%	11.1	7.1	8.2		
Headache		%	8.5	5.8	7.1		
Neutralising antibodies		%	~30	N/A	N/A		

Abbreviations: n.s. – not significant; ABL – abaloparatide; TER – teriparatide; RR – absolute risk reduction; RRR – relative risk reduction; vs. – versus; PBO – placebo; 95% CI – 95% confidence intervals; p – p-value; mITT – modified intent to treat (randomised patients with both pre-treatment and post-baseline evaluable radiologic assessments); ITT - intent to treat (all patients randomised); K-M – Kaplan-Meier; HR - Hazard Ratio; SOC – system organ class; N/A – not applicable; discon – discontinuation; n – number of patients; MACE – major adverse cardiovascular event;
Regarding strengths and weaknesses of the data see sections "Overall conclusion on grounds for re-examination" and B/R section.

6.7. Benefit-risk assessment and discussion

6.7.1. 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 (approximately 60%) asymptomatic. 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 in particular, 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, adequately

powered study, as those fractures, in particular of the hip, are of considerable clinical relevance. Abaloparatide has only been studied in a single pivotal trial with non-vertebral fractures as key secondary endpoint. In this single pivotal trial no statistically significant effect of abaloparatide on non-vertebral fractures has been established.

Other endpoints investigated, e.g. BMD and serum bone markers, support the primary finding of a reduction in the risk of osteoporotic fractures and by showing the same trend of an advantage of abaloparatide over placebo. However, these endpoints are surrogates and they do not establish effects in their own right or allow a valid conclusion on efficacy on an advantage of abaloparatide over teriparatide as claimed by the Applicant.

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 abaloparatide treated patients.

The entry criteria in study BA058-05-003 were restrictive which impacts the generalisability and external validity of the pivotal study. The general elderly osteoporosis population has many concomitant chronic diseases and medications. The marked increase in heart rate is of concern as concomitant cardiovascular diseases are expected to be more common than in the population included in the pivotal trial. The increase in heart rate was more pronounced in patients treated with abaloparatide compared with teriparatide.

An increase in heart rate of the magnitude seen in the clinical trials with abaloparatide may have clinical consequences in vulnerable patients. The pivotal study had several exclusion criteria based on ECG findings and medical history of cardiovascular disease. 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.

To mitigate these risks, the applicant proposed to monitor patients in clinical practice 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 in attendance although this does not prevent events of increased heart rate or hypotension during the later course of the treatment. A contra-indication was proposed for patients with tachyarrhythmia, recent myocardial infarction, unstable angina, significant valvular stenosis, decompensated heart failure or uncontrolled and severe orthostatic hypertension.

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. Information provided through the SmPC in sections 4.3, 4.4, 4.8, and 5.1, as well as the PL were proposed.

The frequency of the development of anti-abaloparatide antibodies and neutralising antibodies is very high. The limited available data do not show an effect of antibodies to abaloparatide on efficacy or safety.

The incidence of hypercalcaemia adverse events is lower in patients treated with abaloparatide than teriparatide, but organ calcification has been identified in preclinical trials. Thus, it can currently not be excluded that abaloparatide might induce organ calcification and e.g. impair renal function.

6.7.2. 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 the study was not designed for direct in-study comparison with teriparatide.

All available data indicate a dose-related increase in heart rate due to abaloparatide. The likely mechanism of the marked increase in heart rate associated with abaloparatide is related to peripheral vasodilation and a direct chronotropic effect on cardiomyocytes as indicated by non-clinical studies. The significance of this finding is as yet unknown, and was therefore of major concern to CHMP.

Marked post-injection increases in heart rate with abaloparatide were observed in healthy volunteers in the thorough QT-study with a mean increase of 14.6 bpm 15 min after the therapeutic dose of 80 µg. Significant increases in mean heart rate persisted for at least 12 hours. This is of concern, particularly as abaloparatide was intended to be given once daily as a subcutaneous injection.

In the pivotal study, the 1 hour post-dose heart rate increased more in abaloparatide treated patients compared to teriparatide. Therefore, safety data from clinical studies and post-marketing experience from teriparatide cannot be extrapolated to abaloparatide. In the pivotal study, for example, 20% of patients treated with abaloparatide experienced an increase in heart rate by >20 bpm at any time point versus 11% of patients treated with teriparatide. Patients that experienced highest increases in HR by >40 bpm (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 more early (≤1 month) drop-outs in the abaloparatide-arm (7.9%) compared to teriparatide (3.9%) or placebo (5.2%).

Risk minimisation measures proposed by the applicant with contraindications in patients with pre-existing cardiac disease may reduce the CV risk associated with heart rate increases. However, thorough screening for undiagnosed conditions (e.g. with echocardiography) for these conditions appears unlikely in a general osteoporosis population. The applicant proposed a Post-Authorisation Safety Study (PASS) to further characterise the cardiovascular risk profile among new users of abaloparatide as well as a Drug Utilisation Study (DUS) to describe prescription patterns, assess whether the medicine would be prescribed according to the Product Information and the risk minimisation measures (Contra-Indications) would be adhered to. The proposed PASS has limitations compared to a randomised, prospective trial, such as lack of full characterisation at baseline of the included patients and potential confounding by indication. Moreover, the foreseen accrual of patients in the EU was considered low in comparison to US patients, considering likely differences in usage and population, with a rather long timeline to complete these studies.

In Europe as well as in the US, guidelines recommend anti-resorptive agents such as bisphosphonates as the first-line osteoporosis treatment. Anabolic agents, such as abaloparatide or teriparatide, could be used if osteoporosis is progressive despite therapy, e.g. manifested by a new fracture. This second line osteoporosis population was not included in the pivotal trial which included a placebo-control arm; only about 1% of subjects listed bisphosphonates as a prior medication whereas US real-world data show that 36% of teriparatide users used anti-osteoporosis medication beyond calcium/vitamin D

before treatment. This second line osteoporosis population is expected to be frail with much concomitant cardiovascular morbidity. However, many of these patients are excluded by the contraindication that was introduced. In light of overall increased heart rate, increase in related adverse events compared to teriparatide and the unknown impact thereof on the risk for cardiovascular events, a reasonable target population for abaloparatide in clinical practice could not be identified.

As a single pivotal trial of a new osteoporosis agent the size of the study was small. Only relatively healthy ambulatory postmenopausal woman, screened for being free from any significant cardiac disturbances, were included and the overall number of serious cardiovascular events during the 18 month study period was low. Therefore, this study is not considered sufficient in order to assess the risk for adverse cardiovascular outcomes associated with heart rate increases in a real-life osteoporosis population generally more vulnerable regarding cardiovascular risk.

Overall, this application for a new osteoporosis agent is not considered to be in accordance with EMA points to consider on application with one pivotal study with "particularly compelling results with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency."

Considering the above mentioned limitations and the potential risks associated with the increase in heart rate, efficacy is not considered demonstrated to an extent to outweigh those risks in the proposed target population.

A positive benefit-risk balance for the proposed target population has therefore not been established for abaloparatide.

6.8. Conclusions

The overall B/R of Eladynos is negative.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product

Whereas

- The efficacy of Eladynos (abaloparatide), for the treatment of osteoporosis, was supported by one pivotal study only. This study failed to demonstrate a statistically significant effect on non-vertebral fractures vs. placebo which is a requirement outlined in the "Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis". In the pivotal study, there were serious GCP related findings and data from two sites had to be excluded which reduced the size of the study population.
- Marked post-injection increases in heart rate 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. In the pivotal phase III study, 1 hour post-dose heart rate increased more in abaloparatide treated patients compared to both placebo and teriparatide

with 42% of patients treated with abaloparatide experiencing an increase in heart rate of >15 bpm at any time.

- No increase in major adverse cardiovascular events in patients treated with abaloparatide was noted compared to comparators. However, more common adverse events such as palpitations, tachycardia, dizziness, nausea and discontinuations were reported more frequently in patients treated with abaloparatide compared to both teriparatide and placebo which may be related to the documented effect of abaloparatide on heart rate. With respect to serious cardiovascular events, the size and other limitations of the study did not allow to draw definitive conclusions on such events. In addition, patients with significant pre-existing cardiovascular disease, being at a higher risk of cardiovascular events, were excluded from the study. Therefore, this study is not considered sufficient in order to assess risk for adverse cardiovascular outcomes associated with heart rate increase in a generally more vulnerable real-life osteoporosis population.

- Risk minimisation measures including contraindications in patients with pre-existing cardiac disease as well as monitoring of patients at risk were considered by CHMP. However, in light of an increased baseline risk of cardiovascular events in the postmenopausal osteoporosis patient population, a reasonable target population for abaloparatide in clinical practice could not be identified.

Due to the aforementioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, and risk management plan cannot be agreed at this stage.

Divergent positions to the majority recommendation are appended to this report.

Appendix

1. Divergent position to the majority recommendation for initial opinion, dated 22 March 2018

Divergent position – Eladynos (EMEA/H/C/004157)

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the refusal of the granting of a Marketing Authorisation for Eladynos.

The reasons for the divergent opinion were as follows:

From the totality of information, including both the data from the pivotal study and knowledge of the effects of teriparatide (same molecule class, same mode of action), we conclude that efficacy of abaloparatide has been sufficiently demonstrated in the applied indication. In particular, there is no 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.

As regards safety we are reassured by the discussion of the experts at the ad hoc expert group convened on request of the CHMP, including their view on the different relevance of a permanent versus a temporary increase in heart rate and the lack of a cardiovascular event signal in the pivotal trial. Although the increase in heart rate with teriparatide is less pronounced than with abaloparatide, the large number of patients having been exposed to teriparatide is expected to have resulted in relevant numbers of patients with a comparably high increase in heart rate. Therefore, further reassurance is seen in the absence of a cardiovascular event signal for teriparatide. We therefore conclude that the observed differences in effects on the cardiovascular system compared to teriparatide could have been addressed by adequate information and restrictions given in the Product Information.

London, 22 March 2018

Andrea Laslop

Jan Mueller-Berghaus

Agnes Gyurasics

Mila Vlaskovska

Harald Enzmann

Hrefna Gudmundsdottir

2. Divergent position to the majority recommendation for final opinion following re-examination, dated 26 July 2018

Divergent position – Eladynos (EMEA/H/C/004157)

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the refusal of the granting of a Marketing Authorisation for Eladynos.

The reasons for the divergent opinion were as follows:

From the totality of information, including both the data from the pivotal study and knowledge of the effects of teriparatide (same molecule class, same mode of action), which was also a comparator in the pivotal trial, we conclude that efficacy of abaloparatide has been sufficiently demonstrated in the applied indication. In particular, there is no 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.

As regards safety we are reassured by the discussion of the experts at the ad hoc expert group convened on request of the CHMP, including their view on the mechanism of the heart rate increase, different relevance of a permanent versus a temporary increase in heart rate and the lack of a cardiovascular event signal in the pivotal trial. Although the increase in heart rate with teriparatide is less pronounced than with abaloparatide, the large number of patients having been exposed to teriparatide is expected to have resulted in relevant numbers of patients with a comparably high increase in heart rate. Therefore, further reassurance is seen in the absence of a cardiovascular event signal for teriparatide. We therefore conclude that the observed differences in effects on the cardiovascular system compared to teriparatide could have been addressed by adequate information and restrictions given in the Product Information.

London, 26 July 2018

Andrea Laslop

Bart Van Der Schueren

Blanka Hirschlerova

Harald Enzmann

Jan Mueller-Berghaus

Koenraad Norga

Mila Vlaskovska

Nevenka Trsinar

Romaldas Maciulaitis

Svein Rune Andersen

Tomas Boran