EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2020
EMA/CHMP/379175/2020
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Livogiva

International non-proprietary name: teriparatide

Procedure No. EMEA/H/C/005087/0000

## Note

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

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# Administrative information

| | |
|---|---|
| Name of the medicinal product: | Livogiva |
| Applicant: | Theramex Ireland Limited<br>3rd Floor, Kilmore House<br>Park Lane, Spencer Dock<br>Dublin 1<br>D01 YE64<br>IRELAND |
| Active substance: | Teriparatide |
| International Non-proprietary Name/Common Name: | teriparatide |
| Pharmaco-therapeutic group (ATC Code): | parathyroid hormones and analogues, parathyroid hormones and analogues (H05AA02) |
| Therapeutic indication(s): | Livogiva is indicated in adults.<br><br>Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture (see section 5.1). In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures have been demonstrated.<br><br>Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture (see section 5.1). |
| Pharmaceutical form(s): | Solution for injection |
| Strength(s): | 20 µg/80 µl |
| Route(s) of administration: | Subcutaneous use |
| Packaging: | cartridge (glass) in a pre-filled pen |
| Package size(s): | 1 pre-filled pen and 3 pre-filled pens |

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# List of abbreviations

| | |
|---|---|
| aFMEA | Application Failure Mode and Effects Analysis |
| µL | Microlitre |
| ADA | Anti-Drug Antibody |
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area under the concentration-time curve |
| AUC%extrap | Percent of AUC0-inf extrapolated |
| AUC0-inf | Area under the concentration-time curve from time 0 extrapolated to infinity |
| AUC0-last | Area under the concentration-time curve from time 0 to the time of the last observed/measured non-zero concentration |
| BE | Bioequivalence |
| BMC | Bone Mineral Content |
| BMD | Bone Mineral Density |
| BSAP | Bone-Specific Alkaline Phosphatase |
| BTM | Bone turnover markers |
| Ca2+ | Calcium |
| cAMP | 3,5-cyclic adenosine monophosphate |
| CI | Confidence Interval |
| CL/F | Apparent total clearance after extravascular administration |
| Cmax | Maximum observed concentration |
| CP | Centralised Procedure |
| CrCl | Creatinine clearance |
| CRF | Case report form |
| CTD | Common Technical Document |
| CTX | C-terminal crosslinked telopeptides of type I collagen |
| CV | Coefficient of Variation |
| Da | Dalton |
| ECG | Electrocardiogram |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| FSH | Follicle-stimulating hormone |
| FTIR | Fourier-transform infrared spectroscopy |
| GLP | Good Laboratory Practice |
| GM | Geometric Mean |
| GMR | Geometric Mean Ratio |
| hr | Hour |
| HRT | Hormonal Replacement Therapy |
| IVR | Insufficient Volume for Reassay |
| K3EDTA | Tripotassium Ethylene Diamine Tetra Acetic Acid |
| LC-MS | Liquid chromatography coupled with mass spectrometry |
| LLOQ | Lower Limit of Quantitation |
| LSM | Least-Squares Means |
| mcg | Micrograms |
| Met | Methionine |
| Met+O(18) | Teriparatide oxidised at Met 18 |
| Met+O(8) | Teriparatide oxidised at Met 8 |
| Met+O(8,18) | Teriparatide oxidised at both Met 8 and Met 18 |
| mg | Milligram |

| | |
|---|---|
| mL | Millilitres |
| mmol | Millimole |
| OVCF | Osteoporotic Vertebral Compression Fractures |
| ng | Nanograms |
| NLT | Not less than |
| NMR | Nuclear Magnetic Resonance. |
| NMT | Not more than |
| NOEL | No observed effect level |
| OC | Osteocalcin |
| OVX | Ovariectomy |
| P fluorescens | Pseudomonas fluorescens |
| P1NP | Procollagen type I N terminal propeptide |
| Ph.Eur. | European Pharmacopeia |
| pg | Picogram |
| PICP | Procollagen I carboxy-terminal propeptide |
| PMO | Postmenopausal osteoporosis |
| ppm | Parts per million |
| pQCT | Peripheral quantitative computed tomography |
| PTH | Parathyroid hormone |
| PTHR1 | Parathyroid Hormone-Receptor-1 |
| QD | Once daily |
| rDNA | Recombinant DNA |
| RLD | Reference listed drug |
| rhPTH [1-34] | 34-amino acid recombinant analog of human PTH |
| RP-HPLC | Reverse phase high performance liquid chromatography |
| SA | Scientific Advice |
| SAE | Serious Adverse Event |
| SC | Subcutaneous |
| SD | Standard Deviation |
| SE-HPLC | Size Exclusion-High Performance Liquid Chromatography |
| SmPC | Summary of Product Characteristics |
| SVD | Sample Volume Depleted |
| T1/2 | Apparent terminal elimination half-life |
| TEAE | Treatment-Emergent Adverse Event |
| TK | Toxicokinetics |
| Tmax | Time of maximum observed concentration |
| TRACP 5b | Tartrate-resistant acid phosphatase isoform 5b |
| USP | United States Pharmacopeia |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Theramex Ireland Limited submitted on 6 May 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Livogiva, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Livogiva is indicated in adults.

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture (see section 5.1). In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures have been demonstrated.

Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture (see section 5.1).

**The legal basis for this application refers to:**

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Forsteo, 20 µg/80 µl - Solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 10-06-2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/247/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Forsteo, 20 µg/80 µl - Solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 10-06-2003
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/247/001-002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Forsteo, 20 µg/80 µl - Solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 10-06-2003

- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/03/247/001-002

### *Information on Paediatric requirements*

Not applicable

### *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.

### *Scientific advice*

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

| Date | Reference | SAWP co-ordinators |
|---|---|---|
| 13 October 2016 | EMEA/H/SA/3420/1/2016/III | Dr Peter Mol, Dr Sheila Killalea |

The scientific advice pertained to the following quality, pre-clinical and clinical aspects:

- Adequacy of the proposed strategy for physicochemical characterisation to demonstrate biosimilarity.
- Appropriateness of the proposed approach to demonstrate physical and functional equivalence of delivery devices.
- Acceptability not to perform *in vivo* animal model studies and toxicological studies if similarity can be demonstrated by analytical and *in vitro* functional data.
- Acceptability of a phase 1 healthy volunteer bioequivalence study performed with US-licensed Forteo if similarity between EU-licensed Forsteo and US-licensed Forteo is supported by 3-way analytical bridging data.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: Milena Stain Co-Rapporteur: Daniela Melchiorri

| | |
|---|---|
| The application was received by the EMA on | 6 May 2019 |
| The procedure started on | 23 May 2019 |

| | |
|---|---|
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 7 August 2019 |
| The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on | 12 August 2019 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 5 September 2019 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 19 September 2019 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 13 December 2019 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 3 February 2020 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 12 February 2020 |
| The CHMP agreed on a list of outstanding issues to be sent to the applicant on | 27 February 2020 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 28 April 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 13 May 2020 |
| The CHMP agreed on a list of outstanding issues to be sent to the applicant on | 28 May 2020 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 2 June 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 10 June 2020 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Livogiva on | 25 June 2020 |

# 2. Scientific discussion

## *2.1. Problem statement*

Osteoporosis, as defined by World Health Organization, is a systemic disease of the skeleton characterised by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue with consequent increased bone fragility that predisposes to fracture risk. Due to the silent progression of bone structure degeneration, osteoporosis diagnosis often follows a painful fracture event.

The diagnosis of osteoporosis is established by means of bone densitometry or by the presence of a fragility fracture. Any bone may be affected; although the skeletal sites most prone to fracture include proximal femur (hip), vertebrae (spine), and distal forearm (wrist). Osteoporotic fractures lead to pain and occasional disability. More importantly, they increase mortality.

Osteoporosis is commonly experienced in postmenopausal women due to declining oestrogen levels. However, osteoporosis can also occur in both sexes as a side effect of prolonged treatment with glucocorticoid medications. Glucocorticoid-induced osteoporosis may be responsible for up to 20% of all osteoporosis cases. Fractures, primarily hip fractures, decrease a patient's quality of life by increasing pain, medical costs, morbidity, and mortality.

In 27 European Union (EU) countries, the prevalence of osteoporosis was estimated to be 6.6 % and 22.1 % in men and women, respectively, aged 50 years or more and 5.5 % in the general population. According to the National (US) Osteoporosis Foundation, up to 25% of men over the age of 50 years will experience a fracture due to osteoporosis, with approximately 80,000 suffering from a broken hip.

Current pharmacological options for the treatment of osteoporosis in Europe include anti-resorptive agents (e.g. bisphosphonates, calcitonin and raloxifene), which reduce osteoclastic activity, strontium ranelate, which reduces osteoclastic activity and may have anabolic properties as well, and parathyroid hormone (PTH) analogues including teriparatide, which stimulate bone turnover with a positive bone balance thereby increasing bone mass. In addition, denosumab, an anti RANKL antibody that reduces osteoclast activity, is available. Romosozumab, an antisclerostin antibody, has been recently authorised in the US.

### *About the product*

Teriparatide, PTH (1-34) is the international non-proprietary name (INN) for the biologically active 34-amino acid N-terminal fragment of the 84-amino acid native parathyroid hormone, PTH (1-84). Synthetic and genetically engineered versions of teriparatide both exist, sharing identical affinity for the parathyroid hormone (PTH) surface receptors as well as possessing the same biological activity.

The active substance in Livogiva biosimilar, teriparatide, is produced in *Pseudomonas fluorescens* using recombinant DNA technology.

Recombinant teriparatide contains no amino acid substitutions or chemical modifications and differs from the synthetic peptide only in its method of production and purification. Recombinant teriparatide contains no glycosylation or other post-translational modifications.

Endogenous PTH (1-84) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Physiological actions of PTH include stimulation of bone formation by direct effects on bone forming cells (osteoblasts) indirectly increasing the intestinal absorption of calcium and increasing the tubular re-absorption of calcium and excretion of phosphate by the kidney.

The molecular effects of teriparatide are mediated by the parathyroid hormone-receptor-1 (PTH-R1), a G–protein-dependent membrane receptor expressed by osteoblasts and renal tubular cells. Teriparatide has similar affinity for the PTH-R1 as PTH (1–84). PTH signalling results in the activation of genes important for the functions of mature osteoblasts, increases in osteoblast number, decreases in the apoptotic rate of osteoblastic cells, and increases in their bone-forming activity. The net result is an increase in the number of active osteoblasts, a decrease in osteoblast apoptosis and probably a recruitment of bone lining cells as newly formed osteoblasts, which are followed by increasing bone strength, mass and diameter and bone structural integrity, as well as increasing levels of biochemical markers of bone turnover (both formation and resorption markers) in serum and urine (Blick et al., 2008).

Pharmacotherapeutic group: Calcium homeostasis, parathyroid hormones and analogues, ATC code: H05AA02

The drug product of Livogiva is a sterile, aqueous, isotonic solution for subcutaneous injection pre-filled in a 3 mL glass cartridge assembled to the pen injector. The cartridge is non-replaceable (integral drug device combination – DDC). The solution for injection is delivered from the manually operated fixed-dose pen injector that delivers 20 micrograms teriparatide per 80 microliters dose. Each pen injector is intended to deliver 28 doses (equivalent to 2.24mL of solution). The product is administered by using commercially available needles.

The recommended dose is 20 µg administered once daily by subcutaneous (SC) injection in the thigh or abdomen. The maximum total duration of treatment with teriparatide should not exceed 24 months. The 24-month course of teriparatide should not be repeated over a patient's lifetime.

In this assessment report, the following names are used for the applied product: Livogiva, PF708 and Pfenex teriparatide.

*Reference medicinal product(s):*

The aim of pharmaceutical development was to develop a drug product as a biosimilar to the reference medicinal product Forsteo, 20 micrograms / 80 mL solution for injection in pre-filled pen, marketed in Europe by Eli Lilly and Company Limited. As part of the global product development approach, the finished product was also developed to be equivalent to the reference listed drug (RLD) Forteo 20 micrograms / 80 mL solution for injection in pre-filled pen, marketed in the United States by Lilly USA.

The entire non-clinical and clinical dossier is based on comparability to the RMP Forteo (US reference medicinal product) and the quality analytical exercise establishes the bridge between US RMP Forteo, EU RMP Forsteo and PF708.

Both Forteo and Forsteo are produced in *E. coli*, while the active substance in Livogiva is produced in Pseudomonas fluorescens.

## *2.2. Quality aspects*

### 2.2.1. Introduction

Livogiva has been developed as a biosimilar to Forsteo. The finished product supplied as a sterile, aqueous, isotonic solution for subcutaneous injection. One pre-filled pen of 2.7 mL contains 675 micrograms of teriparatide as active substance (corresponding to 250 micrograms per mL). Each dose of 80 microliters contains 20 micrograms of teriparatide. Other ingredients are: glacial acetic acid, sodium acetate trihydrate, mannitol, metacresol and water for injections (WFI).

The product is available in 2.7 mL solution in cartridge (siliconised Type I glass) sealed at one end with a bromobutyl rubber plunger and at the other end crimp-sealed with a bi-layer combi-seal (polyisoprene/bromobutyl rubber laminate with aluminium over cap). The cartridge is an integral and non-replaceable part of the pen injector, therefore representing an integral DDC (Drug Device Combination).

## 2.2.2. Active Substance

**General Information**

The active substance, teriparatide (INN) is a recombinant 1-34 N-terminal fragment of endogenous human parathyroid hormone, rhPTH(1-34) produced in *Pseudomonas fluorescens* using recombinant DNA technology and is identical to the 34 N-terminal amino acid sequence of endogenous human parathyroid hormone.

The molecular weight of teriparatide is approximately 4117.8 Dalton ($C_{181}H_{291}N_{55}O_{51}S_2$). The amino acid sequence is as follows:

H-Ser Val Ser Glu Ile Gln Leu Met His Asn Leu Gly Lys His Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val His Asn Phe-OH

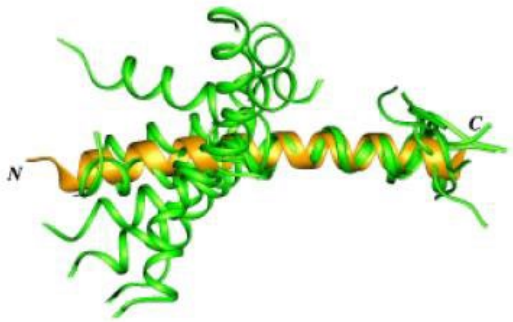
Binding of PTH to PTH-specific cell-surface receptor (PTHR1) mediates the biological action of PTH. The 84-amino acid parathyroid hormone (PTH) stimulates the bone formation by direct effects on bone-forming cells (osteoblasts) indirectly increasing the intestinal absorption of calcium and increasing the tubular re-absorption of calcium and excretion of phosphate by the kidney.

The amino terminus is critical for G-protein linked stimulation of adenylate cyclase that catalyses the formation of second messengers such as cAMP that activates the desired biological effects by phosphorylation of critical intracellular proteins.

*Higher-order structure*

The overall structure of crystalline hPTH (1-34) is a slightly bent helix. In solution, PTH (1-34) forms a N-terminal helix and a C-terminal helix connected be a highly flexible region, as determined by NMR. The extended helical conformation observed in the crystal structure may well represent the active receptor-binding conformation of hPTH (1-34). Figure 1 shows superimposition of the crystal structure of hPTH (1-34) with NMR structures of hPTH(1-34) in solution. Teriparatide contains no glycosylation or other post-translational modifications.

**Figure 1. Superimposition of crystal structure of hPTH (1-34) (gold) with NMR structures of hPTH(1-34) in solution (green).**



The biological activity of teriparatide was determined using a cell-based assay that measures the ability of teriparatide to induce release of cAMP after binding and activation of G-protein coupled receptor PTH-R1 *in vitro* in a rat osteosarcoma cell line (UMR-106, ATCC).

## Manufacture, process controls and characterisation

Manufacturers

GMP compliance for commercial manufacturing sites for active substance was demonstrated.

**Manufacturing process**

The manufacturing process involves the following steps (upstream, recovery and capture, downstream purification):

Upstream process: including vial thaw, shake flask expansion and the fermenter production of the fusion protein and the cell paste stored frozen until further processing.

Recovery and capture: including cell harvest via centrifugation, cell lysis via homogenisation, capture via chelating Sepharose fast flow chromatography and the fusion protein cleavage.

Downstream purification: including various chromatographic steps.

The active substance is filled in bottles and stored.

**Control of materials**

The quality of the materials used in the manufacture of teriparatide active substance is controlled by suitable specifications. Supplier tests performed in line with the in-house specifications for non-compendial raw materials have been provided and are acceptable. Where applicable, compendial tests are used and specifications followed when materials are tested. Information about specifications of the chromatography resins used during the manufacturing process were submitted. Representative analysis certificates for non-compendial raw materials were also provided.

*Expression system:*

Teriparatide is expressed in a recombinant *Pseudomonas fluorescens* expression strain PS708-0336.

Derivatives of a natural isolate of *P. fluorescens* biovar I, designated MB101 were used, which were obtained from lettuce leaves in 1984 by Mycogen Corporation. MB101 is a gram-negative, obligate aerobe that is nonpathogenic for plants and mammals. This species is ubiquitous in soil, water, and plant environments.

The identity of strain MB101 has been verified independently. Phenotypic analyses of strain MB101 involved a variety of biochemical and microbiological characterisations. Genotypic analyses were performed. Sequence analyses corroborate the findings of the phenotypic analyses.

*Cell bank system:*

A standard two-tiered cell banking system consisting of Master Cell Bank (MCB) and Working Cell Bank (WCB) was created and tested under GMP conditions. The MCB was established from a Research cell bank (RCB) of *P. fluorescens* expression strain PS708-0336. Characterisation of the RCB was performed.

Adequate information on the cell bank establishment, storage (WCB at two separate sites), characterisation, stability data and on the establishment of a new WCB were provided. Genetic stability

was shown by characterising an end of production cell line (EPC). The full DNA sequence of the strain PS708-0336 construct was provided.

Control of critical steps and intermediates

The critical steps for teriparatide active substance production process were established through process development and process characterisation. The control strategy is based on a risk evaluation including process parameters as well as critical quality attributes (CQA). A risk assessment was performed to classify and justify the parameters used in the upstream and downstream manufacturing steps of Teriparatide active substance. For every upstream process parameter a PAR (proven acceptable range) was established.

A downstream process risk assessment was performed to classify and justify the parameters used in the downstream manufacturing steps of teriparatide active substance. Critical raw materials, used in the downstream manufacturing process, were further defined.

Critical process parameters (CPP) and in-process controls (IPC) containing respective acceptance criteria were defined for the most manufacturing steps. IPCs are suitable and adequate to control process performance.

The PARs were justified: the operating range that was used in GMP production (NOR) was narrower and provided the most consistent results even if success could be achieved outside the NOR and within the PAR. The following equation shows the relationship between PAR, NOR and the setpoint: PAR ≥ NOR ≥ Setpoint. This justification can be followed.

A risk assessment for identification of material attributes and process parameters with the potential for having an effect on CQAs were provided, as required by ICH Q11.

A summary of the risk assessment performed on the manufacturing process of the active substance in order to classify the criticality of the process parameters and the raw materials and to identify the critical process parameters and raw materials that may impact the critical quality attributes (CQAs) of the active substance, was provided. The development of the used control strategy was sufficiently explained. The provided risk assessments include a criticality rank of the quality attributes. This issue refers to the active substance as well as finished product.

*Process Characterisation*

Process characterisation was performed on qualified scaled-down models of each of the unit operations of the active substance manufacturing process. The purpose of process characterisation was to increase process knowledge and evaluate process robustness.

**Process Validation and Evaluation**

The information for the process validation seems sufficient. Process validation on an adequate number of consecutive active substance commercial-scale batches has been performed. A summary of the results of the individual studies of the process steps investigated where provided, which confirm that the manufacturing process of teriparatide active substance solution seems to be suitable for its intended use. The CPPs and IPCs met the acceptance criteria demonstrating a consistent process performance, repeatable execution of manufacturing operations and the ability to meet final bulk active substance CQAs.

Studies to evaluate column resin cleaning/re-use have been sufficiently performed. Information about the life cycle of the different column types used in the manufacturing process were provided.

A risk assessment in line with guideline ICH Q9 was performed in order to determine the teriparatide active substance process steps to examine for potential extractables and leachables (E&L). Single-use plastic components used at each step in the process were analysed for their materials of construction, time of product contact, temperature at which the contact occurs, nature of the process stream in contact with the material and the step proximity to the final product. The buffers were also examined by these same criteria.

Sufficient investigations for leachables and extractables for the container/closure system and all the single-use production equipment were executed. Storage of the columns for the manufacturing process were validated.

Manufacturing process development

The active substance manufacturing process development was initiated at a development laboratory, and the process was subsequently transferred to the clinical lot manufacturer and subsequently to the commercial active substance manufacturer.

The development of the active substance up to transfer to the commercial manufacturing facility has been described and adequate process validation was conducted in the new site.

A comparison of active substance manufacturing sites for clinical and commercial lots was done and a similarity study of finished product batches manufactured with active substance batches manufactured at either site was provided. Data from the finished product batches where the active substance batches were manufactured at the different sites are acceptable. Where analytical methods were different between buildings, then evidence of bridging was provided. Sufficient information was provided.

**Characterisation**

Elucidation of structure and other characteristics

Several batches were used for the characterisation of teriparatide. Data for several finished product batches manufactured with different active substance batches manufactured were provided.

Impurities

Process- and product-related impurities were sufficiently identified and quantified by state-of-the-art analytical methods including for oxidised and charged variants and high molecular weight impurities.

Process-related impurities were also characterised and details on a risk and safety assessment provided. Host-cell proteins are quantified and justified.

Teriparatide is expressed in *P. fluorescens* as fusion protein. Potential impurities were discussed and adequately justified compared to the reference product.

## Specification, analytical procedures, reference standards, batch analysis, and container closure

The active substance specifications cover tests for identification, appearance, pH, bioassay, impurities, and microbial contamination.

The active substance specification acceptance limits have been adequately set. Acceptable justifications for specifications were provided for all product parameters tested.

The applicant is recommended to re-consider the active substance specification for one test when further stability data is available and adapt the specification accordingly if results show that the limits could be tightened (Recommendation).

Analytical methods

Teriparatide active substance is tested and controlled with verified current compendial and validated non-compendial analytical procedures. The methods used are adequate for routine control of teriparatide active substance.

Batch analysis

Batch analysis data has been provided on several batches of teriparatide active substance, including from the commercial process. Results of all tested active substance batches were in line with the specifications of the active substance.

Reference standard

The applicant justified the proposed strategy for the reference standard use.

Container closure system

Recombinant teriparatide active substance is filled in polyethylene terephthalate Glycol (PETG) square bottles. It is closed with tamper proof high-density polyethylene (HDPE) screw caps.

An extractable substances study was conducted with the bottle. No issues with regard to toxic substances were identified. The information provided about the container closure system is sufficient.

### Stability

Teriparatide active substance stability has been studied under long-term storage conditions in line with ICH. All stability results obtained so far are within the specified ranges or limits for all batches in the long-term stability study.

The applicant is recommended to continue the ongoing stability studies on active substance process validation batches and make available the stability data generated. The applicant also commits to immediately notify OOS results, if these occur (Recommendation).

Several active substance batches were also stored under accelerated conditions acceptance criteria. Submitted results of the tested parameters are within the defined specifications and no trends were observed.

Based on the stability results the claimed shelf life for the active substance is acceptable.

## 2.2.3. Finished Medicinal Product

The documentation for finished product is divided into:

a) Finished product cartridge (representing the injection solution filled in the primary container/closure system (cartridge))

b) Finished product pen injector (representing the filled cartridge assembled to the pen injector)

The finished product pen injector is defined to be the finished medicinal product.

## Description of the product and Pharmaceutical Development

### Description of the product

The finished product is a sterile, aqueous, isotonic solution for subcutaneous injection. It is supplied in a cartridge (siliconised Type I glass) in a pre-filled pen containing teriparatide as active substance. Other excipients are: glacial acetic acid, sodium acetate trihydrate, mannitol, metacresol and water for injections (WFI).

The cartridge (siliconised Type I glass) is sealed at one end with a bromobutyl rubber plunger and at the other end crimp-sealed with a bi-layer combi-seal (polyisoprene/ bromobutyl rubber laminate with aluminium over cap). The cartridges are an integral and non-replaceable part of the pen injector.

The solution for injection is delivered from a manually operated, fixed-dose pen injector that delivers 20 micrograms teriparatide per 80 microliters per dose containing 20 micrograms of teriparatide. Each pre-filled pen contains 250 micrograms per mL of teriparatide.

Each pen injector is intended to be used to deliver 28 doses. An overfill is included and is justified. The overfill ensures the delivery of at least 28 doses as per intended use. Overages are not applicable.

The finished product neither contains ingredients of animal or human origin nor novel excipients.

With regard to the pen injector, the device does not incorporate tissues of animal origin (refer to assessment with regard to Annex I of Medical device directive Section 3.2.R). Therefore, the requirement of Draft Guideline EMA/CHMP/QWP/BWP/259165/2019 to provide a statement on adventitious agents related to the manufacture of the pen injector is covered.

### Pharmaceutical development

#### A) Finished product cartridge:

*Formulation development*

The formulation development was based on the RMPs (reference medicinal products) Forsteo (EU) and Forteo (US). A QTPP (Quality Target Product Profile) as a prospective summary of the primary attributes guided the formulation development studies.

The formulation process was transferred to the finished product manufacturer where engineering runs were performed to further refine and optimise the formulation.

*Manufacturing process development*

Manufacturing process development refers to the development of the finished product cartridge and is divided into the fill process development and the cartridge manufacturing process for registration batches.

Finished product fill process development was illustrated in the dossier by tabling all batches manufactured (placebo, engineering, registration batches, RMP comparability batches, engineering fill study).

A flow chart presenting the manufacturing process used for manufacture of registration batches including in-process parameters has been provided. Bioburden reduction is achieved before filling the cartridge and a final sterile filtration.

Key manufacturing process steps and parameters for the finished product cartridge have remained consistent from the manufacture of the clinical and stability registration batches to the proposed commercial process.

Subsequent optimisation activities were performed but are not considered to have any impact of clinical relevance.

Identification and control as well as risk ranking of CQAs was sufficiently described.

A table clearly assigning active substance batches to finished product batches (cartridge and pen) already manufactured thereof was provided.

*Microbiological attributes*

The preservative metacresol is added to the formulation in the same amount, which is used for the RMPs, and an anti-microbial effectiveness test was performed. Results indicate sufficient antimicrobial preservative effectiveness of metacresol at and below the nominal concentration.

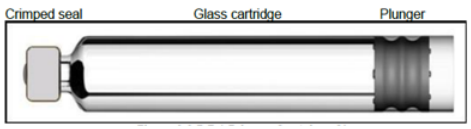
No hold times are applicable to the process, since continuous filling is performed. Current data do not show loss of metacresol during filling process.

An anti-microbial effectiveness study according to requirements of Ph. Eur. 5.1.3 for the finished product with metacresol concentrations near or below the lower specification limit of metacresol in the finished product was performed and revealed acceptable results.

*Description of Container/Closure:*

The siliconised cartridge is made of clear type I glass, closed at one end by a combination seal and on the other end by a bromobutyl rubber plunger and represents the primary container/closure system.

**Figure 2. Primary container closure**




For the glass container compliance is confirmed with Ph. Eur. 3.2.1. "Glass containers for pharmaceutical use", for plunger and combination seal compliance is also confirmed with Ph. Eur. 3.2.9. "Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze-dried powders".

The containers proposed for routine storage are identical to those that have been used in stability studies supporting the shelf life.

With regard to potential formation of silicone aggregates, it was clarified that routine tests would capture any aggregates that might result from the interaction between product and released silicone droplets. GMP batches were essentially free of particular matter and high molecular weight impurities. Stability data do not show any indication or release of silicone oil/formation of aggregates.

*Compatibility:*

The finished product solution contacts only the finished product cartridge and the injection needle. Compatibility was investigated by performing extractable/leachable studies, results remained below the analytical threshold.

## Manufacture of the product and process controls

Manufacture

The GMP status is found acceptable for all finished product manufacturing sites mentioned in the table below.

**Manufacture of the product**

**Finished product cartridge - formulation and fill process:**

After thawing of the active substance, it is mixed with formulation solutions. The solution gained is bioburden reduction filtered and sterile filtered and further transferred to the filling machine. After filling, the cartridges are packaged (bulk-packed cartons).

**Finished product Pen Injector – assembly process:**

Description of assembly of the constituent parts has been provided as well as final assembly. The finished product pen injector is finally labelled and packed into cartons.

A table indicating the manufacturing steps, process parameters and in-process controls has been provided. Subassembly and assembly processes are described via flow-chart and photographs clearly illustrate the mechanical assembly process.

Hold times were indicated and justified. Major equipment was sufficiently summarised. No reprocessing is performed.

**Process controls (cartridge and pen injector processes):**

Process controls have been provided and discussed by step, control, acceptance criteria and criticality. Acceptable process ranges were established during development.

A process parameter is critical when that parameter leads to an impact to a critical quality attribute (CQA). Parameters that are well-controlled through effective in-process controls and/or in-process tests and/or release testing may be considered not critical. The criticality of process controls was evaluated through risk assessments. Critical quality attributes (CQAs) and critical process controls have been listed.

A risk assessment leading to assignment of critical steps was performed following the principles of ICH Q9.

Process validation /verification

Process validation has been performed for the manufacture of teriparatide 20 micrograms/80 microlitres finished product (cartridge) and for the assembly of teriparatide 20 micrograms/80 microlitres finished product (pen injector).

Process validation has been carried out on an adequate number of consecutive commercial-scale batches of teriparatide 20 micrograms / 80 microlitres solution for injection in pre-filled pen. Validation reports for teriparatide finished product (cartridge) and primary packaging assembly (pen injector) have been provided.

Transportation studies have been carried out to support the shipment of the manufactured finished product manufactured. Container closure integrity of the cartrdiges was demonstrated to be maintained when the entire finished product packaging system is subjected to a specified testing schedule to represent the rigors of transportation handling and shipping.

In accordance with EMA/CHMP/CVMP/QWP/850374/2015 "Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container", sterilisation methods for

containers and closures including acceptable validation were provided. Bioburden testing (Ph. Eur. 2-6-12) and media fills were successfully performed. Holding times are mentioned, validation studies have been provided.

Transportation studies have been carried out. No damage to the cartridges was observed and no dye ingress was observed in the test samples. Therefore, the container closure integrity of the PF708 cartridges was demonstrated to be maintained when the entire finished product packaging system is subjected to the specified testing schedule to represent the rigors of transportation handling and shipping.

## Product specification, analytical procedures, batch analysis

The finished product specifications have been developed as per ICH Q6B guidelines and cover identification, assay, pH, impurties, sterility, bacterial endotoxins of teriparatide finished product. Adequate justifications were submitted for each specification

The applicant is recommended to re-consider the specification for one finished product specification when additional stability data on the finished product becomes available (Recommendation).

Analytical procedures

All analytical procedures used in batch release and/or stability testing of teriparatide finished product were described. Test methods are considered suitable for batch release and/or stability testing.

Methods for particulate matter, sterility and bacterial endotoxins are compendial. Due to absence of compendial methods for determination of metacresol content, break-loose and sustaining glide force, dose accuracy and functional operations in-house validated methods are adopted, which is acceptable.

Method validation reports were submitted for all tests. The non-compendial analytical procedures were validated according to ICH Q2 (R1).

Batch analysis

Batch analyses have been provided for a satisfactory number of batches of teriparatide finished product cartridge and batches of teriparatide finished product (pen injector). A summary of teriparatide finished product cartridge batches manufactured has been provided. The respective batch release data for each batch of finished product with the corresponding acceptance criteria has also been presented. Similarly, the batch summary for the teriparatide finished product (pen injector) batches and the respective batch release data have been provided. The certificate of analysis for teriparatide finished product cartridge batches and finished product (pen injector) batches have been provided. The batch analysis confirms consistency of the manufacturing process. This section is acceptable.

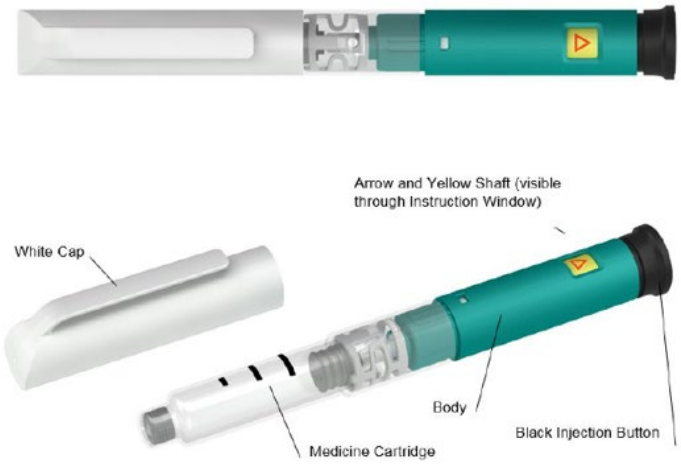
Reference standards

The same reference standards are used for release and stability testing of teriparatide active substance and finished product. Details regarding the description and the qualification of the reference standards are provided in the active substance section.

**Container closure system (pen injector)**

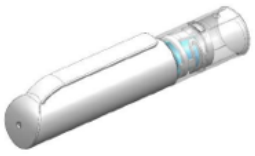
The pen injector represents a not-reusable integral Drug Device Combination (DDC) and is used together with commercially available needles (attached by the user and disposed after every use).

**Figure 3. Pen injector components**




The pen consists of a cartridge subassembly unit (CSU) and a dosing mechanism (DMS), produced by Ypsomed. The pre-filled cartridge is assembled to these two sub-assemblies and is non-replaceable.

**Figure 4. Pen injector subassemblies**

| Sub-assemblies | Description | Function |
|---|---|---|
|  | Dosing Mechanism Subassembly | Enables dose setting and injection. Pushes forward the cartridge plunger. Gives visible and audible feedback during dose setting and injection. |
|  | Cartridge Subassembly Unit | Cartridge holder: Holds the cartridge in its defined position. Includes the screw thread to attach the needle.<br><br>Pen cap: Protects the cartridge from light and dust. |

Therefore, absence of CE-certification and declaration of conformity are acceptable.

Two sets of assessment were provided with regard to applicable essential requirements of Annex I of the Medical Device Directive 93/42/EEC.

It is pointed out that a large amount of data was submitted for the DDC covering most aspects mentioned in Draft Guideline EMA/CHMP/QWP/BWP/259165/2019.

Minor modifications made to the pen injector after clinical trials were described and justified in detail. No changes were made to the materials, user interface, or principle of operation of the device. Therefore, these modifications are considered negligible and bridging studies are not considered necessary from a quality point of view.

Pen injector design verification comprises a dose accuracy study acc. to ISO 11608-1, a storage and functional durability study for subassemblies and pen components, biocompatibility testing per ISO 10993-1, investigation of fit/function of the cartridge, compatibility with other devices (needles), functional operation verification testing, design verification related to prevention of foreseeable misuse, a human factors validation study and use-related hazards.

Given the depth of information that is provided in the different parts of the dossier, it can be concluded that an adequate control strategy was followed for the final assembled product in the pen injector

(DDC) starting with the submitted Quality Target Product Profile comprising certain primary attributes in relation to the DDC.

Important basic parameters were considered such as:

a) Finished product component quality: specifications/drawings, specifications of raw materials, in-use stability of DDC product (device component stability was investigated during development for subassemblies and assembled product). Storage conditions and maximum storage time are defined for subassemblies and DDC).

b) Manufacturing process and design such as e.g.: subassembly and assembly process monitoring, In-process-controls, CQAs (3.2.P.3.4. comprising dose accuracy and control of impurities during pen assembly and packaging), batch analysis data. Sufficient amount of information was submitted to demonstrate that an adequate control strategy is applied.

*Compatibility:*

Compatibility with other devices (needles) and biocompatibility were addressed adequately during Pen injector Design Verification. Instructions for use and handling in the SmPC are found sufficiently supported by these investigations.

## Stability of the product

A shelf life of 30 months when stored at 2°C - 8°C is claimed for the finished product.

Long-term stability and accelerated conditions:

Data from primary stability studies has been provided on commercial-scale batches of Teriparatide finished product cartridges and batches of Teriparatide finished product pen injector batches.

Supporting stability data has also been presented on small-scale and commercial-scale batches of Teriparatide finished product cartridges and Teriparatide finished product pen injector.

These studies are found to be in compliance with the ICH Guidelines. Commercial scale batches were included in the studies packed in the same container closure system proposed for commercial use. Thus, a sufficient representativeness of the commercial product has been ensured. The results do not reveal any significant changes or trends.

*Stability studies with process validation batches:*

The applicant is recommended to continue ongoing stability studies and make available the stability data generated. The applicant also commits to immediately notify OOS results, if these occur (Recommendation).

Impurities are discussed further down below.

*In-use shelf life:*

The proposed in-use shelf life is to use within 28 days of the first use and has been supported by a number of in-use studies.

*Photostability:*

Similar photodegradation profiles were obtained for PF708 finished product and US RMP Forteo with both products being photosensitive.

The pen injector has a cap to minimise photodegradation and physical damage to the cartridge. In addition, as per the SmPC, the finished product should be stored in a refrigerator at all times, and the

pen should be returned to the refrigerator immediately after use. This ensures minimal exposure of the finished drug product pen injector to light. The respective instruction is currently only included in the user manual.

*Break loose and sustaining glide force:*

Data on cartridge batch was used to study break loose and sustaining glide force revealing acceptable results.

*Device related studies:*

The shelf life of the device constituent has been sufficiently addressed. The study design and tests performed at each time point have been presented.

Based on all the stability data provided a shelf life of 30 months when stored at 2°C - 8°C is acceptable for the finished product. Once opened, the medicinal product may be stored for a maximum of 28 days at 2°C to 8°C. Chemical, physical and microbiological in-use stability has been demonstrated for 28 days at 2°C - 8°C. Other in-use storage times and conditions are the responsibility of the user.

**Summary discussion with regard to product-related impurities:**

Specifications at the active substance level have been justified. Specifications/methods used for clinical batches have also been justified in line with applicable standards available at that time. When pharmacopoeial methods and standards became available, these were adopted.

Subsequently, the finished product specification was again updated to include individual impurity limits for relevant impurities.

Limits for impurities are based on the levels of impurities measured in the RMP, supported by batch analysis and stability data generated to date. An analytical bridging study was conducted to support any changes in methods made.

The applicant clearly explained how data for clinical batches were generated and submitted impurity data for both clinical batches and justified these levels with respect to levels in EU-Forsteo and US-Forteo.

Data provided for "primary stability batches" supports the proposed shelf-life of 30 months at 2°C - 8°C. Data submitted for *"supportive batches"* at 2°C - 8°C are ongoing and will be completed.

The applicant is recommended to revise impurity specifications, if required after gaining further stability results (Recommendation).

A risk assessment was conducted for PF708 (Teriparatide [rDNA origin] Injection) to identify potential elemental impurities (EI) that may be present in the finished product. The assessment considered all potential sources of introduction of EI into the finished product. Based on this assessment, it is concluded that no additional controls are required for EI in the finished product and no routine testing for EI are required at release of active substance because EI are controlled through raw material release testing by the manufacturers.

## Biosimilarity

A number of different similarity exercises have been conducted:

a) A quality comparison of multiple batches of PF 708 finished product with US Forteo

b) A quality comparision of multiple batches of EU Forsteo with US Forteo

c) A three-way quality comparison of multiple batches of PF 708 finished product with US Forteo and with EU Forsteo

d) A biosimilarity study comparing additional batches of EU Forsteo with PF708 DP.

The applicant explained that determination of CQAs for PF 708 finished product was performed using risk management techniques on the principles of ICH Q9. A criticality assessment was performed whereby quality attributes were ranked with consideration to impact and uncertainty. Criticality scoring as well as justifications for criticality scores of CQAs were submitted for drug product. The principal strategy for risk evaluation and classification is agreed, and the assigned criticality scores for some quality attributes have been justified.

The applicant explained that the similarity ranges have been set based on all data available at the time from the multiple-lot Comparability Study between US Forteo and EU Forsteo and data from the multiple-lot Biosimilarity Comparability Study between PF 708 finished product, US Forteo and EU Forsteo. Comparability of US Forteo and EU Forsteo could be demonstrated. Consequently, the inclusion of US Forteo batches for the QTPP is acceptable.

It is noted that the number of reference product lots included for establishment of biosimilarity ranges to evaluate similarity of PF 708 with EU Forsteo was somewhat limited for some tests in the initial application. On the other hand, the applicant provided an additional biosimilarity study comparing additional batches of EU Forsteo with additional batches of PF 708 finished product to substantiate the biosimilarity claim and this was acceptable. It is agreed that relevant parameters of the analytical methods used for the biosimilarity demonstration have been investigated and the analytical methods can be considered fit for use.

The information provided is considered acceptable.

**Table 1. Summary of quality attributes included in the biosimilarity exercise and their results**

| Molecular parameter | Attribute | Methods for control and characterisation | Key findings |
|---|---|---|---|
| Safety | pH | USP | Identical pH |
| Safety | Visual inspection | Visual inspection Ph. Eur. | All samples were colourless and essentially free of visible particles |
| Purity and quantity | Identity and content | Reversed Phase HPLC | The identity and content are comparable. |
| Product-related impurities | Oxidised, truncated and succinimide variants | Reversed Phase HPLC | Age dependent increase of rhPTH(1-30) and succinimide -30 variants in both EU Forsteo and PF708 |
| Product-related impurities | High-molecular weight impurities | Size-Exclusion HPLC | Identical high-molecular weight impurities |
| Primary structure | Intact mass | LC-MS | Identical intact mass |
| Primary structure | Peptide mapping | LC-MS | Identical primary sequence |
| Higher order structure | Secondary structure and folding properties | Far UV circular dichoroism spectroscopy | Comparable higher order structure |

| Molecular parameter | Attribute | Methods for control and characterisation | Key findings |
|---|---|---|---|
| Higher order structure | Tertiary structure and folding properties | Intrinsic fluorescence spectroscopy | Comparable higher order structure |
| Higher order structure | High-resolution assessment of higher order structure | Nuclear magnetic resonance | Comparable higher order structure |
| Functional characterisation | Receptor binding | Biolayer interferometry | The receptor binding seems to be similar. |
| Functional characterisation | Biological activity | Bioassay | Comparable biological activity. |

In summary, the initially raised issues on biosimilarity have been resolved based on an additionally conducted similarity exercise which further substantiated the biosimilarity claim. Taking these additional data into account as well as the fact that teriparatide is a rather simple, non-glycosylated polypeptide, the major objection on biosimilarity can be considered resolved.

Comparability study between EU-licensed Forsteo and US-licensed Forteo

The entire non-clinical and clinical development programme of the proposed teriparatide biosimilar PF 708 was conducted with the US comparator product only. A comprehensive and robust quality bridge is a pre-requisite for a biosimilar development using a non-EEA authorised version of the RMP in the non-clinical and clinical comparability programme. Major deficiencies concerning the comparability exercise aiming to demonstrate a comparable quality profile of the EU RMP Forsteo with US comparator product Forteo have been raised at Day120 and in response, additional testing of US Forteo batches was conducted. For relevant physicochemical quality attributes (e.g. purity/impurity profile by RP-HPLC and SE-HPLC) multiple batches of US Forteo batches have been compared with multiple batches of EU Forsteo batches. For other physicochemical quality attributes (e.g. primary structure/peptide mapping, higher order structure by CD, intrinsic fluorescence, and NMR, a reduced number of US Forteo batches was tested. Taking into account that these latter quality attributes have been investigated by qualitative or semi-quantitative tests methods the number of included US Forteo batches can be considered sufficient to gain insight into variability of US Forteo batches on the market.

Also for the biological assays, additional data have been provided: US Forteo batches have been compared with EU Forsteo batches with the rat cell-based bioassay. In addition, the potency of Forteo batches from the US market and Forsteo batches from EU market has been tested as part of the additional comparability study performed between the Forteo, Forsteo and PF 708 finished product, using a human-cell based biological assay. Taking this dataset and the available comparative receptor binding data into account, it can be concluded that there are no significant differences in the biological characteristics between US Forteo and EU Forsteo.

The available quality data generated in various separate comparability/similarity studies is presented and summarised in a "Data Analysis" document that has been provided as an annex to the response document along with statistical analysis that showed a comparable quality profile between US Forteo and EU Forsteo and thus, the major objection on the quality bridge between these two products has been solved.

The suitability of the statistics used for comparability evaluation of US Forteo versus EU Forsteo was questioned and the applicant reanalysed the US Forteo and EU Forsteo data – this reanalysis supported the biosimilarity claim.

It is agreed that the comparison is now enhanced, both, by different comparability ranges and an additional approach based on the comparison of mean values. This approach is considered more complete and appropriate, even if there is no information about the underlying data distribution and if some CQA is analysed in log-scale, when appropriate.

Although slight differences can be deduced from these more conservative approaches in the statistical evaluation, these differences in a limited number of quality attributes might be considered not relevant in view of the intrinsic variability of the molecule and assay methods. The concern is considered resolved.

In summary, the initially raised major objection on the bridge between the EU-licensed Forsteo and US-licensed Forteo at the quality level is considered resolved. Furthermore, based on the available analyses it is highly unlikely that significant differences between the two reference products exist.

### Adventitious agents

No excipients of human or animal origin are used in the manufacturing process of the active substance and finished product. With regard to the pen injector, the manufacturer confirms that the device does not incorporate tissues of animal origin (refer to assessment with regard to Annex I of Medical device directive Section 3.2.R). Therefore, the requirement of Draft Guideline EMA/CHMP/QWP/BWP/259165/2019 to provide a statement on adventitious agents related to the manufacture of the pen injector is already covered.

With regard to TSE the applicant confirmed that during manufacture no TSE-relevant ingredients are used. No concerns were raised regarding the adventitious agent safety evaluation.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

**Active substance:**

- **Manufacturers:** GMP compliance was sufficiently proven for two sites involved in the AS manufacturing
- **Manufacturing Process:** Sufficient information has been provided on cell line development and characterisation.
- **Control strategy:** After clarifications and response to questions, the control strategy was adequately justified.
- **Process Characterisation:** Detailed process characterisation was performed on qualified scaled-down models of each of the unit operations of the drug substance manufacturing process.
- **Process Validation:** A process validation report was provided for the commercial process site and is sufficient to support a consistent process.
- **Process Development:** Development and upgrading studies for the manufacturing site were submitted. As part of technology transfer from the development company to clinical lot manufacturing site, consistency was demonstrated.

A further transfer of the commercial-scale manufacturing process occurred and satisfactory comparability data were submitted and indicated that materials from both facilities are within the specified acceptance ranges.

- **Specification.** The acceptance criteria were evaluated based on a scientific approach or set according to the USP monograph. The specification proposed are acceptable.
- **Stability studies:** Stability studies are ongoing, design and batches used are considered acceptable. A shelf life of 18 months for the active substance when stored at the recommended storage conditions is acceptable.

**Finished product:**

The documentation for the finished product is divided into:

a) Finished product cartridge (representing the injection solution filled in the primary container/closure system (cartridge))

b) Finished product pen injector (representing the filled cartridge assembled to the pen injector)

The finished product pen injector is defined to be the finished medicinal product and an integral drug device combination.

- **Pharmaceutical development:** Satisfactory information relating to preservative efficacy and in-use stability are provided.
- **Control strategy:** The control strategy of the *finished product cartridge process* was sufficiently documented. Information on risk assessments leading to identification of critical process parameters were submitted. With regard to excipients and container/closure system a sufficient control is in place and critical quality attributes were defined and are considered adequately controlled. Taken together, the control strategy confirms that the process is sufficiently controlled to ensure consistent and acceptable quality of the product. No dedicated information on control strategy for the *pen injector process (integral drug device combination-DDC)* as requested by Draft Guideline EMA/CHMP/QWP/BWP/259165/2019 was submitted. However, given the depth of information provided in the different parts of the dossier and taken globally, it can be concluded that an adequate control strategy was followed for the final assembled product in the pen injector (DDC).
- **Process validation:** Results from process validation were submitted for the finished product cartridge manufacturing process and for automated assembly of the drug device combination. Shipment validation was provided. The information provided is acceptable.
- **Product-related impurities:** The proposed shelf-life of 30 months is considered acceptable. For details refer to the end of Subsection "Stability of finished product", where an overall discussion on impurities is provided.
- **Analytical procedures and validation of analytical procedures:** Methods were either compendial or were adequately validated.
- **Container/closure system:** With regard to the container/closure system information provided is found sufficient. Fragmentation and self-sealing was sufficiently considered.
- **Stability studies:** Stability studies of supportive batches are ongoing; 30 months stability data were provided. Design and batches used are considered acceptable.

Several in-use-studies were performed/initiated. Consequently, the requirement of Guideline CPMP/QWP/2934/99 to evaluate a minimum of two batches was followed. Anti-microbial effectiveness under conditions of in-use was considered within two studies. The information provided is sufficient.

Based on all the stability data provided a shelf life of 30 months when stored at 2°C - 8°C is acceptable for the finished product.

**Regional information**

- **Biosimilarity exercise:** An additionally conducted comparability exercise substantiates the biosimilarity claim. Taking these additional data into account, and considering that teriparatide is a rather simple, non-glycosylated polypeptide the biosimilarity exercise is considered acceptable.
- **Comparability exercise between the EU-licensed Forsteo and US-licensed Forteo:** The US-authorised medicinal product Forteo was used as comparator in non-clinical and clinical studies. Thus, evaluation of the similarity and variability of Forteo and the EEA-authorised RMP Forsteo is particularly relevant for acceptability of the non-clinical and clinical study results. The initially raised Major Objection on the quality bridge between the EU-licensed Forsteo and US-licensed Forteo is considered resolved. With the additional testing and statistical analyses conducted the comparability exercise is considered sufficiently robust to exclude significant differences between the two reference products.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Satisfactory documentation has been provided. Overall, the data presented indicate that Livogiva is manufactured by a validated, controlled process taking into consideration relevant guidance documents. Batch release data also confirm that the product is of consistent quality. The results indicate that the finished product can be reproducibly manufactured. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety. The comparability data provided substantiates the biosimilarity claim. From a quality point of view, Livogiva is considered approvable.

### 2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

Teriparatide is a biologically active 34-amino-acid N-terminal fragment of the 84-amino-acid native human parathyroid hormone [PTH(1-84)]. Genetically engineered teriparatide was shown to possess a similar affinity for the parathyroid hormone-receptor-1 (PTHR1) as PTH(1–84). Binding of teriparatide to PTHR1, a seven-membrane spanning G-protein-coupled receptor, and subsequent activation of both the 3,5-cyclic adenosine monophosphate (cAMP)-dependent protein kinase A and the phospholipase C-dependent protein kinase C pathway are the main signal streams to activate genes important for the functions of mature osteoblasts, to increase osteoblast number, to decrease the apoptotic rate of

osteoblastic cells, and to increase their bone-forming activity (Brixen et al., 2004, D'Amelio et al., 2012). This results in increasing bone strength, mass and diameter and bone structural integrity, as well as increasing levels of biochemical markers of bone turnover (both formation and resorption markers) in serum and urine (Blick et al., 2008).

The drug development programme for PF708 has been designed to primarily establish biosimilarity of PF708 to the US-marketed Forteo. Consequently, comparability among PF708, Forteo and the EU-marketed Forsteo needed to be established to support the marketing authorisation of PF708 in EU. Comparability evaluation was based primarily on the development of specific and highly sensitive *in vitro* bioassays which are considered more adequate to detect potential differences between the biosimilar and the reference drug than *in vivo* studies in animals, as agreed by EMA SA.

The nonclinical programme for the development of PF708 is based on the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev 1). It consists of the following studies:

1. *In vitro* studies;

• a receptor binding assay to compare the binding characteristics to the PTHR1
• cell-based bioassays using UMR-106 cells, a rat osteosarcoma cell line, to compare PTHR1 mediated cAMP release. Both submitted among the tests included in the Three-Way Comparability Study for the analytical assessment of comparability of PF708 to EU-Licensed Forsteo and US-Licensed Forteo.

2. *In vivo* studies comprising of one Primary PD Study and one Tox study;

• 6-week pharmacology study evaluating effects of PF708 and Forteo in a rat ovariectomy (OVX) model
• 4-week toxicity study of PF708 and Forteo in rats, which includes anti-drug antibody (ADA) assessments.

## 2.3.2. Pharmacology

**Primary pharmacodynamic studies**

The provided non-clinical comparability exercise primarily consisted of *in vitro* assays, which were developed and validated to evaluate comparability and demonstrate similarity between the biosimilar PF708 and the reference medicinal product Forsteo. Assessment of *in vitro* comparability studies is located in the quality part of the assessment report.

An *in vivo* PD study in rats using the US reference product Forteo was also submitted. Ovariectomised Sprague Dawley rats (9/control and 18/treatment groups) were treated subcutaneously with PF708, respectively Forteo at a dose of 8 µg/kg/d for 6 weeks. No significant differences between the two products were observed. Analyses included the assessment of body weight, relative uterine weight, metaphyseal, trabecular, diaphyseal and cortical bone parameters measured by pQCT, and serum levels of bone turnover markers. Treatment effects on metaphyseal trabecular bone were similar between PF708 and Forteo.

**Secondary pharmacodynamics, Safety pharmacology, Pharmacodynamic drug interactions studies**

In line with the current EU biosimilar guidelines no studies have been provided by the applicant.

## 2.3.3. Pharmacokinetics

The pharmacokinetic profile of PF708 was investigated and compared with Forsteo incorporated in a 4-week repeat dose toxicity and toxicokinetic study in Sprague Dawley rats (described under Toxicology Section). No dedicated *in vivo* studies on ADME or other PK studies have been conducted to assess the pharmacokinetics of the biosimilar in accordance with guidance (EMEA/CHMP/BMWP/42832/2005 Rev1). An ELISA method was validated to determine PF708 (rhPTH(1-34)) and Forteo levels in Sprague Dawley rat plasma (K3EDTA) in a toxicokinetic study conducted in the frame of the repeat-dose toxicity study.

## 2.3.4. Toxicology

In the repeat-dose toxicology rat study 30 µg/kg/day of PF708 or Forteo were administered daily via the subcutaneous route for 4 weeks. The dose of 30 µg/kg/day was chosen according to historical Forteo data, not expected to result in significant toxicity and provided a safety margin of ~15-fold over the proposed clinical dose based on AUC. The NOAEL for rats chronically treated with Forteo was considered to be 10 µg/kg.

Treatment resulted in non-adverse effects on haematology and clinical chemistry. An increase in bone formation occurred in the sternum and in the distal femur and proximal tibia of femoro-tibial joint. Extramedullary haematopoiesis in the spleen was also found increased. Both, PF708 and the US reference product, showed similarity with regard to incidence as well as severity of these findings. These findings are the result of the known hormonal effect of the drug product in bone and spleen due to compensatory responses. No antidrug antibodies were detected throughout the study. Gender differences in systemic exposure were not observed.

For toxicokinetic comparison between PF708 and Forteo, 30 µg/kg/day of either of the teriparatide drug products was dosed to rats of both sexes. Mean Cmax and AUC were comparable between PF708 and Forteo on day 1 and 28 in female, and on day 28 in male animals. However, clear differences in plasma levels were observed in male rats after the first day of dosing. Thus, the applicant's statement in the non-clinical summary 'Mean overall concentrations were similar between day 1 and day 28 for both PF708 and Forteo. No gender differences were observed' could not be agreed upon. However, as stated in the respective study report, on day 28 mean TK parameters were indeed comparable for PF708 and Forteo in both sexes. Although variability on day 1 was also high in male rats treated with Forteo, the overall differences in mean TK parameters are considered attributable to the high variability of individual TK values measured in male rats of both treatment groups. Moreover, only 3 individual animals per sex and group were tested.

In accordance with guideline on development of biosimilar medicinal products (EMEA/CHMP/BMWP/42832/2005 Rev1), other toxicological specific studies on genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance have not been conducted, as PF 708 has been developed as a proposed biosimilar to Forsteo.

## 2.3.5. Ecotoxicity/environmental risk assessment

PF708, being developed as a biosimilar to Forsteo, and with teriparatide as the active substance being a recombinant human peptide, is not expected to pose a risk to the environment and thus, specific studies to evaluate the environmental risk are not required for this medicinal product. The applicant provided an appropriate justification for not submitting an Environmental Risk Assessment, as postulated in the CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

## 2.3.6. Discussion on non-clinical aspects

For discussion of the *in vitro* data, reference is made to the respective chapter under 'Quality aspects'.

*In vivo* PD studies are usually not required for a biosimilar application according to recent guidance, as long as no specific concerns arise during *in vitro* comparability assessment that would require further elaboration on the level of *in vivo* studies. The submitted PD study was conducted using only Forteo, the approved US reference product, as comparator. In general, this approach would not be in line with recent EU guidance, where it is stated that 'the reference medicinal product must be authorised in the EEA under Article 6, in accordance with the provisions of Article 8 of Directive 2001/83/EC'. Moreover, the bridging study between Forsteo and Forteo on the quality level was not regarded sufficient (under 'Quality aspects'). However, for this type of MAA, non-clinical PD data is considered supportive only. Thus, the deficiencies of the conducted PD study discussed above are not deemed a blocking issue.

In summary, supportive PD data did not reveal any significant differences between PF708 and the US reference product Forteo, which would warrant additional studies.

Studies on secondary PD, safety pharmacology, and pharmacodynamic drug interactions were not conducted, which is in agreement with recent guidance on MAA for biosimilar medicinal products.

Dedicated studies on ADME or other PK studies have not been conducted, in accordance with recent guidance. An ELISA was validated to determine PF708 (rhPTH(1-34)) and Forteo levels in Sprague Dawley rat plasma (K3EDTA) in a toxicokinetic study conducted in the frame of the repeat-dose toxicity study.

The repeated-dose toxicology study, including the studies on toxicokinetics and immunogenicity, was conducted in compliance with GLP. US reference product Forteo was administered in this study – thus, this data is regarded to be supportive. Toxicity data shows that subcutaneous dosing of PF708 or Forteo at 30 µg/kg/day resulted in comparable responses, including expected effects on bone and extramedullary haematopoiesis.

Mean Cmax and AUC were comparable between PF708 and Forteo on day 1 and 28 in female, and on day 28 in male animals. However, clear differences in plasma levels were observed in male rats after the first day of dosing). Thus, the applicant's statement in the non-clinical summary 'Mean overall concentrations were similar between day 1 and day 28 for both PF708 and Forteo. No gender differences were observed' could not be agreed upon. However, as stated in the respective study report, on day 28 mean TK parameters were indeed comparable for PF708 and Forteo in both sexes. Although variability on day 1 was also high in male rats treated with Forteo, the overall differences in mean TK parameters are considered attributable to the high variability of individual TK values measured in male rats of both treatment groups. Moreover, only 3 individual animals per sex and group were tested.

The ADA assays appear comprehensively validated to detect potential differences between PF708 and the reference product. No anti-drug antibodies were detected for either PF708 or Forteo in the immunogenicity study conducted.

In accordance with guidance on development of biosimilar medicinal products, specific studies on genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance have not been conducted.

The applicant provided an appropriate justification (Module 1.6.1.) for not submitting dedicated studies to support the Environmental Risk Assessment, as postulated in the CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00). Additionally, the approval of the biosimilar medicinal product is not considered to lead to an increase of

the total quantity of teriparatide released into the environment, and therefore will not result in an increase of risk to the environment during storage, distribution, use and disposal.

### 2.3.7. Conclusion on the non-clinical aspects

The non-clinical comparability exercise primarily consisted of *in vitro* assays developed and validated to evaluate comparability and demonstrate similarity between the biosimilar PF708 and the reference medicinal product Forsteo. The respective results and assessment of the *in vitro* comparability studies are located in the quality part of the assessment report.

The non-clinical *in vivo* studies provided as a part of the comparability programme are considered supportive data, because the biosimilar was only compared to the US reference product Forteo. Overall, the studies did not reveal any significant differences between PF708 and the US reference product Forteo.

No major objections have been identified on the supportive *in vivo* studies and no concerns are raised with regard to PD, PK, and toxicology studies in animals.

## *2.4. Clinical aspects*

The clinical development programme to show biosimilarity between PF708 (Livogiva; teriparatide 20 mcg/80 µL solution for injection) and US-marketed Forteo consists of one comparative pharmacokinetic (PK) study in 70 healthy subjects (PF708-101) and one clinical immunogenicity study (PF708-301) in 181 in women with postmenopausal osteoporosis and men with primary osteoporosis.

**Tabular overview of clinical studies**

**Table 2.7.3-1. Description of Clinical Study Designs**

| Study Number | Study Design | Study and Control Drugs Dose/ Regimen | Study Objectives | Number of Subjects by Arm Entered Analysis Populations | Gender M/F Age (Range) | Diagnosis and Main Inclusion Criteria | Efficacy or Primary End Point |
|---|---|---|---|---|---|---|---|
| **Phase 1 Clinical Studies** | | | | | | | |
| *PF708-101* | Phase 1 double-masked, randomized, 2-treatment, cross-over, single-center study in healthy adult subjects after single sc doses of PF708 and Forteo | Single sc injections of PF708 20 mcg and Forteo 20 mcg with 3-day washout between doses | **Primary objective**: To evaluate the PK of PF708 and Forteo **Secondary objective**: To evaluate the PD of PF708 and Forteo. | **Sequence A**[a]: 35 subjects **Sequence B**[a]: 35 subjects **PK population**: 70 subjects **PD population**: 70 subjects **All subjects population**: 70 subjects | **F:** 27 (39%) **M:** 43 (61%) Mean age: 33 yrs (20 to 53 yrs) | Healthy adult male and female subjects aged 18 to 55 yrs, inclusive, with female subjects constituting approx. 40% of the study population. | Comparison of plasma concentrations of PF708 versus Forteo to evaluate bioequivalence. |
| **Phase 3 Clinical Studies** | | | | | | | |
| *PF708-301* | Phase 3, randomized, parallel-group, open-label, multi-center study comparing the effects of PF708 and Forteo after 24 weeks of treatment | PF708 20 mcg qd for 24 weeks or Forteo 20 mcg qd for 24 weeks | **Primary objective:** To compare the effects of PF708 and Forteo on immunogenicity after 24 weeks sc daily dosing | **PF708 arm:** 90 subjects (53 subjects 65 to 85 years of age) **Forteo arm:** 91 subjects (53 subjects 65 to 85 years of age) | **F:** 131 (72.4%) **M:** 50 (27.6%) Mean age: 66.6 yrs (41 to 85 yrs) | Female subjects with PMO Male subjects with primary osteoporosis | • Incidence of ADAs after 24 weeks of treatment with PF708 or Forteo. • For ADA-positive subjects, ADA titer, incidence and titer of NAb, and incidence and titer of ADA that cross-react with endogenous PTH. |

| Table 2.7.3-1. Description of Clinical Study Designs | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study Number** | **Study Design** | **Study and Control Drugs Dose/ Regimen** | **Study Objectives** | **Number of Subjects by Arm Entered Analysis Populations** | **Gender M/F Age (Range)** | **Diagnosis and Main Inclusion Criteria** | **Efficacy or Primary End Point** |
| | | | **Secondary objective**: To compare the PK and PD of PF708 and Forteo. | **Immunogenicity population**: 179 (88 PF708) subjects<br>**BMD population**: 170 (84 PF708) subjects<br>**PK population**: 180 (89 PF708) subjects | | | • Plasma PK parameter values of teriparatide after a single injection of PF708 or Forteo.<br>• Mean percentage change in lumbar-spine (L1-L4) BMD after 24 weeks of treatment with PF708 or Forteo.<br>• Median percentage change in serum BTM concentrations of P1NP and CTX after 24 weeks of treatment with PF708 or Forteo. |
| ADA = antidrug antibody; approx. = approximately; BMD = bone mineral density; BTM = bone turnover marker; CTX = crosslinked C-terminal telopeptide of type 1 collagen; F = female; M = male; Nab = neutralizing antibodies; P1NP = N-terminal propeptide of type 1 procollagen; PD = pharmacodynamics; PK = pharmacokinetics; PMO = postmenopausal osteoporosis; PTH = parathyroid hormone; qd = every day; sc = subcutaneous; yrs = years.<br>[a] = Sequence A 20 mcg PF708 sc injection in Period 1 and 20 mcg Forteo sc injection in Period 2.<br>Sequence B: 20 mcg Forteo sc injection in Period 1 and 20 mcg PF708 sc injection in Period 2. | | | | | | | |

Method

The validation data for the bioanalytical assays (ELISA, ECL immunoassay, Radioimmunoassay) used in the two clinical studies were submitted. Clinical Study PF708- 101 was designed to assess bioequivalence of the PK of PF708 and Forteo. Clinical Study PF708-301 compared the immunogenicity, PK, PD, and safety of PF708 drug product pen injector and Forteo.

SOPs were submitted for a method description. The validation of the used assays followed the Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2).

A cross validation study with the ELISA method was performed between the reference product Forteo and PF708.Validation was sufficiently executed.

## 2.4.1. Pharmacokinetics

The comparison of the PK profiles of PF708 and Forteo was the primary objective of study PF708-101.

PK profiles were secondary objectives in the clinical study PF708-301.

***Comparative PK-study PF708-101***

Study title

A double-masked, randomised, two-treatment cross-over study comparing the pharmacokinetics of PF708 and Forteo administered by subcutaneous injection in healthy adult subjects.

Study Design

Study PF708-101 was a randomised, double-masked, single-centre, single 20 mcg fixed-dose, two-way crossover study, planned to compare the PK of PF708 (biosimilar teriparatide) with that of the reference medicinal product Forteo (US-sourced) in 70 healthy adults.

Subjects were randomised to treatment sequences A (PF708 → Forteo) or B (Forteo → PF708).

A single 20 mcg/80 µL SC injection of PF708 or Forteo was administered in the morning in each period.

There were two dosing days (Period 1 Day 1 and Period 2 Day 5), which were separated by a washout period of 3 days (+ up to 1 hour). In each period blood sampling for PK evaluation was performed before dosing and at 5, 10, 20, 30, 40, 50 (± 1 minutes), 60, 90, 120, 180, 240, 360 and 480 minutes (± 5 minutes) post-dose.

Objectives

The primary objective was to demonstrate PK-equivalence between PF708 and the reference product Forteo following a 20 mcg/80 µL SC injection in healthy adult subjects.

The secondary objective was to evaluate the PD, safety and tolerability of a single 20 mcg/80 µL SC injection of PF708 as compared to data gained for Forteo.

Study participants

70 healthy adult subjects entered the study and were randomised to either of the two treatment arms, A (test → reference) or B (reference → test), meaning they acted as their own control group [Sequence A (n=35), Sequence B (n=35)].

Of the 70 subjects, approximately 40% of the study population were female subjects. 34 subjects were white, 31 subjects were Black or African American, 5 subjects were classified as `Others´. The mean age for all subjects was 33 years (range 20–53 years), the mean weight was 76.2 kg (range 47.7 – 101.4 kg), the mean height was 173 cm (range 154–191.9 cm), and the mean body mass index (BMI) was 25.3 kg/m2 (range 20–29.9 kg/m2). There were no findings in the medical history of clinical concern for any subject and no baseline signs/ symptoms of clinical concern prior to dosing.

Treatments

- PF708 (test): A single 20 mcg/80 µL SC injection of PF708 (Pfenex Inc.)
- Forteo (reference): A single 20 mcg/80 µL SC injection of Forteo (Eli Lilly and Company)

PF708 and Forteo were supplied as teriparatide 20 mcg/80 µL SC solution for injection.

Both study drugs, PF708 and Forteo were supplied as teriparatide 20 mcg/80 µL SC solution for injection in a cartridge inserted in a reusable, multi-dose disposable delivery device (pen). One PF708 cartridge of 2.4 mL contains 600 mcg of teriparatide (corresponding to 250 mcg per ml). The cartridge itself has a holding capacity of 3 ml, is made of siliconised Type I glass, supplied with a plunger stopper (halobutyl rubber) and disc seal (aluminium and polyisoprene/bromobutyl rubber laminate) assembled into a disposable pen.

Subjects received the SC injection in the lower quadrants of the abdomen: in period 1 (Day 1) in the lower right quadrant, in period 2 (Day 5) in the lower left quadrant. Subjects were sitting or lying down during dose administration.

PK parameters

*Primary PK parameters*

| | |
|---|---|
| AUC0-tlast | Area under the concentration-time curve up to the last quantifiable concentration |
| AUC0-inf | Area under the concentration-time curve up extrapolated to infinity |
| Cmax | Maximum observed concentration |

Equivalence for the primary endpoints was to be concluded if the 90% CIs of the ratios of least squares means (LSMs) (derived from the analyses on the natural log (ln)-transformed PK parameters AUC0-

tlast, AUC0-inf and Cmax of PF708 to the reference product Forteo were completely within the acceptance interval of 80.00-125.00 %.

*Secondary PK parameters*

| | |
|---|---|
| tmax | Time to reach Cmax |
| t½ | Apparent terminal elimination half-life |
| CL/F | Apparent total plasma clearance after extravascular administration |
| kel | Apparent terminal elimination rate constant |

The plasma teriparatide PK parameters (AUC0-t, AUC0-∞, Cmax, Tmax, Kel, t½, and CL/F) were to be listed and summary statistics (n, Mean, SD, CV%, SEM, minimum, median, maximum, GM, GCV%, and 95% CI) were be calculated for each treatment separately in the PK evaluable population. Data from excluded subjects were to be listed by subject but excluded from the summary statistics and noted as such in the tables.

**Results**

Participant Flow

Of the 70 healthy adult subjects entering the study and being randomised to either of the two treatment arms, all 70 completed both periods, and all were included in the final PK-analysis set.

Primary PK-parameters

**Table 11–2: Summary of Statistical Comparisons of Plasma Teriparatide Pharmacokinetic Parameters AUC0-t, AUC0-inf, and Cmax for PF708 Versus Forteo**

| | PF708 (Test) | | Forteo (Reference) | | | Confidence Intervals | |
|---|---|---|---|---|---|---|---|
| Pharmacokinetic Parameter | Geometric LSMs | n | Geometric LSMs | n | GMR (%) | 90% Confidence | Intra-subject CV% |
| AUC0-t (pg*hr/mL) | 75.71 | 66 | 78.43 | 66 | 96.53 | 90.01 - 103.52 | 24.41 |
| AUC0-inf (pg*hr/mL) | 86.67 | 54 | 87.56 | 61 | 98.99 | 92.54 - 105.89 | 21.03 |
| Cmax (pg/mL) | 74.15 | 66 | 78.04 | 66 | 95.02 | 88.41 - 102.12 | 25.19 |

PF708: A single 20 µg SC dose of teriparatide (Test)
Forteo: A single 20 µg SC dose of teriparatide (Reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from ANOVA.
Geometric mean ratio (GMR) = 100 x (test/reference)
Intra-subject CV% was calculated as 100 x square root(exp[residual variance]-1).
n = Number of observations used in the analysis.
Source: Table 14.2.1.7
Program: /CA18469/sas_prg/pksas/intext-stats-tables-mixed.sas 19MAY2016 14:33

Source: PK Report, Appendix 16.2.5.3

Other PK-parameters

**Table 11–1: Summary of Plasma Teriparatide Pharmacokinetic Parameters Following Administration of PF708 Versus Forteo**

| Pharmacokinetic Parameters | Statistic | PF708 | n | Forteo | n |
|---|---|---|---|---|---|
| AUC0-t (pg*hr/mL) | GM (GCV%) | 75.88 (47.5) | 66 | 78.67 (43.8) | 66 |
| AUC0-inf (pg*hr/mL) | GM (GCV%) | 85.83 (38.7) | 54 | 87.22 (39.6) | 61 |
| AUC%extrap (%) | Mean ± SD | 11.70 ± 6.4680 | 54 | 10.89 ± 5.7344 | 61 |
| Cmax (pg/mL) | GM (GCV%) | 74.28 (44.0) | 66 | 78.21 (38.9) | 66 |
| Tmax (hr) | Median (Min, Max) | 0.1667 (0.0833, 0.500) | 66 | 0.1667 (0.0833, 0.833) | 66 |
| Kel (1/hr) | Mean ± SD | 0.9093 ± 0.30578 | 54 | 0.9696 ± 0.34566 | 61 |
| T1/2 (hr) | Mean ± SD | 0.8933 ± 0.47564 | 54 | 0.8103 ± 0.29094 | 61 |
| CL/F (L/hr) | Mean ± SD | 250.1 ± 100.74 | 54 | 246.3 ± 98.107 | 61 |
| PF708: A single 20 µg SC dose of teriparatide (Test)<br>Forteo: A single 20 µg SC dose of teriparatide (Reference)<br>Source: Tables 14.2.1.3 and 14.2.1.4<br>Program: /CA18469/sas_prg/pksas/intext-pk-tables.sas 14JUN2016 17:42 | | | | | |

Source: PK Report, Appendix 16.2.5.3

Remark: These results represent the geometric mean values from the measured results (without any corrections) in comparison to the corrected values from the table above (concerning mainly the primary endpoints).

***Supportive PK analysis of Immunogenicity Study PF708-301***

For methodological Study planning and safety assessment (primary endpoint) see Clinical safety.

Study Design

Study PF708-301 was a randomised, multicentre, parallel-group, open-label study designed to compare the effects of PF708 and Forteo on immunogenicity after 24 weeks of daily subcutaneous administration in patients with osteoporosis. Secondary objectives of the study included the comparison of PK (and PD) for PF708 and Forteo.

Patients received 20 mcg doses of PF708 or Forteo once daily for 24 weeks using a disposable delivery pen, with each pen containing enough study drug to deliver one dose per day for 28 days.

Blood samples for PK evaluation were collected on Day 1 within 30 minutes before dosing and at 10, 15, 30, 60, 90, 120, 180, 240 minutes post-dose.

PK parameters (Secondary endpoints in clinical study)

| | |
|---|---|
| AUC0-tlast | Area under the concentration-time curve up to the last quantifiable concentration |
| AUC0-inf | Area under the concentration-time curve up extrapolated to infinity |
| AUC%extrap | Percent of AUC0-inf extrapolated |
| Cmax | Maximum observed concentration |
| t½ | Apparent terminal elimination half-life |
| CL/F | Apparent total plasma clearance after extravascular administration |
| tmax | Time to reach Cmax |

kel Apparent terminal elimination rate constant

**Results**

Participant Flow

A total of 182 osteoporosis patients entered the study and were randomised to either of the two treatment arms, PF708 or Forteo. One patient randomised to receive PF708 withdrew from the study before the first dose of study drug was administered [PF708 (n=90), Forteo (n=91)]. Patient 115011 had unevaluable samples due to a shipping error. The PF708 group consisted of 89 patients (97.8%) and were compared for PK analysis to all 91 patients (100%) of the Forteo group.

PK parameters

*Arithmetic mean plasma teriparatide concentrations versus time profiles (linear scale)*

**Table 6-7 Summary of Statistical Comparisons of Plasma Teriparatide Pharmacokinetic Parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and $C_{max}$ for PF708 Versus Forteo**

| | PF708 | | Forteo | | | Confidence Intervals | |
|---|---|---|---|---|---|---|---|
| Parameter | Geometric LSM | n | Geometric LSM | n | GMR (%) | 90% Confidence | Inter-subject CV% |
| $AUC_{0\text{-last}}$ (pg*hr/mL) | 111.4 | 83 | 122.0 | 84 | 91.33 | 78.03 - 106.90 | 67.76 |
| $AUC_{0\text{-inf}}$ (pg*hr/mL) | 133.6 | 72 | 141.5 | 76 | 94.39 | 82.40 - 108.12 | 53.16 |
| $C_{max}$ (pg/mL) | 92.45 | 83 | 111.8 | 84 | 82.67 | 72.02 - 94.88 | 57.98 |

PF708: PF708 20 mcg SC QD for 24 weeks
Forteo: Forteo 20 mcg SC QD for 24 weeks
Parameters were ln-transformed prior to analysis.
Geometric least squares means (LSMs) are calculated by exponentiating the LSMs derived from the analysis of variance (ANOVA).
Geometric mean ratio (GMR) = 100 x (test/reference)
Inter-subject CV% = 100 x square root(exp[MSE]-1); MSE = Residual variance from ANOVA
n = Number of observations used in the analysis
Source: Table 14.2.1.6 in the Celerion ADA/BTM/PK report, Appendix 16.5

**Table 6-6 Summary of Plasma Teriparatide Pharmacokinetic Parameters Following Administration of PF708 Versus Forteo**

| Pharmacokinetic Parameters | PF708 | n | Forteo | n |
|---|---|---|---|---|
| $AUC_{0\text{-last}}$ (pg*hr/mL) | 111.4 (75.3) | 83 | 122.0 (60.0) | 84 |
| $AUC_{0\text{-inf}}$ (pg*hr/mL) | 133.6 (54.6) | 72 | 141.5 (51.8) | 76 |
| AUC%extrap (%) | 10.18 ± 6.4743 | 72 | 9.822 ± 5.9313 | 76 |
| $C_{max}$ (pg/mL) | 92.45 (67.8) | 83 | 111.8 (47.4) | 84 |
| $T_{max}$ (hr) | 0.25 (0.12, 1.08) | 83 | 0.25 (0.12, 1.00) | 84 |
| $K_{el}$ (1/hr) | 1.02 ± 0.37 | 72 | 1.16 ± 0.43 | 76 |
| $t_{1/2}$ (hr) | 0.79 ± 0.35 | 72 | 0.70 ± 0.30 | 76 |
| CL/F (L/hr) | 173.2 ± 112.26 | 72 | 160.5 ± 91.940 | 76 |

PF708: PF708 20 mcg subcutaneously (SC), once daily (QD) for 24 weeks
Forteo: Forteo 20 mcg SC QD for 24 weeks
$AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and $C_{max}$ are presented as geometric mean (geometric coefficient of variation).
$T_{max}$ is presented as median (minimum, maximum).
AUC%extrap, $K_{el}$, $t_{1/2}$, and CL/F are presented as arithmetic mean ± SD.
n = Number of observations used in the analysis
Source: Tables 14.2.1.3 through 14.2.1.4 in the Celerion ADA/BTM/PK report, Appendix 16.5

## 2.4.2. Pharmacodynamics

PD was a secondary endpoint in Study PF708-101 and in Study PF708-301.

***Study PF708-101***

PD samples were collected within 30 min predose and postdose at 1, 2, 3, 4, 6, 8, 12, and 24 hours (±5 min) in Period 1 (Day 1-2) and Period 2 (Day 5-6).

PD parameter

The PD endpoint for the study PF708-101 included serum ionised Ca2+ concentrations and changes from baseline after SC administration of a single 20 mcg dose of PF708 or Forteo in healthy volunteers.

Serum calcium concentrations were summarised by treatment received and presented graphically. For the statistical analysis, raw data for changes from baseline were analysed using a mixed model. The model included sequence, period, treatment, time, and treatment by time interaction as fixed effects and subject (sequence) as a random effect. The least squares (LS) means and 90% confidence intervals (CIs) for the difference between the PF708 and Forteo were calculated. In addition, the P-values for the differences between both treatments at each specified time-point were calculated.

**Results**

Participant Flow

All 70 subjects were included in the PD analyses.

PD parameter

**Table 11-5: Statistical Analysis of Change From Baseline in Serum Ionized $Ca^{2+}$ (normalized to pH 7.4) After Treatment With PF708 or Forteo**

Parameter: Change from Baseline in Ionized Serum $Ca^{2+}$ at pH 7.4 (mmol/L)

| | 20 mcg PF708 (Test) | | 20 mcg Forteo (Reference) | | | | |
|---|---|---|---|---|---|---|---|
| Timepoint | n[a] | LS Mean[b] | n[a] | LS Mean[b] | Test-Reference[c] | 90% Confidence Interval[d] | p-value |
| 1 h | 70 | 0.00729 | 70 | 0.00814 | -0.000857 | (-0.00861, 0.00690) | 0.8556 |
| 2 h | 70 | 0.0131 | 70 | 0.00657 | 0.00657 | (-0.00119, 0.0143) | 0.1633 |
| 3 h | 70 | 0.0136 | 70 | 0.0133 | 0.000286 | (-0.00747, 0.00804) | 0.9516 |
| 4 h | 70 | -0.00186 | 70 | -0.00157 | -0.000286 | (-0.00804, 0.00747) | 0.9516 |
| 6 h | 70 | 0.0216 | 70 | 0.0204 | 0.00114 | (-0.00661, 0.00890) | 0.8083 |
| 8 h | 70 | 0.00529 | 70 | 0.00229 | 0.00300 | (-0.00476, 0.0108) | 0.5243 |
| 12 h | 70 | -0.0173 | 70 | -0.0179 | 0.000571 | (-0.00719, 0.00833) | 0.9035 |
| 24 h | 70 | -0.00500 | 70 | -0.00857 | 0.00357 | (-0.00419, 0.0113) | 0.4485 |

[a] n was the number of observations for each treatment used in the model.
[b] Least squares means from mixed model with sequence, period, treatment, time, treatment by time interaction as fixed effects and subject within sequence as a random effect with the autoregressive(1) covariance structure.
[c] Difference of least squares means for parameter between test and reference(ie, test - reference).
[d] The 90% confidence interval for difference of least squares means.
Reference: Table 14.2.2-1
Program Location: /cvn/projects/prj/development/000000146883/dev/tables/t_pd_stat.sas
Program Run: 12MAY16 cvn_x1chen Program Status: FINAL

Data from Day 1 and Day 5 were pooled, and the LS means for changes from baseline for each treatment and at each specified timepoint were shown in the table. The calculated *P*-values at alpha level = 0.1 demonstrated that there were no significant differences between PF708 and Forteo in change from baseline of serum ionised $Ca^{2+}$ normalised to pH 7.4 at any specified time-point from 1 – 24 hours post dosing.

***Study PF708-301***

The PD endpoints for the study PF708-301 included the mean percentage change in lumbar-spine (L1-L4) bone mineral density (BMD) and the median percentage change in serum BTM concentrations of P1NP (N-terminal propeptide of type 1 collagen) and CTX (crosslinked C-terminal telopeptide of type 1 collagen) after baseline, 12 and 24 weeks of treatment with PF708 or Forteo.

PD parameters

- *Bone Mineral Density*

Lumbar-spine (L1-L4) BMD was assessed using dual-energy x-ray absorptiometry (DXA), which is consistent with clinical practice and most clinical research protocols and is therefore supported. Scans were performed at screening to assess eligibility and to serve as baseline, at week 12, and at week 24.

The analysis and comparison of lumbar-spine BMD data were performed separately for male and female patients.

- *Change in Serum BTM Concentrations of P1NP and CTX*

Blood serum was analysed for changes from baseline in P1NP and CTX. Blood was drawn for analysis on Day 1 (pre-dose) as baseline, at Week 12, and at Week 24.

**Results**

Participant Flow

84 PF708-treated patients (92.3%) and 86 Forteo-treated patients were included (94.5%) in the BMD population that compromised all patients in the safety population with a non-missing baseline value and at least one post-dose DXA assessment.

PD parameter

- *Bone Mineral Density*

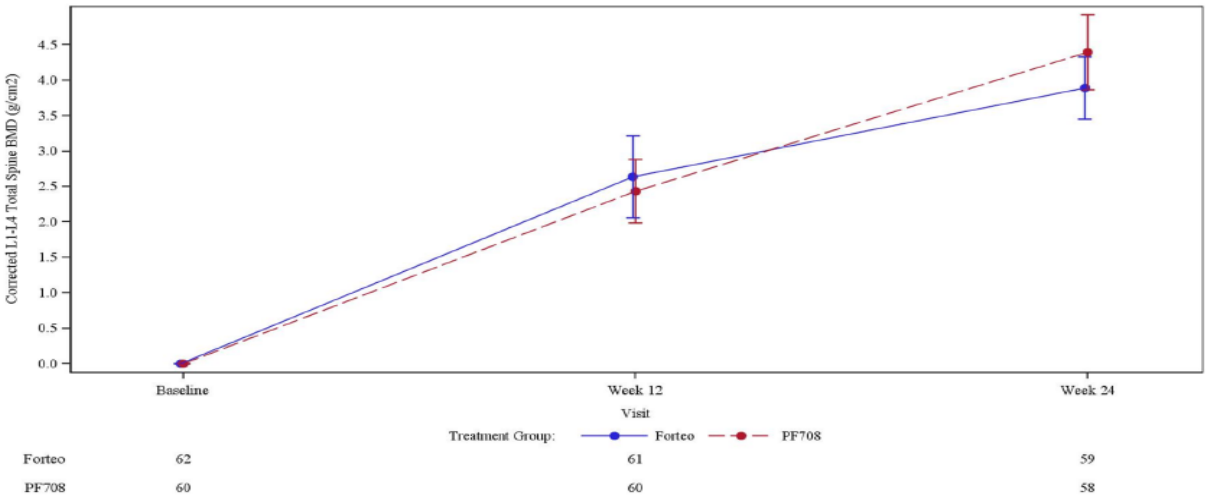
The percent change from baseline in L1-L4 total spine BMD is summarised for females and males in separated tables.

*Bone Mineral Density Results in Female Patients*

Mean baseline corrected L1-L4 total spine BMD values were similar for female patients in the PF708 and Forteo groups. Mean BMD values increased to 0.8643 and 0.8642 for patients in the PF708 and Forteo groups, respectively at Week 12 (2.4324% and 2.6389% increase from baseline) and at Week 24 to 0.8789 and 0.8744 (4.3955% and 3.8911% increase from baseline).

Difference in percent increase in corrected L1-L4 total spine BMD at Week 24 was not considered as clinically meaningful or statistically different (P-value = 0.568) between PF708 and Forteo.

**Figure 6-1 Line Plot of Percent Change from Baseline in Corrected L1-L4 Total Spine BMD in Females (BMD Population)**




Abbreviation: BMD, bone mineral density.
Mean ± standard error is presented by visit in each treatment group.
Baseline was defined as the last nonmissing measurement prior to dosing. Percent change from baseline: (postbaseline value – baseline value) / baseline value × 100%. For percent change from baseline, only patients with a value at both the baseline visit and the specific postbaseline visit were included.
Source: Figure 14.2.3.3.

Statistical analysis of corrected total hip BMD and corrected femoral neck BMD demonstrated similar results for female patients. The percent increases in corrected total hip BMD and corrected total femoral neck BMD at Week 24 were not statistically significant (corrected total hip BMD: P=0.828 and corrected total femoral neck BMD: P=0.228).

**Table 6-3 Percent Change from Baseline in Bone Mineral Density at Week 24 in Females, MMRM Analysis (BMD Population)**

| Variable | Group | n | Estimated LS Mean in Percent Change from Baseline[a] | Comparison between PF708 and Forteo | | |
|---|---|---|---|---|---|---|
| | | | | Estimated LS Mean Difference | 95% CI | *P* value |
| Corrected L1-L4 Total Spine BMD (g/cm$^2$) | PF708 | 60 | 4.4 | 0.4 | (–0.9, 1.7) | 0.568 |
| | Forteo | 62 | 4.0 | | | |
| Corrected Total Hip BMD (g/cm$^2$) | PF708 | 60 | 0.7 | –0.1 | (–1.1, 0.9) | 0.828 |
| | Forteo | 63 | 0.8 | | | |
| Corrected Total Femoral Neck BMD (g/cm$^2$) | PF708 | 60 | 0.8 | 0.8 | (–0.5, 2.1) | 0.228 |
| | Forteo | 63 | 0.0 | | | |

Abbreviations: BMD, bone mineral density; LS; least square; MMRM, mixed model repeated measures; n, number.

Baseline was defined as the last nonmissing measurement prior to dosing. The percent changes from baseline of PF708 and Forteo were analyzed using MMRM analysis, which included treatment group, study visit, baseline value, and treatment-by-visit interaction as the fixed effects. The variance-covariance matrix was assumed to be unstructured. A mean difference greater than 0 favored the PF708 treatment group.

[a] Percent change from baseline: (postbaseline value – baseline value) / baseline value × 100.

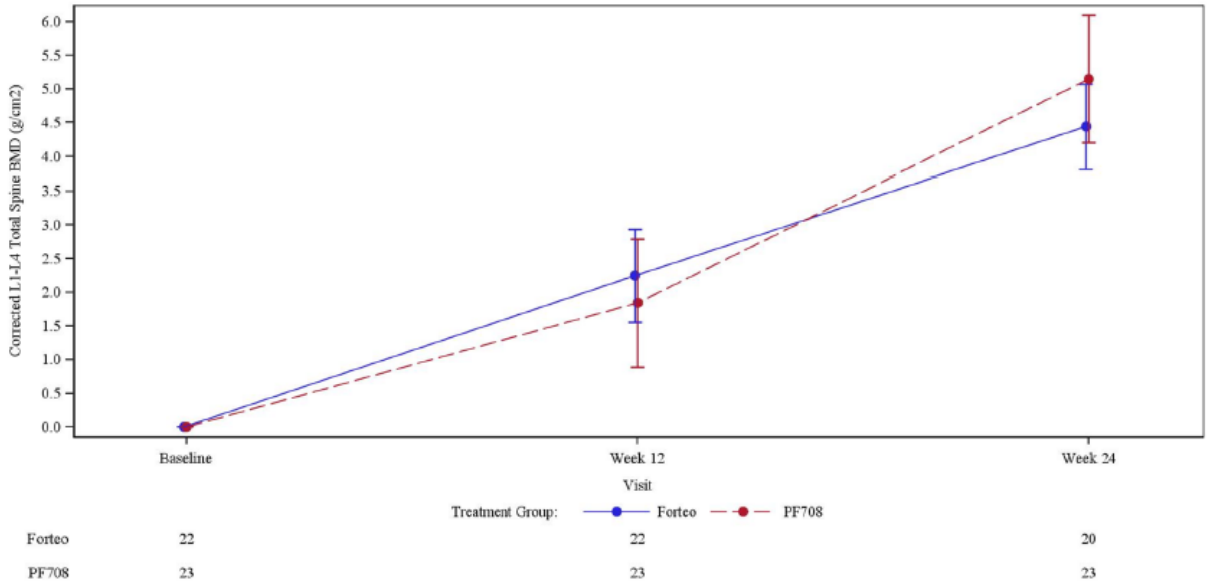
Source: Table 14.2.4.1.

*Bone Mineral Density Results in Male Patients*

The mean baseline corrected L1-L4 total spine BMD values of the male population were similar in the PF708 and Forteo groups. Mean BMD values increased at Week 12 to 0.9731 and 0.9945 for patients in the PF708 and Forteo groups, respectively (increase from baseline of 1.8445% and 2.2451%, respectively) at Week 24 (5.1491% and 4.4415%, respectively).

The difference in percent increase was not considered clinically meaningful, and statistical analysis of these results indicated that the percent increases in corrected L1-L4 total spine BMD at Week 24 were not statistically significant (*P*=0.529).

**Figure 6-2 Line Plot of Percent Change from Baseline in Corrected L1-L4 Total Spine BMD in Males (BMD Population)**




Abbreviation: BMD, bone mineral density.

Mean ± standard error is presented by visit in each treatment group.

Baseline was defined as the last nonmissing measurement prior to dosing. Percent change from baseline: (postbaseline value – baseline value) / baseline value × 100%. For percent change from baseline, only patients with a value at both the baseline visit and the specific postbaseline visit were included.

Source: Figure 14.2.3.4.

Results for corrected total hip BMD and corrected total femoral neck BMD demonstrated slightly greater variability than those for total spine BMD, but statistical analysis of the percent increases in corrected total hip BMD and corrected total femoral neck BMD at Week 24 were not statistically significant (*P*=0.441 and *P*=0.107, respectively).

**Table 6-5 Percent Change from Baseline in Bone Mineral Density at Week 24 in Males, MMRM Analysis (BMD Population)**

| Variable | Group | n | Estimated LS Mean in Percent Change from Baseline[a] | Comparison between PF708 and Forteo | | |
|---|---|---|---|---|---|---|
| | | | | Estimated LS Mean Difference | 95% CI | *P* value |
| Corrected L1-L4 Total Spine BMD (g/cm$^2$) | PF708 | 23 | 5.1 | 0.8 | (–1.6, 3.1) | 0.529 |
| | Forteo | 22 | 4.4 | | | |
| Corrected Total Hip BMD (g/cm$^2$) | PF708 | 24 | 0.5 | –0.8 | (–2.9, 1.3) | 0.441 |
| | Forteo | 23 | 1.3 | | | |
| Corrected Total Femoral Neck BMD (g/cm$^2$) | PF708 | 24 | 1.9 | 1.9 | (–0.4, 4.3) | 0.107 |
| | Forteo | 23 | 0.0 | | | |

Abbreviations: BMD, bone mineral density; LS; least square; MMRM, mixed model repeated measures; n, number.

Baseline was defined as the last nonmissing measurement prior to dosing. The percent changes from baseline of PF708 and Forteo were analyzed using MMRM analysis, which included treatment group, study visit, baseline value, and treatment-by-visit interaction as the fixed effects. The variance-covariance matrix was assumed to be unstructured. A mean difference greater than 0 favored the PF708 treatment group.

[a] Percent change from baseline: (postbaseline value – baseline value) / baseline value × 100.

Source: Table 14.2.4.2.

- *Change in Serum BTM Concentrations of P1NP and CTX*

*P1NP concentrations*

**Table 6-9 Summary of Statistical Comparisons of Serum P1NP Concentration Values**

| Week | PF708 Geometric LSM | PF708 n | Forteo Geometric LSM | Forteo n | Confidence Intervals GMR (%) | 90% Confidence | *P* value |
|---|---|---|---|---|---|---|---|
| Week 12 | 82.30 | 79 | 80.99 | 84 | 101.62 | 88.36 - 116.85 | 0.8499 |
| Week 24 | 101.3 | 78 | 86.51 | 80 | 117.04 | 101.70 - 134.70 | 0.0657 |

Abbreviations: GMR = geometric mean ratio; n = number of observations used in the analysis; P1NP = N-terminal propeptide of type 1 procollagen
PF708: PF708 20 mcg subcutaneously (SC), once daily (QD) for 24 weeks (test)
Forteo: Forteo 20 mcg SC QD for 24 weeks (reference)
Concentrations were ln-transformed prior to analysis.
Geometric least squares means (LSMs) are calculated by exponentiating the LSMs derived from the analysis of covariance (ANCOVA).
Geometric mean ratio was estimated by taking the antilog of the difference in the treatment LSM and associated confidence interval.
Treatments are considered statistically significantly different if the observed *P* value is <0.05.
Source: Table 14.2.3.2, Appendix 16.5

The GMR values for P1NP were 101.62% at Week 12 and 117.04% at Week 24 for PF708 and Forteo, which resulted in statistically non-significant *P* values (at Week 12 *P* = 0.8499 and at Week 24 *P* = 0.0657).

*CTX concentrations*

**Table 6-11 Summary of Statistical Comparisons of Serum CTX Concentration Values**

| | PF708 | | Forteo | | Confidence Intervals | | |
|---|---|---|---|---|---|---|---|
| Week | Geometric LSM | n | Geometric LSM | n | GMR (%) | 90% Confidence | *P* value |
| Week 12 | 0.5675 | 79 | 0.5450 | 85 | 104.13 | 89.57 - 121.06 | 0.6577 |
| Week 24 | 0.6408 | 76 | 0.6299 | 79 | 101.72 | 87.29 - 118.53 | 0.8543 |

Abbreviations: CTX = cross-linked C-terminal telopeptide of type 1 collagen; GMR = geometric mean ratio; n = number of observations used in the analysis
PF708: PF708 20 mcg subcutaneously (SC), once daily (QD) for 24 weeks (test
Forteo: Forteo 20 mcg SC QD for 24 weeks (reference)
Concentrations were ln-transformed prior to analysis.
Geometric least squares means (LSMs) are calculated by exponentiating the LSMs derived from the analysis of covariance (ANCOVA).
Geometric mean ratio was estimated by taking the antilog of the difference in the treatment LSM and associated confidence interval.
Treatments are considered statistically significantly different if the observed *P* value is <0.05.
Source: Table 14.2.3.3, Appendix 16.5

The GMR values for CTX (PF708 as test and Forteo as reference) were 104.13% at Week 12 and approximately 101.72% at Week 24. Statistical analysis for both time points (Week 12, *P*-value 0.6577 and Week 24, *P*-value 0.8543) demonstrated statistically non-significant differences in CTX concentration in patients either treated with PF708 or Forteo.

## 2.4.3. Discussion on clinical pharmacology

*Pharmacokinetics*

In general, and aside from the raised and resolved quality concerns (e.g. regarding biosimilarity, material used in clinical trials, and bridging from EU to US reference), the development programme to demonstrate similarity between PF708 and Forteo with respect to PK is considered adequate and was performed in line with the guidance on similar biological products and broadly in line with Scientific advice obtained from the EMA.

The clinical programme of PF708 is comprised of two studies with pharmacokinetic, pharmacodynamic and immunogenicity endpoints.

Pivotal evidence for PK biosimilarity assessment is derived from the single dose, crossover study PF708-101 in healthy volunteers, where PF708 and Forteo (US-originator) were administered. This study used the 20 mcg dose, and included PK parameters as primary endpoints and PD parameters as secondary endpoints.

Supportive patient PK data is derived from immunogenicity trial PF708-301 that also used the fixed 20 mcg dose and evaluated PK concentrations and PK parameters as secondary endpoints.

Study PF708-101 was conducted in healthy subjects. This is in line with applicable guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) stating that "in order to reduce variability not related to differences between products, the studies should normally be performed in healthy volunteers unless the drug carries safety concerns that make this unethical". The *in vivo* healthy volunteer model is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the reference medicinal product is approved (the elderly, children,

patients with renal or liver impairment, etc.). Therefore, it is agreed that healthy volunteers represent the most sensitive study population for conducting the PK comparison.

A crossover design was chosen to evaluate PK and PD comparability of PF708 and Forteo. A wash-out period of 3 days was applied between treatments to avoid bias in the PK analysis. Teriparatide concentrations in plasma were measured before dosing and at several time-points post-dosing. Narrower sampling times around Tmax would have better recorded the course of concentration and thus contributed to the assessment of biosimilarity. However, it can be assumed that the non-optimal sampling pattern did not introduce any systematic bias for the analysis, nor affect the analysis of the primary endpoints.

The 90.00% CIs for the ratio of the test and reference product geometric means for the PK parameters AUC0-last, AUC0-inf and Cmax were fully contained within the standard BE acceptance interval of 80.00-125.00%.

Study PF708-301 was not intended to evaluate PK equivalence between PF708 and Forteo. However, based on sparse PK sampling, similar PK profiles were observed. Even though PK was not the primary objective of this trial (but rather comparability in immunogenicity), the applicant presented the 90% CI for several PK parameters. Observed variability for Cmax and AUC 0-tlast resulted in 90% CIs broader than expected and the 90% CI were not entirely contained in the 80% - 125% acceptance range; hence, equivalence criteria were formally not met. Furthermore, the resulting 90% for Cmax does not cover "1" indicating a statistically significant difference. The applicant argued that the differences could be due to several factors, including a parallel study design, a heterogeneous study population, and multi-centre study conduct. Several patients had one or more missing samples that may have further increased data variability. Overall, study design was not optimal to demonstrate bioequivalence in the intended patient population.

Nevertheless, PK similarity was demonstrated in the pivotal PK-trial PF708-101 in healthy volunteers. No concern is raised regarding the patient PK data that - on a general level - seem rather confirmatory of the observed PK similarity in the more sensitive, healthy volunteer model.

*Pharmacodynamics*

The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1, states that "in exceptional cases, the confirmatory clinical trial may be waived if physicochemical, structural and *in vitro* biological analyses and human PK studies together with a combination of PD markers that reflect the pharmacological action and concentration of the active substance, can provide robust evidence for biosimilar comparability."

For teriparatide, considering the simplicity of the molecule that makes investigation of similarity on a quality level easier and potentially less prone to uncertainty regarding its translatability to clinical level, a dedicated comparative efficacy trial is in principle not considered necessary.

PD data (serum ionised Ca2+) from study PF708-101 in healthy volunteers; was evaluated as a surrogate marker of clinical efficacy and support of biosimilarity of both products. The difference between the LSMs for PF708 and Forteo, the respective 90% CI and p-values for the differences between the treatments at each specified time point were calculated.

Analyses of concentration-time profiles and statistical analyses of changes from baseline indicate that PF708 and Forteo had similar effects on the serum concentrations of ionised Ca2+ after single 20 mcg SC injections in healthy volunteers.

The fixed dose of 20 mcg PF708 was also tested in the repeat dose study PF708-301. The endpoints for PD comparability included the mean percentage change in lumbar-spine (L1-L4) bone mineral density (BMD) and the median percentage change in serum concentrations of the bone turn-over markers P1NP and CTX after 12 and 24 weeks of treatment with PF708 or Forteo.

Lumbar-spine (L1-L4) BMD was assessed using DXA and scans were performed at screening to assess eligibility and at Week 12, and at Week 24. For BTM analysis, blood was drawn for analysis pre-dose and at Week 12, and at Week 24 and serum was analysed for changes from baseline in P1NP and CTX.

Administration of PF708 and Forteo resulted in similar increases in lumbar-spine (L1-L4) BMD. Percent increases from baseline were comparable between both treatments in female and male patients at Week 12 and at Week 24. Total hip BMD and femoral neck BMD showed similar results. The percent increases in hip and femoral neck regions were smaller than those reported for total spine; however, results are in accordance with historical Forteo data.

Serum P1NP and CTX concentrations and median percent changes were similar after PF708 or Forteo treatment. Although P1NP concentrations showed larger variability in the PF708 test group than in the Forteo group, there were no statistically significant differences in these parameters.

The PD data could be considered supportive and the (secondary) PD endpoints have been met in both studies supporting comparability of PF708 and Forteo in PD.

### 2.4.4. Conclusions on clinical pharmacology

From a clinical point of view, all quality issues were resolved, PK/PD biosimilarity between PF708 and Forteo is considered to be supported. Comparability of the EU and US reference products Forsteo and Forteo (and thus, biosimilarity between PF708 and the EU reference product) has been demonstrated.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response studies

No dose-response study is required in the development of a biosimilar medicine. The proposed dosing regimen for Livogiva is identical to those approved for Forsteo.

### 2.5.2. Main study(ies)

Efficacy, safety and immunogenicity supportive data was generated in study PF708-101 and in study PF708-301. No dedicated efficacy study has been performed.

Clinical efficacy of PF708 was investigated based on the PD parameters:

- Serum ionised Ca2+ concentrations (Study PF708-101)
- Bone mineral density (Study PF708-301)
- Serum BTM (P1NP and CTX) concentrations (Study PF708-301).

The clinical development programme of PF708, conducted in sensitive study settings in healthy volunteers and osteoporosis patients, demonstrated comparability to Forteo with regard to serum ionised Ca2+ concentrations, BMD, and serum BTM concentrations of P1NP and CTX.

Detailed information in section Pharmacodynamics.

## Summary of main study(ies)

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 biosimilarity assessment (see later sections).

**Table 2. Summary of Efficacy for trial PF708-301**

| **Title**: A Randomized Study Comparing the Effects of PF708 and Forteo in Patients with Osteoporosis | | | |
|---|---|---|---|
| Study identifier | PF708-301 | | |
| Design | Randomised, multi-centre, parallel-group, open-label phase 3 study to compare the effects of PF708 and Forteo after 24 weeks of treatment. A total of 182 men and women with osteoporosis were randomly assigned to receive PF708 or Forteo (randomisation ratio 1:1). Randomisation was stratified according to sex. Each study patient received 24 weeks of 20-mcg dose of PF708 or Forteo by daily SC self-injection in the abdomen or thigh (the first dose was administered at the clinic). | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 24 weeks<br>not applicable<br>1 week safety follow-up |
| Hypothesis | Equivalence | | |
| Treatments groups | PF708 | | 20 mcg/80 µL once daily for 24 weeks by SC self-injection in the abdomen or thighs using disposable delivery device (pen; each pen delivers a daily dose for 28 days).<br>91 subjects randomised |
| | Forteo | | 20 mcg/80 µL once daily for 24 weeks by SC self-injection in the abdomen or thighs using disposable delivery device (pen; each pen delivers a daily dose for 28 days).<br>91 subjects randomised |
| Endpoints and definitions | Primary endpoint | ADA (incidence) | Incidence of ADA after 24 weeks of treatment |
| | Secondary endpoint | ADA (titre) | For ADA-positive patients ADA titre at week 24 |
| | | NAb (incidence) | For ADA-positive patients incidence of neutralising antibodies (NAb) at week 24 |
| | | ADA cross-reacting with endogenous $PTH_{1-84}$ (incidence, titre) | For ADA-positive patients incidence and titre of ADA that cross-react with endogenous $PTH_{1-84}$ at week 24 |
| | | Change in L1-L4 BMD (mean %) | Mean percentage change in lumbar-spine (L1-L4) BMD after 24 weeks of treatment |
| | | AUC0-last | Plasma area-under-the-curve (AUC0-last) of teriparatide after a single injection |
| | | AUC0-inf | Plasma area-under-the-curve (AUC0-inf) of teriparatide after a single injection |
| | | Cmax | Plasma maximum concentration (Cmax) of teriparatide after a single injection |
| | | t1/2 | Plasma elimination half-life (t1/2) of teriparatide after a single injection |
| | | CL/f | Plasma clearance (CL/f) of teriparatide after a single injection |
| | | Tmax | Plasma time to maximum concentration (Tmax) of teriparatide after a single injection |
| | | Kel | Plasma elimination rate constant (Kel) of teriparatide after a single injection |

| | | | |
|---|---|---|---|
| | | Change in P1NP (median %) | Median percentage change in serum BTM concentrations of N-terminal propeptide of type 1 procollagen (P1NP) (reflecting bone formation) after 24 weeks of treatment |
| | | Change in CTX (median %) | Median percentage change in serum BTM concentrations of crosslinked C-terminal telopeptide of type 1 collagen (CTX) (reflecting bone resorption) after 24 weeks of treatment |
| | Safety endpoint | AE (incidence) | AE incidence |
| | | SAE (incidence) | Serious AE (SAE) incidences |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Safety population: subjects who receive at least 1 dose of study drug<br>Immunogenicity population: all subjects in the Safety Population, with a nonmissing baseline value and at least one post-dose blood sample analysed for ADA.<br>Week 24 | | |
| Descriptive statistics and estimate variability | Treatment group | PF708 | Forteo |
| | Number of subjects | 81 | 81 |
| | ADA incidence (N) | 2 | 0 |
| | % | 2.47 | 0 |
| Effect estimate per comparison | ADA incidence | Comparison groups | PF708 vs Forteo |
| | | Fisher's Exact Test | |
| | | variability statistic | -- |
| | | P-value | 0.4969 |

| **Analysis description** | **Secondary analysis** | | |
|---|---|---|---|
| Analysis population and time point description | ADA-positive patients.<br>BMD Population: all subjects in the Safety Population, with a non-missing baseline value and at least one post-dose DXA assessment.<br>PK Population: all subjects in the Safety Population who receive both PF708 and Forteo, with at least one post-dose blood sample analysed for PK.<br>Week 24 | | |
| Descriptive statistics and estimate variability | Treatment group | PF708 | Forteo |
| | Number of subjects | 60 (ADA-positive)<br>84 (BMD)<br>89 (PK) | 63 (ADA-positive)<br>86 (BMD)<br>91 (PK) |
| | ADA titre | ~1 | - |
| | variability statistic | - | - |
| | NAb incidence (N) | 0 | 0 |
| | % | 0 | 0 |
| | ADA cross-reacting with endogenous $PTH_{1-84}$ incidence, titre (N) | 0 | 0 |
| | % | 0 | 0 |
| | Change in L1-L4 BMD (mean %) | F: 4.3955<br>M: 5.1491 | F: 3.8911<br>M: 4.4415 |
| | SE | F: 0.52920<br>M: 0.94750 | F: 0.43812<br>M: 0.62893 |
| | AUC0-last pg*hr/mL (geom. mean) | 111.4 | 122.0 |
| | Geom. coeff. var. | 75.3 | 60.0 |
| | AUC0-inf pg*hr/mL (geom. mean) | 133.6 | 141.5 |
| | Geom. coeff. var. | 54.6 | 51.8 |
| | Cmax pg/mL (geom. mean) | 92.45 | 111.8 |
| | Geom. coeff. var. | 67.8 | 47.4 |
| | t1/2 hr (ar. mean) | 0.79 | 0.70 |
| | SD | 0.35 | 0.30 |
| | CL/f L/hr (ar. mean) | 173.2 | 160.5 |

| | | | |
|---|---|---|---|
| | SD | 112.26 | 91.940 |
| | Tmax hr (median) | 0.25 | 0.25 |
| | Min, max | (0.12, 1.08) | (0.12, 1.00) |
| | Kel 1/hr (ar. mean) | 1.02 | 1.16 |
| | SD | 0.37 | 0.43 |
| | Change in P1NP ng/mL (median %) | 100.93 | 87.744 |
| | Min ; max | -34.04 ; 1720 | -39.89 ; 818.6 |
| | Change in CTX ng/mL (median %) | 85.839 | 89.167 |
| | Min ; max | -51.98 ; 895.6 | -60.52 ; 658.2 |
| Effect estimate per comparison | ADA titre, NAb incidence, ADA cross-reacting with endogenous $PTH_{1-84}$ incidence, titre | Comparison groups | PF708 vs Forteo |
| | | test statistic | -- |
| | | variability statistic | -- |
| | | P-value | -- |
| | Change in L1-L4 BMD g/cm$^2$ (mean %) | Comparison groups | PF708 vs Forteo |
| | | LS Mean Difference | F: 0.4<br>M: 0.8 |
| | | 95% CI | F: (−0.9, 1.7)<br>M: (−1.6, 3.1) |
| | | P-value | F: 0.568<br>M: 0.529 |
| | AUC0-last pg*hr/mL (ln-transformed) | Comparison groups | PF708 vs Forteo |
| | | GMR (%) | 91.33 |
| | | 90% CI | 78.03 - 106.90 |
| | | Intersubject CV% | 67.76 |
| | AUC0-inf pg*hr/mL (ln-transformed) | Comparison groups | PF708 vs Forteo |
| | | GMR (%) | 94.39 |
| | | 90% CI | 82.40 - 108.12 |
| | | Intersubject CV% | 53.16 |
| | Cmax pg/mL (ln-transformed) | Comparison groups | PF708 vs Forteo |
| | | GMR (%) | 82.67 |
| | | 90% CI | 72.02 - 94.88 |
| | | Intersubject CV% | 57.98 |
| | t1/2, CL/f, Tmax, Kel | Comparison groups | PF708 vs Forteo |
| | | test statistic | -- |
| | | variability statistic | -- |
| | | P-value | -- |
| | Serum P1NP concentration (ln-transformed) | Comparison groups | PF708 vs Forteo |
| | | GMR (%) | 117.04 |
| | | 90% CI | 101.70 - 134.70 |
| | | P-value | 0.0657 |
| | Change in CTX concentration (ln-transformed) | Comparison groups | PF708 vs Forteo |
| | | GMR (%) | 101.72 |
| | | 90% CI | 87.29 - 118.53 |
| | | P-value | 0.8543 |
| **Analysis description** | **Safety analysis** | | |
| Analysis population and time point description | Safety population: subjects who receive at least 1 dose of study drug<br>Week 24 | | |
| Descriptive statistics and estimate variability | Treatment group | PF708 | Forteo |
| | Number of subjects | 90 | 91 |
| | AE incidence (N) | 75 | 73 |
| | % | 83.3 | 80.2 |
| | SAE incidence (N) | 6 | 8 |
| | % | 6.7 | 8.8 |

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

Not applicable.

## Clinical studies in special populations

Not applicable for biosimilars.

### *Supportive study(ies)*

***Human Factors Validation Study***

The PF708 pen injector was evaluated during a single-centre, unblinded, observational, simulated use Human Factors validation study. The PF708 Human Factors Validation Study was developed to identify usage errors along with their reported causes of 95 participants, consisting of representative trained/ untrained patients and caregivers, untrained HCPs, and untrained Forteo-experienced user groups.

The performance of the participants has been defined as critical tasks (defined as tasks associated with a potential use error with significant harm) and essential tasks (defined as tasks that must be performed to use the device for the intended purpose but that are associated with a potential use error with a less severity of harm).

Participants were evaluated based on objective observations made by the moderator and objective third-party personnel observing the sessions, as well as subjective feedback from the participant at the end of a simulated use exercise. A root cause analysis to assess the potential for harm that could be caused by any use error was conducted. Recommendations for mitigations were made to further reduce these errors.

The findings showed that the Pfenex PF708 pen injector can be safely and successfully used by Forteo-experienced and Forteo-naïve osteoporosis patients as well as caregivers and HCPs.

## 2.5.3. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

Not applicable.

### *Efficacy data and additional analyses*

Similar efficacy for a biosimilar medicinal product can only be assumed if – in a stepwise approach – comparability to the reference product has been established on the physicochemical, biological and non-clinical level, and comparable clinical results are shown.

No dedicated efficacy study has been performed, which is acceptable for teriparatide in principle. Biosimilarity testing at the clinical level is based on the comparative PK study performed in healthy subjects (under Pharmacokinetics section). The applicant further conducted an immunogenicity study (under safety section). Several PD parameters (serum calcium, BMD and bone turnover markers P1NP and CTX) were analysed comparatively in these two studies as surrogates for efficacy; results are overall supportive of similar efficacy of the biosimilar candidate and the reference product Forteo.

## 2.5.4. Conclusions on the clinical efficacy

Under Conclusion on clinical pharmacology and Discussion on Benefit/Risk.

## *2.6. Clinical safety*

The safety evaluation regarding PF708 is based on two clinical studies. Safety data provided in support of this biosimilarity application was from the bioequivalence study PF708-101 in 70 healthy subjects and the comparative clinical immunogenicity study PF708-301 conducted in 191 women with PMO and men with primary osteoporosis.

***Immunogenicity Study PF708-301***

Study title

A randomised study comparing the effects of PF708 and Forteo in patients with osteoporosis.

Study centres

This was a multi-centre study in 27 study centres in the United States.

Study design

This was a randomised, multi-centre, parallel-group, open-label study conducted in the United States to compare the effects of PF708 and Forteo after 24 weeks of treatment. A total of 182 men and women with osteoporosis were randomly assigned to treatment. Half of the patients were randomly assigned to receive PF708, and the other half were randomly assigned to receive Forteo. Each patient received 24 weeks of PF708 or Forteo by daily SC self-injection in the abdomen or thigh, except the first dose, which was administered by the Principal Investigator or a trained and qualified designee at the clinic.

Objectives

The primary objective was to compare the effects of PF708 and Forteo on immunogenicity after 24 weeks of SC daily dosing in patients with osteoporosis.

The secondary objective was to compare the PK, PD, and AE profile of PF708 and Forteo in patients with osteoporosis.

Study participants

Patients were 66.6 (± 8.38) years of age, and 58.6% were between the ages of 65 and 85 years. The majority of subjects were female (72.4%) and white (90.1%). Mean body mass index (BMI) was 26.42 kg/m2. The number and percentage of patients who met the spinal fracture eligibility criteria was similar between the PF708 and Forteo groups. Of the 29 female subjects in each group who had their spine x-ray assessed, 16 (24.6%) of the 65 females in the PF708 group and 17 (25.8%) of the 66 females in the PF708 group met spine x ray eligibility criteria.

The most frequently observed concomitant medications in PF708- and Forteo-treated groups were calcium (by 75.6% and 68.1% of patients, respectively) and cholecalciferol by 57.8% and 63.7% of patients, respectively. The incidences of concomitant use of Vitamin D analogues and calcium by patients in the PF708 and Forteo groups were similar.

Treatments

- PF708 (test): Daily doses for 24 weeks of 20 mcg/80 µL SC injection of PF708 (Pfenex Inc.)

- Forteo (reference): Daily doses for 24 weeks of 20 mcg/80 µL SC injection of Forteo (Eli Lilly and Company).

PF708 and Forteo were supplied as teriparatide 20 mcg/80 µL SC solution for injection. Each drug was supplied as a sterile, colourless, clear, isotonic solution in a glass cartridge, which was pre-assembled into a disposable delivery device (pen) for SC injection.

## *Patient exposure*

All randomised patients received 24 weeks of PF708 or Forteo by daily SC self-injection, except of the first dose, which was administered by the investigator or a trained and qualified designee in the clinic.

82 (90.1%) patients in the PF708 group and 81 (89.0%) patients in the Forteo group completed active study treatment. The safety analysis (safety population) included all subjects who received at least one dose of study drug. 181 patients (99.5%) were included in the safety analysis.

The immunogenicity population included all patients in the safety population with a non-missing baseline value and at least 1 post-dose blood sample analysed for ADA. 179 patients (98.4%) were included in the immunogenicity analysis.

### *Adverse events*

**Table 7-4 Unrelated and Related Treatment-Emergent Adverse Events Occurring in More Than 5% of Patients in Either Treatment Group (Safety Population)**

| System organ class<br>Preferred term | PF708 (N = 90) n (%) | | Forteo (N = 91) n (%) | | Total (N = 181) n (%) | |
|---|---|---|---|---|---|---|
| | Unrelated | Related | Unrelated | Related | Unrelated | Related |
| Total number of TEAEs | 156 | 105 | 168 | 108 | 324 | 213 |
| Number of patients with at least one TEAE | 27 (30.0) | 48 (53.3) | 28 (30.8) | 45 (49.5) | 55 (30.4) | 93 (51.4) |
| General disorders and administration site conditions | 5 (5.6) | 27 (30.0) | 7 (7.7) | 25 (27.5) | 12 (6.6) | 52 (28.7) |
| Injection site bruising | 3 (3.3) | 5 (5.6) | 0 | 7 (7.7) | 3 (1.7) | 12 (6.6) |
| Injection site erythema | 0 | 21 (23.3) | 0 | 15 (16.5) | 0 | 36 (19.9) |
| Injection site reaction | 0 | 3 (3.3) | 0 | 5 (5.5) | 0 | 8 (4.4) |
| Nervous system disorders | 9 (10.0) | 11 (12.2) | 8 (8.8) | 8 (8.8) | 17 (9.4) | 19 (10.5) |
| Headache | 3 (3.3) | 6 (6.7) | 0 | 4 (4.4) | 3 (1.7) | 10 (5.5) |
| Gastrointestinal disorders | 10 (11.1) | 3 (3.3) | 13 (14.3) | 6 (6.6) | 23 (12.7) | 9 (5.0) |
| Diarrhoea | 0 | 0 | 6 (6.6) | 0 | 6 (3.3) | 0 |
| Nausea | 5 (5.6) | 1 (1.1) | 3 (3.3) | 2 (2.2) | 8 (4.4) | 3 (1.7) |
| Infections and infestations | 31 (34.4) | 0 | 27 (29.7) | 1 (1.1) | 58 (32.0) | 1 (0.6) |
| Nasopharyngitis | 7 (7.8) | 0 | 9 (9.9) | 0 | 16 (8.8) | 0 |
| Sinusitis | 6 (6.7) | 0 | 2 (2.2) | 0 | 8 (4.4) | 0 |
| Upper respiratory tract infection | 5 (5.6) | 0 | 4 (4.4) | 0 | 9 (5.0) | 0 |
| Urinary tract infection | 8 (8.9) | 0 | 4 (4.4) | 0 | 12 (6.6) | 0 |

Abbreviations: TEAE, treatment-emergent adverse event.

The total number of adverse events counted all TEAEs for patients. At each level of patient summarization, a patient was counted once for the most related event if the patient reported one or more events. "Related" was defined as a relationship of possible, probable, or definite. "Not related" was defined as a relationship of unlikely or not related. If the relationship of an adverse event was missing, the adverse event was reported as "Definite". Adverse events were coded using MedDRA, Version 19.1.

Source: Table 14.3.2.2

Of the subjects dosed, 261 TEAEs were reported in the PF708 group and 276 TEAEs in the Forteo group. 53.3% of the patients in the PF708 group and 49.5% of the patients in the Forteo group reported a total of 213 TEAEs that were considered as related to study drug. 30% of the patients in the PF708-treated group and 30.8% of the Forteo-treated patients reported a total of 324 TEAE that was classified as unrelated to study drug.

Most TEAEs were judged with a Grade 1 and Grade 2 intensity. 22 patients (24.4%) were judged as Grade 1 within the PF708 group compared to 35 patients (38.5%) in the Forteo group. 47 patients (52.2%) of the PF708 group suffered from Grade 2 intensity compared to 27 patients (29.7%). 4 PF708-treated patients (4.4%) and 8 Forteo-treated patients (8.8%) had a severity of Grade 3

whereas 2 PF708-treated patients (2.2%) and 3 Forteo-treated patients (3.3%) had a severity of Grade 4.

The most common related TEAEs of both groups were in line with those listed in the Forsteo SmPC, mostly injection site erythema/ bruising/ reactions, and headache. A numerical imbalance was found in the occurrence of diarrhea (0 versus 6 patients [6.6% in the Forteo group]. However, diarrhea is considered to be a rather unspecific symptom that can be caused by multiple origins and is furthermore not known as a treatment-relevant adverse event of teriparatide.

No relevant difference in the occurrence of TEAES between Forteo and PF708 was observed.

### *Serious adverse event/deaths/other significant events*

**Table 7-5 Number (%) of Patients With Unrelated and Related Serious Treatment-Emergent Adverse Events (Safety Population)**

| | PF708 (N = 90) n (%) | | Forteo (N = 91) n (%) | | Total (N = 181) n (%) | |
|---|---|---|---|---|---|---|
| Description | Unrelated | Related | Unrelated | Related | Unrelated | Related |
| Total number of serious TEAEs | 6 | 1 | 9 | 0 | 15 | 1 |
| Number of patients with at least one serious TEAE | 5 (5.6) | 1 (1.1) | 8 (8.8) | 0 | 13 (7.2) | 1 (0.6) |
| Pneumonia | 1 (1.1) | 0 | 1 (1.1) | 0 | 2 (1.1) | 0 |
| Syncope | 1 (1.1) | 0 | 1 (1.1) | 0 | 2 (1.1) | 0 |
| Abdominal pain | 1 (1.1) | 0 | 0 | 0 | 1 (0.6) | 0 |
| Anaphylactic reaction | 0 | 1 (1.1) | 0 | 0 | 0 | 1 (0.6) |
| Asthenia | 0 | 0 | 1 (1.1) | 0 | 1 (0.6) | 0 |
| Atrial fibrillation | 1 (1.1) | 0 | 0 | 0 | 1 (0.6) | 0 |
| Carotid artery stenosis | 0 | 0 | 1 (1.1) | 0 | 1 (0.6) | 0 |
| Chronic obstructive pulmonary disease | 0 | 0 | 1 (1.1) | 0 | 1 (0.6) | 0 |
| Myocardial infarction | 1 (1.1) | 0 | 0 | 0 | 1 (0.6) | 0 |
| Non-cardiac chest pain | 1 (1.1) | 0 | 0 | 0 | 1 (0.6) | 0 |
| Non-small cell lung cancer | 0 | 0 | 1 (1.1) | 0 | 1 (0.6) | 0 |
| Pancreatitis | 0 | 0 | 1 (1.1) | 0 | 1 (0.6) | 0 |
| Paralysis | 0 | 0 | 1 (1.1) | 0 | 1 (0.6) | 0 |
| Squamous cell carcinoma of lung | 0 | 0 | 1 (1.1) | 0 | 1 (0.6) | 0 |

Abbreviations: TEAE, treatment-emergent adverse event.

The total number of adverse events counted all serious TEAEs for patients. At each level of patient summarization, a patient was counted once for the most related event if the patient reported one or more events. "Related" was defined as a relationship of possible, probable, or definite. "Not related" was defined as a relationship of unlikely or not related. If the relationship of an adverse event was missing, the adverse event was reported as "Definite". Adverse events were coded using MedDRA, Version 19.1.

Source: Table 14.3.2.4

Fourteen patients (7.7%) had SAEs during the study, 6 patients (6.7%) in the PF708 group and 8 patients (8.8%) in the Forteo group.

Except for one case of SAE (patient 127006, PF708 group), none of the SAEs that occurred during study PF708-301 were considered to be related to any of the study drugs, PF708 or Forteo.

Patient 127006 (PF708 group): On Day 5, the patient was found to have a SAE of anaphylactic reaction that was experienced as tongue and throat swelling. The patient reported in the hospital that the night prior, she started a topical facial cream (metronidazole) for rosacea. The emergency department diagnosis was allergic reaction and angioedema. The patient was discharged in a stable condition the same day and the swelling had resolved. 3 days later the patient gave herself another injection of the study drug and there were no AEs reported afterwards, although it was reported that the patient was not taking any anti-allergic treatment. When the patient visited the clinical site, no signs or symptoms indicated allergy to the additional dose of study drug she received the prior day.

The Investigator assigned anaphylaxis as the final diagnosis. The Medical Monitor independently assessed the event and deemed the patient's clinical presentation and physical findings to be more consistent with allergic reaction instead of anaphylaxis. Additionally, the Medical Monitor deemed the relationship to study drug as not related, due to: (1) the lengthy (>20 hours) temporal relationship of the event to study drug exposure, (2) potential confounding variables, including the start of a new medication the night prior to the event, and (3) the absence of AEs after repeated exposure to study drug. The patient received her last dose of study drug on Day 9. The study drug was withdrawn per decision by the investigator. The patient did not complete study treatment.

According to the clinical study report, it rather looked more like an allergic reaction than an anaphylactic shock.

No deaths were reported.

## *Laboratory findings*

Laboratory assessment was done at screening and at Week 1, 12 and 24. Chemistry, haematology, and urinalysis and incidence of hypercalcemia, medical history, vital sign measurements, physical examination, spinal x-ray, 12-lead ECG assessment, and concomitant medication use were evaluated.

Overall, changes in clinical chemistry and haematology parameters were generally similar for the PF708 and Forteo groups and no potential clinical concerns were reported for any laboratory test parameters.

No clinically meaningful observations or differences in vital signs or ECG findings were observed for the PF708 and Forteo groups.

The administration of PF708 seemed generally safe and well tolerated as a single daily 20 mcg SC injection.

## *Immunological events*

Immunogenicity was evaluated in the Phase 3 study PF708-301 as primary objective.

*Assay Validation*

Bioanalytical Methods Related to PF708-101

RPTX-0254 (CA17791-04) – Screening assay:

Immunogenicity was not specified as a study objective of study CA17791-02, due to single-dose, short-term treatment which was not expected to result in anti-drug antibody formation. However, to ensure a complete assessment and identify potential pre-existing antibodies in patients, a screening

assay was validated and performed. No assay for the detection of potential neutralising anti-drug antibodies was validated. According to recent guidance an assay for detection of neutralising antibodies (nAbs) should be validated irrespective of the expected outcome of the screening assay. However, no binding ADAs were detected in the course of this Phase I study (as expected due to the low immunogenic potential of the drug product as well as due to single-dose, short term treatment). A comprehensive assay validation was conducted for the nAb-assay for the Phase III study. Overall, lack of a validated nAb-assay for study PF708-101 is deemed acceptable considering the arguments listed.

The direct bridging ELISA method for the determination of anti-human PTH 1-34 (PF708) antibodies in human serum met the requirements as specified in the Study Validation Protocol. The ELISA method was validated with respect to precision, selectivity, specificity, sensitivity and titre precision, and stability. Stability was demonstrated for anti-PF708 antibodies in human serum samples under varying conditions of storage. It is acknowledged that validation report RPTX-0254 is the ADA validation report for study PF708-101. The applicant clarified that the used assay was further improved for the Phase III study. In the frame of this adaptation, the assay was additionally validated for its drug tolerance, with regard to interference in haemolysed samples, and high-dose hook effect.

Bioanalytical Methods Related to PF708-301

RPTX-0051 (ZZ49532-01) - Screening assay:

Human serum ADA levels were analysed using an ELISA method validated with respect to sensitivity, specificity, intra- and inter-assay precision, and short- and long-term stability. PF708 and Forteo showed similar results during cross validation of the screening assay, thus justifying the use of a single-assay approach for detection of both, biosimilar and reference product. With exception of the product specific correction factor, all important parameters (validation cut point, specificity cut point, assay sensitivity) appeared similar between the two products.

The validation screening cut point (vCP) was determined from sufficient individual lots of human serum, repeatedly analysed on different days, by different analysts, which is deemed acceptable.

Rabbit PF708 anti-drug antibody was used as the positive control. The antibody was specifically generated for this study. A COA for the PC antibody was provided.

Overall, it can be concluded that based on the cross validation of the assay, PF708 drug product and Forteo appear similar and a single-assay approach can be utilised for the measurement of both, anti-PF708 and anti-Forteo antibodies. The requirements as specified in the Validation Protocol were met.

RPTX-0022 (CA19715-01) - Neutralisation assay:

A bioassay kit based on signal luminescence was used for determination of potential anti-PF708 neutralising antibodies in human serum. The assay sensitivity was calculated to be 27.7 ng/ml (50% confidence interval). According to the submitted data, this value represents the assay sensitivity for anti-PTH mAb neutralising antibodies in human serum (82.5 ng/ml at 99% CI). Assay sensitivity for anti-PF708 neutralising antibodies in human serum was determined to be much higher (875.9 ng/ml at 99% CI). Assay sensitivity established with anti-PTH antibody was deemed more representative by the applicant, because it is known to be a monoclonal, neutralising antibody compared to PF708, which is of polyclonal nature containing both, binding and neutralising antibodies.

During selectivity testing, 4 out of 10 lots of osteoporotic human serum showed detectable levels of neutralising antibody in the unfortified matrix, whereas only one osteoporotic subject was reported with a positive nAb finding after treatment with PF708 or reference product, respectively. This was due to use of different cut point correction factors (established from either NHS or pre-dose samples, respectively). When using the correction factor established from pre-dose samples for selectivity testing in the assay validation none of the 10 osteoporotic lots would show positive results. PF708 was

used for assay validation of the applied neutralisation assay. No data on cross validation of the nAb assay was submitted. The applicant followed a risk-based approach during assessment of neutralising potential of ADAs, testing the neutralising impact of the PC only on PF708. This approach ensures that any nAbs against PF708 will be detected. Potential insensitivity against the reference product is regarded negligible in this approach which is in agreement with valid guidance. Additional dose-response curves were provided by the applicant. These data confirm similar assay response for both, PF708 and reference product.

*Statistical Methods*

The frequencies of ADA positive and -negative patients at Week 1, 4, 12, and 24 were analysed using Fisher's exact test. The two treatments were planned be considered statistically significantly different if the observed *P* value from the Fisher's exact test was <0.05.

With the chosen statistical testing approach, it was not investigated whether the effects of PF708 and Forteo on immunogenicity were equivalent. Interpreting non-significant results of a Fisher-Test as absence of a relevant difference in ADA incidence is not acceptable from a methodological point of view. In addition, no correction for multiple testing (statistical testing for 4 time points) was foreseen. Hence, the interpretation of trial outcome concerning non-relevant ADA incidence differences between the two treatments required further elaboration (in the Results section).

*Results*

Two PF708-treated patients and two Forteo-treated patients developed ADAs during the study. At Week 24, there were two ADA-positive findings for PF708 compared with none for Forteo; the difference was not statistically significant. Upon additional request, the difference in immunogenicity incidence between treatments (PF708 – Forteo) was estimated via 95% confidence intervals: incidence differences were 0.11% (with 95% CI: -15.1%; 15.4%) at week 12 and 2.47% (with 95% CI: -13.5%; 18.3%) at week 24. Overall, point estimates for immunogenicity incidence seemed comparable between treatment groups and low rates of immunogenicity observed in the study would be consistent with historical Forteo findings. However, for the assessment of biosimilarity, the upper limits of the derived confidence intervals need to be taken into consideration. When doing so, the magnitude of incidence differences that cannot be ruled out (based on the evidence generated in Study PF708-301) appears large.

PF708- related ADA findings were low in titre and became undetectable after cessation of therapy during follow-up, without apparent correlation with AEs of special interest or SAEs.

One PF708-treated patient had antibodies with neutralising activity transiently detected at Week 4. Since the values of % change in BMD for this single patient were compared to the collective of either PF708 or Forteo-treated male population, the discrepancy seen in % change in BMD is not considered meaningful. It seems however, that the transient *in vitro* neutralising activity did not correlate with an apparent loss of pharmacological activity.

However, while only one patient with positive nAb after treatment with PF708 was reported, selectivity testing reported 4 of 10 lots of osteoporotic human serum as positive; this needed further explanation (above in "Bioanalytical Methods Related to PF708-301").

## *Safety related to drug-drug interactions and other interactions*

Not applicable for biosimilars.

## *Discontinuation due to adverse events*

In the PF708 group were 3 patients (3.3%) and in the Forteo group were 5 patients (5.5%) that had at least one TEAE leading to treatment discontinuation. The total number of TEAEs leading to study treatment discontinuation was similar between the groups.

In the Forteo group 2 cases of lung cancer emerged during the treatment with the reference medicinal product Forteo, which were both not considered as study drug-related condition. Arthralgia was the only condition that occurred in both groups and was considered as possible-related. The other TEAEs leading to treatment discontinuation had only frequencies of 1 patient per group, which is deemed negligible. It is assumed that there were no relevant differences in the occurrence of TEAES between PF708 and reference product Forteo.

***Supportive safety data of Study PF708-101 (Pivotal biosimilar trial)***

Patient exposure

All 70 enrolled subjects were included in the safety evaluation.

Adverse events

The number of TEAEs was similar between the PF708 and Forteo treatment groups. 64.3% of the subjects in the PF708 treatment group 62.9% of the subjects in the Forteo treatment group reported a total of 61 TEAEs.

114 TEAEs were judged as mild (Grade 1), and within the PF708-treated group, 1 TEAE was judged as moderate (Grade 2). Of the 115 TEAEs, 110 were considered to be possibly or probably related to study drug, and 5 were considered to be unrelated to study drug.

The proportion of TEAEs seemed to be similarly distributed between the two groups.

The most frequently reported TEAEs were related to injection site findings (injection site erythema, haemorrhage, and pruritus). An approximately equal number of these TEAEs were reported in the PF708 treatment group (N=46) and the Forteo treatment group (N=44). All of these injection site TEAEs were considered to be related to study treatment by the Investigator.

Only one of the TEAEs (headache, Subject 148) was judged to be moderate (Grade 2), and the rest of the TEAEs were judged as mild (Grade 1). All TEAEs resolved by the end of the study, with the exception of 1 TEAE (ecchymosis; Subject 128) that was unrelated to study drug with an outcome listed as "Unknown" (Listing 16.2.7-1).

The symptoms of the PF708 test group (erythema, haemorrhage, pruritus, headache, dizziness, and nausea) are included in the spectrum of known side effects of teriparatide.

Adverse events in both groups PF708 and Forteo seem balanced.

Serious adverse events and deaths

No serious adverse event (SAE) or death occurred.

Laboratory findings

Laboratory assessment was done at screening and at Day 2, 4 and 6. Safety was evaluated by clinical laboratory tests (chemistry, haematology, and urinalysis), physical examination, vital signs, 12-lead electrocardiograms (ECGs), medical history, concomitant medication use, incidence of hypercalcemia, adverse events (AEs), anti-drug antibody (ADA) assessment and local/ systemic reaction assessments.

Changes in clinical chemistry and haematology parameters were generally similar for the PF708 and Forteo groups. Differences between treatment groups in the incidence rates of patients with significant abnormalities were not reported for any laboratory test parameters.

Immunological events

Serum ADA was measured from predose on Day 1 and Day 5 of each period in each subject.

No positive serum ADA samples were found.

Discontinuation due to AES

No AES lead to study discontinuation.

### *Post marketing experience*

PF708 has not yet been marketed and hence no post marketing data are available for PF708.

## 2.6.1. Discussion on clinical safety

*Adverse events*

The overall proportion of TEAEs observed in the immunogenicity study PF708-301 seemed to be similarly distributed between the two treatment groups. Also, the incidence of study drug-related or -unrelated TEAEs between patients of the PF708 group and the Forteo group was considered balanced. Most of the TEAEs reported were judged as Grade 1 and Grade 2 intensity. There were less Grade 1 and more Grade 2 TEAEs found in the PF708 test product- compared to the reference product arm. However, fewer patients were reported in the PF708 group with a more severe Grade 3 or even Grade 4 intensity. The type of AEs reported was in line with those listed in Forteo SmPC, mostly nausea, headache, and injection site erythema. Injection site reactions that occurred after PF708 treatment were identified in same frequencies as for Forteo (wherein is stated that mild and transient injection site findings are common). Adverse events reported in both study arms appeared in a balanced ratio.

The supportive safety data obtained from study PF708-101 demonstrated similar distribution of adverse events between PF708 and Forteo that were broadly judged from mild intensity and were also resolved by the end of the study. More subjects of the PF708 group suffered from erythema (44 events) compared to subjects from the Forteo group (40 events) and less subjects reported nervous system disorders (10 events) than subjects from the PF708 group (7 events). However, the differences between the groups seem rather negligible. The most frequently reported TEAEs were related to injection site findings (injection site erythema, haemorrhage, and pruritus). An approximately equal number of these TEAEs were reported between the study arms. The symptoms of the PF708 test group (erythema, haemorrhage, pruritus, headache, dizziness, and nausea) are included in the spectrum of known side effects of teriparatide. In this respect, adverse events in both groups PF708 and Forteo seem overall balanced.

*Serious adverse events and deaths*

Several SAEs that lead to study discontinuation occurred during trial PF708-301 but only one was considered from the Investigator as PF708 treatment-related. The patient of the PF708 group started (during daily PF708 injection) a metronidazole therapy for the treatment of rosacea, next day the patient experienced an anaphylactic reaction. Notwithstanding the above, the Medical Monitor assessed the SAE to be more consistent with allergic reaction instead of anaphylaxis due to (i) the lengthy (>20 hours) temporal relationship of the event to study drug exposure, (ii) potential confounding variables, including the start of a new medication the night prior to the event, and (iii) the

absence of AEs after repeated exposure to study drug. Taken this into consideration, the ratio of SAEs between the PF708 and Forteo seemed balanced and no deaths occurred during the immunogenicity study PF708-301.

Supportive safety data from study PF708-101 reported no SAEs and deaths.

*Immunogenicity*

In healthy subjects (study PF708-101), none of the samples were positive for neutralising antibodies, whereas in osteoporotic patients (study PF708-301) one sample of the PF708 group was (transiently) positive for nAbs. No clinically meaningful adverse effects associated with either pre-existing- or induced ADAs were apparent. However, the magnitude of ADA incidence differences that cannot be ruled out based on the evidence generated in Study PF708-301 requires adequate reflection in the evaluation of uncertainties in the (overall) biosimilarity assessment.

### 2.6.2. Conclusions on the clinical safety

The totality of the safety results supports the biosimilarity PF708 and Forteo.

## *2.7. Risk Management Plan*

### *Safety concerns*

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

### *Pharmacovigilance plan*

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

### *Risk minimisation measures*

| Safety concern | Routine risk minimisation activities |
|---|---|
| **Important Identified Risks** | |
| None. | N/A |
| **Important Potential Risks** | |
| None. | N/A |
| **Missing information** | |
| None. | N/A |

### *Conclusion*

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

## *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.

### *Periodic Safety Update Reports submission requirements*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Livogiva (teriparatide) is included in the additional monitoring list as a new biological product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Biosimilarity assessment

## *3.1. Comparability exercise and indications claimed*

The applicant seeked approval for all the indications as approved for Forsteo:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture;
- Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

Analytical and functional biosimilarity exercise

The analytical and functional biosimilarity exercise was performed in a three-way comparison between Pfenex Teriparatide solution for injection, Forsteo and Forteo. For that purpose, multiple different aged batches of each product were analysed. The analytical and functional testing panel is reasonable for a teriparatide biosimilar and overall adequate for the comparability testing of Pfenex Teriparatide DP, Forsteo and Forteo. Generally, orthogonal and state-of-the art methods were used and quality attributes relevant for the safety and efficacy of Teriparatide were included into the analysis.

Clinical programme

The clinical development plan for Pfenex Teriparatide solution for injection consists of one comparative pharmacokinetic (PK) study and one clinical comparative immunogenicity study.

Study PF708-101 was a double-masked, randomised, two-treatment cross-over study that compared the PK of PF708 and US-approved Forteo, conducted at a single centre. 70 healthy male and female subjects received a single SC injection of PF708 20 mcg and Forteo 20 mcg separated by a 3-day wash-out phase. PK was assessed by the primary endpoints AUC0-tlast, AUC0-inf and Cmax.

The secondary objective of Study PF708-101 was to evaluate the pharmacodynamics (PD) of PF708 and Forteo and included serum ionised Ca2+ concentrations and changes from baseline. The safety objective of this study was the comparison of the adverse event (AE) profile and the evaluation of anti-drug antibodies (ADAs).

Study PF708-301 was a randomised, multi-centre, parallel group, open-label study that assessed the comparability of the immunogenicity of PF708 and Forteo. 182 females with PMO and males with primary osteoporosis received 24 weeks of treatment with PF708 or Forteo by daily SC self-injection.

The secondary objective was to compare the PK and PD comparability and included the mean percentage change in lumbar-spine (L1-L4) bone mineral density (BMD) and the median percentage change in serum concentrations of the bone turn-over markers P1NP and CTX after 12 and 24 weeks of treatment. The safety objective was to compare the AE profile of PF708 and Forteo.

## *3.2. Results supporting biosimilarity*

### *Quality*

The determination of high molecular weight impurities by SE-HPLC, analysis of the molecular weight by LC-MS and determination of the primary structure by peptide mapping indicate that Pfenex Teriparatide DP, Forteo and Forsteo are similar. Comparison of the higher order structure, for which far-UV circular

dichroism, intrinsic fluorescence and NMR were applied, also indicates similarity between Pfenex Teriparatide DP and both reference medicinal products. PTH(1-34) receptor binding rates and potency between Pfenex Teriparatide DP, Forsteo and Forteo seem similar.

An additional biosimilarity exercise comparing multiple PF708 DP batches and multiple EU Forsteo lots was conducted; results support the biosimilarity claim. Furthermore, a comparative accelerated stability study showed a similar degradation profile of EU Forsteo and PF708 DP.

Results supporting positive B/R balance:

- DS Description of manufacturing process and process controls: Suppliers tests performed in line with the in-house specifications for non-compendial raw materials are provided and seem acceptable.
- Specifications DS/DP: The acceptance criteria of the specifications were evaluated based on a scientific approach or set according to pharmacopoeial monographs.
- Expression vector and system: The cell bank system is well characterised.
- DS Process characterisation was performed on qualified scaled-down models of each of the unit operations of the drug substance manufacturing process and detailed information was submitted.
- DS Process validation was performed on multiple consecutive DS commercial-scale batches. This approach is acceptable and structure of the study is very detailed.
- DS Process Development: Information about the transfer of the downscale process from the development laboratory to clinical manufacturing site and the necessary adaptations/modifications and improvements, which were necessary because of another manufacturing site and a different company, were submitted in detail and is acceptable.
- Analytical comparability between drug substance batches manufactured at clinical manufacturing site and drug substance batches manufactured at commercial scale site was presented to a sufficient level.
- Several aspects regarding product related oxidised impurities/methionyl sulfoxides defined as critical quality attributes have been sufficiently clarified and are followed up.
- Proposed shelf-life of 30 months is acceptable. Stability data currently at hand support the proposed shelf life to an acceptable extent.
- Documentation with regard to the integral drug device combination (pen injector) is comprehensive and well structured, facilitating in depth assessment. Evidence of conformity with Medical Device Directive Annex I, with applicable ISO standards and even with Draft Guideline EMA/CHMP/QWP/BWP/259165/2019 "Guideline on the quality requirements for drug-device combinations" is provided for most of the relevant subject areas.

### *Clinical*

*Pharmacokinetics*

PK analysis of the comparative biosimilarity trial (PF708-101) showed that the 90.00% CIs of the geometric mean ratios of the ln-transformed endpoints AUC0-tlast, AUC0-inf and Cmax (primary endpoints) were within the predefined limits of 80.00 to 125.00% and hence supportive of similarity. The resulting primary parameters were:

For AUC0-tlast, the GMR (PF708/Forteo) was 96.53%, 90.00% CI [90.01 - 103.52].

For AUC0-inf, the GMR (PF708/Forteo) was 98.99 %, 90.00% CI [92.54 - 105.89].

For Cmax, the GMR (PF708/Forteo) was 95.02 %, 90.00% CI [88.41 - 102.12].

*Pharmacodynamics*

The mean changes from baseline of serum calcium levels over time after single 20 mcg SC injections of the biosimilar candidate and the RMP, respectively, show similar and overlapping profiles in healthy volunteers. The calculated 90%CIs showed no significant differences between PF708 and Forteo in change from baseline of serum ionised Ca2+ at any specified time-point from 1 – 24 hours post dosing.

The effects of teriparatide administered to osteoporotic patients as the biosimilar candidate and the RMP, respectively, were comparable after 12 and 24 weeks of treatment. In terms of lumbar-spine (L1-L4) bone mineral density, the percent increases from baseline to week 24 were comparable between PF708 and Forteo in both female ($P$ = 0.568) and male ($P$ = 0.529) subjects for calculated 95% CIs. The percent increase in corrected total hip BMD and corrected total femoral neck BMD at Week 24 in female and male patients did not differ significantly between treatments.

90% CIs were calculated for bone turnover markers (P1NP and CTX) demonstrating similar median serum P1NP and CTX concentrations at baseline, week 12 and week 24 for PF708 and Forteo.

*Safety*

The incidence of treatment emergent adverse events (TEAE) was comparable between Pfenex Teriparatide solution and Forteo in healthy subjects and osteoporosis patients.

No serious adverse events (SAEs) occurred in healthy volunteers and the ratio of SAEs between the Pfenex Teriparatide and Forteo seemed balanced in patients with osteoporosis.

The type and incidence of adverse events with PF708 and the reference product were broadly comparable and largely in line with those expected based on the Forteo SmPC.

*Immunogenicity*

Immunogenicity seems comparable between treatment groups and rates of ADAs observed in the study are consistent with historical Forteo findings. At week 12, the incidence of ADA positive patients was 2/82 (2.44%) in the PF708 arm and 2/86 (2.33%) in the Forteo arm; ADA incidence was 2/81 (2.47%) and 0/81 (0%), in the PF708 and Forteo arms, respectively, at week 24.

## *3.3. Uncertainties and limitations about biosimilarity*

### *Clinical*

*Immunogenicity*

Study PF708-301 investigated whether the effects of PF708 and Forteo on immunogenicity were equivalent. Following the originally applied statistical evaluation, a non-significant outcome of a superiority test was interpreted as evidence of equivalence in immunogenicity incidence. However, in the assessment of uncertainty of biosimilarity, the upper limits of the derived confidence intervals need to be taken into consideration for a worst-case evaluation. The applicant finally provided an estimate for the difference in ADA incidences between treatment groups at the 12- and 24-week time-points, with a confidence interval (95%, two-sided) for this difference: The upper limit was 15.4%-points for week 12 and 18.3%-points for week 24. It is acknowledged that the magnitude of these worst-case estimates for the incidence-difference can generally be explained by the low precision in estimation for

a binary outcome in consequence of the sample size chosen. However, the magnitude of potential differences in immunogenicity incidence that cannot be ruled out by the data generated in PF708-301 constituted an uncertainty for biosimilarity assessment calling for a risk assessment.

## *3.4. Discussion on biosimilarity*

Initially identified deficiencies of the biosimilarity exercise comparing PF708 DP with EU-Forsteo have been sufficiently addressed. In particular, the additionally conducted similarity exercise including multiple PF708 DP batches and additionally sourced EU Forsteo lots substantiates the biosimilarity claim. Taking the additional data into account and considering that teriparatide is a rather simple, non-glycosylated polypeptide, it is concluded that biosimilarity has been demonstrated.

The entire non-clinical and clinical development programme of PF708 was conducted exclusively with the US comparator; a robust quality bridge is the pre-requisite for a biosimilar application in the EU when using a non-EEA authorised version of the RMP in the non-clinical and clinical comparability programme. The initially raised major issues on comparability of US Forteo with EU Forsteo and concerns on the suitability of the used statistics have been addressed. Based on all available data it is highly unlikely that real differences in the quality profile of US and EU reference product exist; thus, a reliable bridge between EU Forsteo and US Forteo has been established.

The clinical data derived from the pivotal PK trial in healthy volunteers and an immunogenicity study in osteoporosis patients is suggestive of similarity between PF708 and the US reference.

**Challenge in conclusiveness regarding comparable immunogenicity**

Due to a different expression system as compared to originator Forsteo (*P.fluorescens* and *E.coli)*, the applicant was advised to present a comparative immunogenicity study at time of MAA (EMEA/H/SA/3420/1/2016/III). The applicant followed this approach and presented a comparative PhIII trial in PMO patients (PF708-301) with comparative ADA incidence as the primary objective.

The methodology of comparatively assessing this primary outcome was subject to several limitations and uncertainties, whose full scope only became obvious in the applicant's d180 responses (see section above, for a full narrative of the methodological issue). The applicant provided an estimate for the difference in ADA incidences between treatment groups at time-points 12 and 24 weeks by making use of a confidence interval (95% two-sided). In the assessment of uncertainties of biosimilarity, the upper limits of these derived confidence intervals need to be taken into consideration for a worst case evaluation: for week 12 the upper limit was 15.4%-points ADA incidence in the investigated population, whereas for week 24 the upper limit was 18.3%-points, which appears a rather large difference.

**Concerning risk assessment of this issue, the following considerations are taken into account:**

- Except for the differences in expression system, no dedicated immunogenicity trial was required, due to the simplicity of the molecule (a polypeptide consisting of 34 amino acids, without glycosylation or other post-translational modifications)
- Similarity with regard to structure, biological characteristics and purity/impurity profiles between EU-Forsteo and Livogiva could be demonstrated by appropriate analytical methods. No significant differences in relevant quality attributes of this rather simple molecule were detected.
- The molecule can also be synthesised and authorised via the generic/hybrid route, without presenting any immunogenicity data.

- EMA biosimilar guidance does not ask for confirmative equivalence testing of ADA incidence, and numerical results of ADAs in the study do not give rise to concern (Livogiva vs US Forteo, week 12: 2 vs 2 patients; week 24: 2 vs 0 patients).
- According to current knowledge, ADAs to teriparatide are not considered to have adverse clinical impact.
- The clinical programme does not give rise to concern on the similarity of Livogiva and US Forteo.

In conclusion, considering the totality of evidence on the quality, non-clinical and PK/PD level, the risk of a true difference in the immunogenicity profile of Livogiva vs Forsteo is considered low. The actual incidence of ADA positive patients was low and comparable and any clinical impact of the immunogenicity results as described in study PF708-301 would be considered unlikely.

### *3.5. Extrapolation of safety and efficacy*

The molecular effects of teriparatide are mediated by the parathyroid hormone-receptor-1 (PTH-R1), a G–protein-dependent membrane receptor expressed by osteoblasts and renal tubular cells. Teriparatide has similar affinity for the PTH-R1 as PTH(1–84). Ligand-bound PTH-R1 activates adenylate cyclase and certain phospholipases (A, C, and D), thereby increasing intracellular levels of cyclic adenosine monophosphate and calcium (Brixen et al, 2004). PTH signalling results in the activation of genes important for the functions of mature osteoblasts, increases in osteoblast number, decreases in the apoptotic rate of osteoblastic cells, and increases in their bone-forming activity (D'Amelio et al, 2012). This is followed by an increase in the number of active osteoblasts, a decrease in osteoblast apoptosis and probably a recruitment of bone lining cells as newly formed osteoblasts, which are followed by increasing bone strength, mass and diameter and bone structural integrity, as well as increasing levels of bone turnover marker in serum and urine (Blick et al, 2008).

It is assumed that this mechanism of action is the same for all approved indications of Forsteo. Hence, extrapolation to all approved indications of Forsteo is possible.

### *3.6. Conclusions on biosimilarity and benefit risk balance*

Based on the review of the submitted data, Livogiva is considered biosimilar to Forsteo. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

## 4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Livogiva is favourable in the following indication:

Livogiva is indicated in adults.

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture (see section 5.1). In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures have been demonstrated.

Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

## *Conditions or restrictions regarding supply and use*

Medicinal product subject to medical prescription.

## *Other conditions and requirements of the marketing authorisation*

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.