10 November 2016
EMA/88527/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Movymia

International non-proprietary name: teriparatide

Procedure No. EMEA/H/C/004368/0000

Note

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

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List of abbreviations

α	Alpha
°C	Degrees Celsius
µg	Microgram
µL	Microlitre
AE	Adverse event
ALP	Alkaline phosphatase
AM	Arithmetic mean
ANOVA	Analysis of variance
AUC	Area under the plasma concentration versus time curve
$AUC_{\%extrap}$	Percent of area under the plasma concentration versus time curve to infinity extrapolated
$AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve to infinity
$AUC_{0\text{-}tlast}$	Area under the plasma concentration versus time curve to the last measurable concentration
BE	Bioequivalence
BLQ	Below limit of quantitation
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body Mass Index
BP	Blood pressure
bpm	Beats per minute
C0	Teriparatide predose concentration
Ca	Calcium
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
CL/F	The apparent total plasma clearance after extravascular administration
CLID	Client ID number
cm	Centimetre
C_{max}	Maximum measured plasma concentration
CO	Carbon monoxide
CRF	Case report form
CRO	Clinical research organisation
CRU	Clinical research unit

CS	Clinically significant
CV%	Coefficient of variation
dL	Decilitre
DNA	Deoxyribonucleic acid
E. coli	Escherichia coli
EC	European Commission
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GCV%	Geometric CV%
GM	Geometric mean
GMR	Geometric mean ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hr	Hour
HR	Heart rate
IB	Investigator´s brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
K3EDTA	Tripotassium ethylenediaminetetraacetic acid
k_{el}	Apparent terminal elimination rate constant
kg	Kilogram
kg/m^2	Kilogram per metre square
L	Litre
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
ln	Natural log
LSM	Least-squares means
MedDRAsq	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency

mIU	Million International Units
mL	Millilitre
mmHg	Millimetre of mercury
mmol	Millimole
msec	Millisecond
N	Sample size; number of observations
NCS	Not clinically significant
No.	Number
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	Interval between the P and R waves on the ECG
PTH	Parathyroid hormone
PTH (1-84)	Full-length parathyroid hormone
PTH1R	Parathyroid hormone-receptor-1
QA	Quality Assurance
QC	Quality Control
QRS	Value of the interval between the Q and S waves on the electrocardiogram tracing
QT	Value of the interval between the Q and T waves on the ECG
QTc	Corrected value of the interval between the Q and T waves on the ECG tracing using Bazett´s [QTcB] and Fridericia´s [QTcF] corrections
R2	Coefficient of determination
RBA	Receptor Binding Assay
RDTS	Repeat Dose Toxicity Study
REC	Research Ethics Committee
RMP	Reference Medicinal Product
rhPTH (1-34)	Recombinant human parathyroid hormone 1-34
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SID	Screening identification number
SIV	Site initiation visit
SmPC	Summary of Product Characteristics
SOC	System Organ Class

SOP	Standard Operating Procedure
SST	System Suitability Test
STRAW	Stages of Reproductive Aging Workshop
$t_{1/2}$	Apparent terminal elimination half-life
TEAEs	Treatment-emergent AEs
TK	Toxicokinetic(s)
t_{last}	Last measurable concentration
t_{max}	Time of the maximum measured plasma concentration
TP	Time point
U	Units
ULN	Upper limit of normal
ULOQ	Upper limit of quantitation
USA	United States of America
V_d	Volume of distribution
V_z/F	The apparent volume of distribution after extravascular administration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant STADA Arzneimittel AG. submitted on 30 November 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Movymia, 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:

Movymia is indicated in adults.

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and nonvertebral fractures but not hip fractures has been demonstrated.

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

The legal basis for this application refers to:

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

This application is submitted as a multiple of Terrosa simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

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.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Forsteo 20 micrograms/80 microliters solution for injection in pre-filled pen
- Marketing authorisation holder: Eli Lilly Nederland B.V
- Date of authorisation: 10-06-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: : EU/1/04/247/001-002

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

- Product name, strength, pharmaceutical form: Fortseo 20 micrograms/80 microliters solution for injection in pre-filled pen
- Marketing authorisation holder: Eli Lilly Nederland B.V
- Date of authorisation: 10-06-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/03/247/001-002

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which comparability tests have been concluded:

- Product name, strength, pharmaceutical form: Forsteo 20 micrograms/80 microliters solution for injection in pre-filled pen
- Marketing authorisation holder: Eli Lilly Nederland B.V
- Date of authorisation: 10-06-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number(s): EU/1/03/247/001-002
- Bioavailability study number(s): AA99812 (Eudra CT No. 2013-004040-31)

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19/04/2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Milena Stain Co-Rapporteur: Greg Markey

- The application was received by the EMA on 30 November 2015.
- The procedure started on 16 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 March 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 4 April 2016.
- During the meeting on 28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 29 April 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 July 2016.
- In cases when a pre-authorisation inspection has been conducted, please reflect the following steps (include/delete information as applicable):
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 22 August 2016.
- During the PRAC meeting on 2 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 5 September 2016.
- During the CHMP meeting on 15 September 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 7 October 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 25 October 2016.
- During the meeting on 10 November 2016, 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 Movymia on 10 November 2016.

2. Scientific discussion

2.1. Introduction

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 include antiresorptive agents (e.g. bisphosphonates, calcitonin and raloxifene) which reduce osteoclastic activity, strontium ranelate which reduces osteoclastic activity and may demonstrate anabolic properties as well, and parathyroid hormone (PTH, aminoterminal portion: teriparatide), the first anabolic agent, which stimulates bone turnover with a positive bone balance thereby increasing bone mass.

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 Movymia, biosimilar teriparatide (also referred to as RGB-10 throughout the document), is produced in *E. coli* using recombinant DNA technology, so is the case with its reference medicinal product Forsteo.

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 signaling 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).

The therapeutic indications, posology and route of administration proposed for Movymia are identical to those for Forsteo, to which similarity is claimed.

Forsteo is authorised for the following therapeutic indications within the EU:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture. In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures has been demonstrated.
- Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

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.

Forsteo (20 µg/80 µL solution for injection) is supplied in a pre-filled disposable pen containing 28 doses. RGB-10 (biosimilar teriparatide, 20 µg/80 µL solution for injection) is supplied in a cartridge that is to be inserted in a dedicated multi-dose pen injector.

The development programme

RGB-10 (teriparatide 20 µg/80 µL solution for injection) has been developed as a biological medicinal product and is claimed to be biosimilar to Forsteo which contains recombinant human teriparatide (rhPTH (1-34)) as active substance (20 µg/80 µL solution for injection).

Further to the demonstration of comparability between RGB-10 and the reference medicinal product Forsteo at the analytical and the non-clinical levels, the Applicant aimed at demonstrating therapeutic equivalence of RGB-10 to Forsteo in one comparative pharmacokinetic (PK) study in 54 healthy women. Apart from the abridged clinical comparability exercise that consists of a single bioequivalence study RGB-10-001, the Applicant has not conducted any clinical efficacy (or safety) studies on the treatment of osteoporosis in postmenopausal women, men at risk or osteoporosis associated with sustained systemic glucocorticoid therapy.

CHMP guidance:

The development programme of RGB-10 has in general been aligned to the respective EU guidance, in particular:

- Guideline on similar biological medicinal products (CHMP/437/04 Rev 1);
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance - non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1);
- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**);
- Guideline on similar medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMA/CHMP/BWP/247713/2012)
- Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009)

2.2. Quality aspects

2.2.1. Introduction

The finished product (Movymia) is presented as solution for injection containing 20 micrograms/80 microliters (20 µg/80 µL) of Teriparatide as active substance. Each cartridge contains 2.4 mL of solution.

Other ingredients are: Glacial acetic acid, Mannitol, Metacresol, Sodium acetate trihydrate, Hydrochloric acid, Sodium hydroxide, Water for injection.

The product is available in a 3 mL cartridge (siliconised Type I glass), with a plunger stopper (bromobutyl) and disc seal (aluminium and rubber liner seals), packed in a plastic tray sealed with lid foil and a carton. Movymia cartridges are designed to be used only with the ServoPen Fix reusable, multidose delivery system and compatible pen needles.

Movymia 20 micrograms/80 microliters solution for injection (INN of active substance: teriparatide has been developed as an intended biosimilar medicinal product of Forsteo (marketing authorisation holder: Eli Lilly Nederland B.V.).

2.2.2. Active Substance

General information

The active substance of Movymia is teriparatide. Teriparatide is a recombinant 1-34 N-terminal fragment of endogenous human parathyroid hormone, rhPTH(1-34) produced in *E. coli* using recombinant DNA technology.

The theoretical monoisotopic mass of Teriparatide is 4115.1309 Dalton (C181H291N55O51S2). The amino acid sequence is:

S V S E I Q L M H N L G K H L N S M E R V E W L R K K L Q D V H N F

Teriparatide monomer is a slightly curved helix. Residues 6–20 and 21–33 form two amphiphilic helices with their hydrophobic side chains facing in different directions.

Teriparatide contains no glycosylation or other post-translational modifications.

Biological activity: Teriparatide is a recombinant 1-34 N-terminal fragment of endogenous human parathyroid hormone (rhPTH(1-34)), which is critical for G-protein linked stimulation of adenylate cyclase that catalyzes the formation of second messengers such as cAMP. 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.

The biological activity of teriparatide is determined using a cell-based assay.

Manufacture, characterisation and process controls

Manufacturer

Teriparatide is manufactured at Richter-Helm BioLogics (RHB) in Bovenau/Germany.

Description of manufacturing process and process controls

The process has been sufficiently described and in-process controls are adequately set to control the process.

Control of materials

Expression system:

Teriparatide is expressed in a recombinant commercially available *E. coli* BL21 strain, transformed with a proprietary expression plasmid, carrying the coding sequence for rhPTH.

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 in accordance with current guidelines (ICH Q5B, Q5D) under GMP conditions. The MCB was established from a preliminary cell bank derived from a selected single colony of *E. coli* BL21. Information on the cell bank establishment, storage, and characterization were provided, as well as stability data and the procedure to be used for establishing future WCBs.

Genetic stability was shown by end of production cell line (EPC) characterisation.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Control of critical steps and intermediates

Critical quality attributes (CQAs) were defined in early process development. The Company´s control strategy is based on a risk assessment of process parameters and quality attributes controlled by in-process controls (IPCs). The CPPs (critical process parameters) and IPCs suitable to control the teriparatide manufacturing process and the product quality were also identified via the risk assessment exercise.

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the teriparatide active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

Validation of the teriparatide active substance manufacturing process has been performed according to the cGMP principles and the current guidelines on validation on three consecutive full scale batches at the manufacturing site in Bovenau.

The process validation plan was based on the overall manufacturing experience from optimization. It comprised evaluation of the capacity to remove process- and product-related impurities and validation of all process steps. Depletion of product related and process related impurities and resin life time and storage were used to characterise teriparatide active substance during process validation).

Hold times of the manufacturing process were submitted. Process validation and transport validation were sufficiently done. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the manufacturing process consistently produces teriparatide active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

The original manufacturing process was developed at laboratory scale. The non-clinical material was supplied from a pre-commercial DSP scale, pre-final process version. A comparison of batch release data along with some additional data comparing primary, secondary and tertiary structures has been provided for one batch of product at the pre-commercial scale (used in non-clinical studies) and one batch of process validation product. There is good comparability between the two sets of data, though it is noted that purity regarding product related impurities is improved with the commercial scale, due to process improvements. Thus the pre-commercial scale product (used in non-clinical studies) could be regarded as worst case.
Descriptions of the development stages are provided including process upscale and changes/optimizations introduced during development. Respective changes and their impact to the quality of the active substance have been evaluated and considered satisfactory. The clinical batch is representative of the proposed commercial manufacture process.

Characterization

The data on the structural characteristics of the recombinant teriparatide result from investigations performed on several batches. The characterisation of the active substance has been performed with orthogonal methods appropriate for this molecule and it is satisfactory.

These studies comprised confirmation of the amino acid and the nucleotide sequence, analysis of peptide properties such as molecular mass, isoelectric point and UV spectrum, studies to elucidate primary, secondary and tertiary structure, investigations on purity, content and related substances, and physicochemical characteristics such as clarity, colour and pH value.

For biological and immunochemical characterization a cell-based potency assay and an ELISA, respectively, were used.

Product-related impurities were shown to be reduced during the commercial manufacturing process and are monitored during manufacturing, release and stability testing.

As for the process-related impurities, clearance validation studies have been performed to demonstrate that the manufacturing process provides adequate removal of such impurities.

Specification

The active substance specification tests and limits are acceptable; the specification includes general tests, identity, content, potency, purity, product and process-related impurities and microbial purity.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. For compendial methods, method verification was demonstrated.

Batch analysis

The batch release data from process validation batches and commercial scale batches conform to specifications. In addition, data from several pre-commercial DSP scale batches, including the non-clinical batch also conform to the specifications which were in force at the time of manufacture.

Reference materials

The WHO International Standard Parathyroid Hormone 1-34 (teriparatide) was used as the standard during potency calibration and content determination of the applicant´s in-house teriparatide reference standards.

Detailed data for these calibrations and calibrations against the WHO international reference standard of the in-house reference standard were submitted.

Stability

The stability results (long term, accelerated and stress studies) indicate that the active substance is sufficiently stable and justify the proposed self-life in the proposed container. The parameters tested are the same as for release. Photostability studies indicate that the active substance is photolabile and should be protected from light.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the product

Teriparatide 20 micrograms/80 microliters (20 µg/80 µL) solution for injection is a clear, colourless solution. Each cartridge contains 2.4 mL of solution.

The excipients of the finished product are acetic acid glacial, sodium acetate trihydrate, mannitol, metacresol, water for injections, hydrochlorid acid 10% solution (for pH adjustment) and sodium hydroxide 10% solution (for pH adjustment).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The primary packaging is a glass cartridge (siliconised Type I glass), with a plunger stopper (bromobutyl) and disc seal (aluminium and rubber liner seals). The material complies with Ph.Eur. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The aim of the formulation development programme for Teriparatide 20µg/80µL solution for injection was to develop a stable injection formulation, which is biosimilar to the reference medicinal product, Forsteo.

The route of administration and volume to be administered are identical to those of the reference product.

At the early stage of product development an initial assessment of critical quality attributes (CQA) was performed to evaluate typical aspects of sterile liquid dosage forms that could potentially affect the product purity, strength and stability. These potential CQAs were derived from the QTPP and prior knowledge and were used to guide the product and process development.

Target values of quality attributes were determined based on the relevant Ph. Eur. chapters and regulatory guidelines.

Manufacture of the product and process controls

Manufacture

The finished product is manufactured, assembled and primary and secondary packed at Gedeon Richter Plc. The manufacturing method consists of 5 stages, namely: dispensing, preparation of the concentrated formulation buffer, filtration and dilution of the concentrated formulation buffer, preparation of the bulk drug product solution with pre-filtration, final sterile filtration and filling of the siliconized sterilised cartridges. The cartridges are sealed with plunger stoppers and disc seals. Adequate in-process controls are in place for each stage.

Process validation

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

Container Closure System

The pen (ServoPen Fix) is customized for use with Teriparatide 20 micrograms/80 microliters solution for injection only, and its construction is based on reusable, multidose ServoPen platform from Ypsomed.

Specifications for the pen and the needles are presented as well as a declaration of conformity from the notified body (Ypsomed).

Compliance with ISO 11608-3 for the commercial cartridge system for use in needle based injection systems (NIS) with pen needles was demonstrated.

Dose accuracy testing according to ISO 11608-1:2012 was performed and the data indicate compliance.

Product specification

The product specification includes physical, identification, purity tests, and assays.

The tests, acceptance criteria and methods are considered adequate. During the review specification limits were tightened, but no substantial changes were implemented.

The level of impurities is generally very low in the finished product. Their reduction/elimination by the manufacturing process is appropriately controlled. The related substances specification limits were tightened during the procedure. Discrepancies of the extractable volume between the finished product specification and test method description were appropriately explained.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. For compendial methods, method verification was demonstrated.

Batch analysis

Batch analysis data of the finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Characterization of impurities

The manufacturing process of the active substance and finished product has been optimised to eliminate or sufficiently reduce the formation of product-related impurities and to maintain their level below the acceptable limit up to the end of shelf life of the finished product.

Reference materials

The teriparatide in house standard is discussed in detail in the active substance part.

For related substances PTH(1-30) standard was used as reference substance only for analytical method validation.

Stability of the product

Based on available stability data, the 24 months at 2-8°C shelf-life and storage conditions (*Store in a refrigerator (2-8°C). Do not freeze. Keep cartridge in the outer carton*), as stated in the SmPC, are acceptable.

The evaluation of stability data of Teriparatide 20 micrograms/80 microliters solution for injection – further supported by the statistical analysis – proves that 24 months of shelf-life can be agreed.
Additionally, the applicant has agreed to place a batch of drug product which is made from drug substance held at 2-8°C for 3 months into a GMP stability study, as requested to provide further data to support use of the active substance stored under these conditions for manufacture of finished product.

In-use stability

In-use stability tests were performed to demonstrate that the multi-dose product is capable of withstanding the conditions of repeated use according to the Note for guidance on in-use stability testing of human medicinal product (CPMP/QWP/2934/99, 2001).

The in-use stability study of batches was planned within the period of the ICH long-term stability study of each batch. All parameters tested met the acceptance criteria described in the specification at all testing time points (day 14 and day 28) and support an in-use shelf life of 28 days at 2-8°C.

Photostability testing

Photostability testing was conducted according to the recommendations of ICH Q1B. The results show that the finished product is sensitive to light. This is in accordance with the observations made on the active substance. Consequently, the SmPC includes appropriate statement with regard to keeping the product protected from light.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Biosimilarity

Comparability ranges

To claim similarity of Movymia to the reference medicinal product, Forsteo (Eli Lilly Nederland B.V.) a thorough physicochemical, structural and biological characterisation as well as impurity profiling have been performed. Multiple batches of reference Forsteo medicinal product (EU sourced) were comprehensively analysed in order to generate a representative quality profile. Reference ranges were established using appropriate statistical methods. Multiple Movymia batches were used for the determination of variability ranges for critical quality attributes for the biosimilar.

Descriptive statistics were used for establishment of the comparability ranges.
In the case of purity tests and assays, the results were subjected to the same statistical analyses as data obtained on reference product batches. For parameters exhibiting time dependence, stability data of the batches was integrated also into the discussion.

The detected impurity levels in Movymia and Forsteo were overall comparable. The degradation patterns of the two products were also found to be similar and the amounts of impurities were within the comparability ranges for both tested products.

Stability:

Comparison of purity and biological activity during an *accelerated stability study* (storage condition of 25 ± 2°C for 3 months) was done with one 18 months old Forsteo batch. The results were compared with 3-month accelerated stability data of representative Movymia finished product batches. Results by RP-HPLC showed that impurities observed after storage at 25°C are present in Forsteo as well as in the RGB-10 finished product sample. According to the comparative LC-MS studies the structure of the observed degradation products was identical in Forsteoand RGB-10 finished product.

Furthermore a sample of Forsteo after 2 months of storage at accelerated storage (25 ± 2°C) was subjected to LC-MS analysis for peak identification (age of batch at start of storage was 18 months). For comparative purposes one 2-month accelerated stability sample of RGB-10 finished product was analysed, as well, and the degradation patterns were compared. The observed degradation products could be identified as oxidized and mostly deamidated isoforms. Structure of the common components proved to be identical in both product samples.

Side-by-side comparison

The parameters tested were physical tests (appearance, pH both Ph.Eur), molecular weight, primary structure, secondary structure, identification tests, purity tests, biological characterisation (Cell-based Bioassay , receptor binding assay) and assay (teriparatide/rh PTH(1-34)). The data indicate that all relevant parameters are comparable between Movymia and Forsteo; where slight variations between the two products are observed, these are within the comparability ranges and do not give reason to question similarity.

The comparability program was extended to stress studies and the results reveal similar behaviour (including for product degradation pattern, comparable decrease in biological activity) of both products at the various conditions applied. Quantitative differences were noted between Movymia and Forsteo when subjected to light exposure - mainly attributed to oxidation products. However, as the product is stored in the carton, comparability is not affected.

Dose accuracy

A comparative dose accuracy study with the Forsteo pen system and the ServoPen Fix system used for Movymia was conducted. From a quality point of view accurate dosing of at least 20µg/80µl was demonstrated for both device systems.

Conclusion

Teriparatide is a relatively simple molecule, as it is a monomer and contains no glycosylation or other post-translational modifications. To claim the similarity of Movymia to its reference medicinal product, a thorough physicochemical, structural and biological characterisation as well as impurity profiling has been performed. Multiple batches of reference Forsteo medicinal product (EU sourced) were comprehensively analysed in order to generate a representative quality profile, i.e. to determine the reference ranges using appropriate statistical methods. All reference product batches used for the comparability tests were from commercial markets of the European Union. Multiple Movymia batches were used for the determination of the reference ranges. Descriptive statistics were used for establishment of the comparability ranges.

A satisfactory side by side comparison was performed on three batches of the proposed product.

Additionally, comparability was also demonstrated during stability and stress testing studies.

The biosimilarity exercise is robust and that there are no residual uncertainties arising from the quality comparison. Based on the results from the comparability exercise it can be concluded that Movymia is similar to Forsteo, from a quality perspective.

Adventitious agents

No materials of animal or human origin are used for manufacturing of Teriparatide 20 micrograms/80 microliters solution for injection.

In addition, the active substance is manufactured by fermentation using an *Escherichia coli* expression system.
This prokaryotic expression system does not support the growth of viral adventitious agents in the active substance and therefore there are no viral risks associated with this product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

As discussed under specification of the active substance, specifications that are appropriate for this product have been approved.

No Major Objections were raised during the procedure. However, a number of Other Concerns were initially identified, which were all adequately addressed during the evaluation process.

Extensive physicochemical, structural and biological characterisation as well as impurity profiling of both Movymia and the reference product Forsteo has been undertaken and a high degree of similarity has been demonstrated. Head-to-head comparability data has been provided for three batches of each product, and the results support the conclusion that Movymia can be considered biosimilar to Forsteo. Additionally, biosimilarity was also demonstrated during stability and stress testing studies. The statistical approach used was sufficiently explained.

Differences between Forsteo and Movymia in certain impurity parameters were appropriately discussed and justified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented and is satisfactory. The batch data results indicate consistency and uniformity of important product quality characteristics through shelf life, and these in turn substantiate a satisfactory and uniform performance in clinical use.

The active substance and the finished product have been appropriately characterised and satisfactory documentation has been provided. The description of the manufacturing process and the manufacturing development is adequate.

Based on the quality data provided, Movymia is considered to be biosimilar to Forsteo.

2.2.6. Recommendation(s) 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 two points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical programme for the development of RGB-10 (teriparatide biosimilar product) focused on the investigation of comparability and the demonstration of similarity between RGB-10 and the reference medicinal product Forsteo.

2.3.2. Pharmacology

A panel of *in vitro* and *in vivo* assays were developed, used to generate similarity limits derived from originator batches and test for comparability of the biosimilar candidate with the reference medicinal product.

The Applicant has chosen a competitive ELISA assay to test for receptor binding. The Applicant conducted no ICH Q2(R1) compliant validation (i.e. a reportable value of the RBA was not defined prior validation), which is acceptable recognizing the comparatively simple structure of the protein and also limitations of the method (difficulty of expressing full length PTH1R and providing results for two cell-based bioassays). Detailed information about the PTH1R, being a critical reagent for the RBA, has been provided.

Reference ranges were calculated based on results for relative potency of five Forsteo batches tested in three independent assays. 3σ limits were calculated from the geometric mean (100.915 U/mg) corresponding to a relative interval of 83 -120%. Accordingly, the reference range was defined as 80 to 125% of the mean receptor binding activity of Forsteo (80.732 – 126.144 U/mg). Side-by-side comparisons were performed using 3 Forsteo and 3 RGB-10 DP batches from commercial scale and site, indicating similarity (106, 103 and 106 % potency for the three RGB DP batches related to the Forsteo reference range mean binding activity 100.915 U/mg = 100%).

The calculation of reference limits is based on 5 different reference medicinal product (RMP) batches.only, calculating 3σ limits from the geometric mean of three independent determinations. For the purposes of testing biosimilarity the use of different batches increases the number of determinations and is as such supportable. Two cell-based bioassays were applied to comparatively measure activation of the PTHR1 by detecting the release of cAMP after teriparatide binding and activation of PTHRusing the rat osteosarcoma cell line UMR-106 and the human osteosarcoma Saos-2 cells together with the WHO international standard (NIBSC code 04/200).

The rat osteosarcoma cell line UMR-106 based bioassay was validated according to ICH Q2(R1) for intermediate precision, accuracy, linearity, repeatability, specificity (using the drug product formulation buffer) applying an acceptance criterion of GCV ≤ 20 %. Multifactorial design of experiments identified that the parameter operator has a significant effect on the final potency result (in contrast to parameters days of starvation, control sample and plate). However, the validation parameter accuracy was met for each operator. The definition of the reference range based on the calculation of 3σ limits from the geometric mean of testing five Forsteo batches, leading to a less stringent range of 8409.3 to 13139.5 IU/mg. However, side-by-side analysis in 3 individual assessments indicates high comparability (105%, 97% and 99% for the three tested RGB-10 batches, relative to a mean activity value for Forsteo).

Also for the Saos-2 cell based bioassay comparability was shown for the three tested RGB-10 batches (i.e. 101%, 101% and 109%, respectively) relative to a mean activity value for Forsteo).

Putative product-related impurities/substances were assayed with both bioassays, confirming the expected reduction or nullification of potency for truncated and deamidated versions of teriparatide. These results provide additional evidence for the sensitivity and discriminatory power of both bioassays.

Regarding the non-clinical development the Applicant provided *in vitro* binding data and *in vitro* functional data by a bioassay using human bone osteoblasts and osteoclasts.

In addition the applicant also provided within this MAA results of a 4-week, comparative PK/PD study in female SD rats (daily sc dosing of 10 or 40 µg/kg/day).

The subcutaneous administration of RGB-10 or Forsteo at 10 and 40 µg/kg/day to female rats for 4 weeks resulted in similar dose-dependent increases in bone mass (bone mineral content) and/or bone geometry at the distal femur metaphysis and femur diaphysis. At a concentration of 10 µg/kg/day no statistically significant difference in bone densitometry parameters was observed between the RGB-10 and Forsteo groups. However, in the 40 µg/kg/day groups, effects on the bone mineral content at the distal femur metaphysis and the diaphysis in RGB-10-dosed rats were statistically higher than those administered Forsteo.

The pharmacokinetics of RGB-10 or Forsteo was also assessed in this study. Overall, no relevant differences in the exposure between RGB-10 and Forsteo were observed.

2.3.3. Pharmacokinetics

The pharmacokinetic parameters of RGB-10 were studied in rats. The type of studies conducted to compare the pharmacokinetics of RGB-10 and Forsteo is considered to be acceptable.

The methods of analysis to determine levels of teriparatide and anti-teriparatide antibodies in rat plasma or serum and cAMP in cell extracts have been provided. Validation reports for the assays are considered adequate. The methods are generally considered to be suitably validated.

In the 4-week pharmacodynamics/pharmacokinetic study in rats subcutaneously administered 10 and 40 µg/kg doses of Forsteo or RGB-10, an increase in C_{max} and $AUC_{(0\text{-}inf)}$ was observed with increasing dose of RGB-10 and Forsteo. The increase in C_{max} was slightly less than dose proportional between the 10 and 40 µg/kg doses of Forsteo or RGB-10. The increase in $AUC_{(0\text{-}inf)}$ was approximately dose proportional for RGB-10 but slightly greater than dose proportional for Forsteo. Exposure to RGB-10 appeared to be higher than to Forsteo by up to 1.7-fold.

No distribution, metabolism, excretion or drug interaction studies were conducted with teriparatide. In compliance with ICH guidance (EMEA/CHMP/BMWP/42832), this is acceptable.

2.3.4. Toxicology

A 4-week toxicology study was conducted in rats subcutaneously administered 30, 100 or 300µg/kg/day RGB-10 or Forsteo. Comparable increases in bone mass and/or bone geometry were observed in animals treated with either Forsteo or RGB-10. The changes in multiple bones observed (such as increased bone/bone formation, epiphyseal thickening/thinning, and/or focal resorption) were attributed to the pharmacological action of RGB-10 and Forsteo.

Slight changes in haematology and clinical chemistry parameters, considered secondary to the pharmacological effects of both test compounds as bone anabolic agents, were associated with treatment-

related effects in the spleen (increased weight, enlargement and extramedullary haematopoiesis), and adrenal gland (cortical vacuolation).

Based on the treatment-related changes in the spleen and the increased bone/bone formation in high dose animals, the no observed adverse effect level (NOAEL) was considered to be 100 µg/kg/day.

In a 4-week repeat dose toxicity study in rats subcutaneously administered Forsteo or RGB-10 at 30, 100 and 300µg/kg/day, the systemic exposure (in terms of C_{max} and AUC) to Forsteo and RGB-10 increased with dose levels, but was not consistently dose proportional. At Day 1, exposure to RGB-10 appeared to be higher (up to 3.2-fold) than to Forsteo; however, differences in exposure appeared less at Day 28.

The formation of ADAs was assessed. No significant difference was observed between the incidence of anti-Forsteo and anti-RGB-10 antibodies at any dose level and no neutralizing anti-teriparatide antibodies were detected. The ADA formation appeared to have had no impact on the toxicokinetic parameters or pharmacological activity determined for Forsteo and RGB-10.

For the determination of anti-drug antibody (ADA) formation, blood samples were taken pre-treatment and at the end of the dosing period (Day 29). Immunogenicity was evaluated as part of the 4-week repeat-dose toxicity study.

A dose-related effect was observed regarding the incidence of samples confirmed positive for anti-drug antibodies against both, RGB-10 and Forsteo. The incidence of confirmed positive samples was higher for RGB-10 in comparison with Forsteo at all dose levels. In addition, RGB-10 samples at 30 µg/kg/day displayed higher antibody titers than observed at 100µg/kg/day; however these were not associated with any effects on the pharmacological action of the compounds. None of the samples confirmed positive for the presence of either anti-Forsteo or anti-RGB-10 antibodies were found positive for the presence of neutralising anti-teriparatide antibodies.

The clinical relevance of anti-teriparatide antibodies is considered negligible, as stated in the EPAR of Forsteo. There is no evidence that these antibodies neutralise the biological activity of teriparatide or produce any adverse clinical outcomes. However, these non-clinical results support the requests for further investigation and follow up of immunogenicity, as concluded in the clinical assessment of immunogenicity.

No new genotoxicity studies were conducted with teriparatide. In compliance with ICH guidance, this is acceptable. No carcinogenicity studies were conducted with teriparatide. In compliance with ICH guidance (EMEA/CHMP/BMWP/42832), this is acceptable.

No reproductive and developmental toxicity studies were conducted with teriparatide. In compliance with ICH guidance (EMEA/CHMP/BMWP/42832), this can be accepted.

Local tolerance was assessed as part of the 4-week repeated dose toxicity study of RGB-10 and Forsteo. Findings similar in appearance and incidence were observed across all groups. The findings were therefore considered to be related to the experimental procedure and / or the vehicle and not to teriparatide treatment.

Dependence studies were not conducted. There is no indication that this compound would cause dependence.

No metabolites of this compound have been reported. Therefore the applicant has not discussed the metabolism of teriparatide. The peptide is expected to be broken down into constituent amino acids and therefore studies on metabolites are not required.

2.3.5. Ecotoxicity/environmental risk assessment

RGB-10, as teriparatide is the active substance, is a recombinant human peptide and therefore not expected to pose a risk to the environment.

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

In support of the development programme for a biosimilar to teriparatide, the preclinical development programme was designed to show biosimilarity of RGB-10 to the reference medicinal product Forsteo by applying different comparative methods.

The biosimilar candidate presents a rather simple, non-glycosylated structure; it is produced in the same host cell type as the innovator product and also the same DP formulation is used. Thus from this perspective, no special considerations are to be raised.

Results of a competitive ELISA to test receptor binding were provided and generally proved comparability. Regarding receptor binding, no orthogonal method was presented, which is considered sufficient given (i) the comparatively simple structure of teriparatide, (ii) that PTH1R expression is anyway limited to the extracellular domain (representing the binding site, while whole length PTH1R includes a challenging-to-express and purify transmembrane region, which is also known to contain a low affinity binding structure, but is also capable of activating the receptor) and (iii) the provision of bioassays sufficiently reflecting pharmacology.

Consequently *in vitro* assessment focussed on the development and validation of a cell-based bioassay, making use of a rat osteosarcoma cell line UMR-106 and measuring intracellular rise in cAMP concentration upon activation of the PTHR1. Besides that, human osteosarcoma cell line Saos-2 cells were used to setup a second bioassay, to provide potency readouts for a cell line of human origin. Both assays also showed reduced or completely diminished potency as the expected behaviour for truncated and deamidated versions of teriparatide, which generally supports applicability and sensitivity of both methods.

Biosimilarity was generally shown at the *in vitro* level, with the additional data considered as being supportive.

2.3.7. Conclusion on non-clinical aspects

The provided non-clinical comparability testing strategy is regarded as sufficient in the context of a biosimilar development. Applicable regulatory guidelines were taken into consideration and recommendations provided in the frame of scientific advice procedures were followed. Comparative pharmacodynamic, pharmacokinetic and toxicology data demonstrated biosimilarity between RGB-10 and the reference product Forsteo.

2.4. Clinical aspects

The clinical development programme to show biosimilarity between RGB-10 (teriparatide 20 µg/80 µL solution for injection) and Forsteo consists of a single comparative pharmacokinetic (PK) study in 54 healthy women (Celerion Project No. AA99812, Richter Project No. RGB-10-001, EudraCT No. 2013-004040-31).

- **Tabular overview of clinical studies**

Table 1:

Tabular Listing of all Clinical Studies

Location of Study Report / CTD Code	Type of Study	Study Identifier (Study / Report Number)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Module 5.3.1.2	Phase I: Comparative PK; Safety / Local Tolerance Equivalence Study	**RGB-10-001** EudraCT No. 2013-004040-31	Primary To demonstrate PK equivalence between RGB-10 and reference product Forsteo® Secondary To evaluate safety / local tolerance of RGB-10 as compared to reference product Forsteo®	Randomised, double-blind*, single-centre, single-dose, fixed-dose, 2-way cross-over, comparative PK study#; Active-controlled (vs. EU-sourced teriparatide reference product [Forsteo®])	Teriparatide 20 µg/80 µL s.c. Treatment A RGB-10 (Batch No. E41002) 20 µg/80 µL, single dose; s.c. injection Treatment B Forsteo® (Batch No. C142910F) 20 µg/80 µL, single dose; s.c. injection	Enrolled: N=54 Completed: N=53 PK analysis set: N=51**	Healthy adult female pre-menopausal subjects	Single-dose; 2 periods of approx. 12 hours each; washout phase of 24 hours (+ up to 1 hour) between both doses	Completed; Final CSR

CSR: clinical study report; PK: pharmacokinetics; s.c.: subcutaneous; * via third party; # planned in 2 stages, following completion of Stage 1, an interim analysis was performed using unblinded PK data from Stage 1, and a decision was made to consider the study complete; ** 3 subjects excluded due to not completing both study periods, pre-dose concentrations > 5% of C_{max}, and missing several PK blood draws

2.4.1. Pharmacokinetics

The comparison of the PK profiles of RGB-10 and Forsteo was the primary objective of study RBG-10-001, which is described below.

Study Design

Study RGB-10-001 was a randomised, active-controlled, double-blind (via 3rd party), single-centre, single 20-µg fixed-dose, (planned for) 2-stage, 2-period, 2-sequence crossover study, planned to compare the PK of RGB-10 (biosimilar teriparatide) with that of the reference medicinal product Forsteo (EU-sourced) in 54 healthy adult female premenopausal subjects.

Subjects were randomised to treatment sequences AB or BA, where treatment A was the single-dose administration of RGB-10 and treatment B was the single-dose administration of Forsteo.

A single 20 µg/80 µL sc injection of RGB-10 or Forsteo was administered in the morning (around 08:00) of each period.

There were two dosing days (Period 1 Day 1 and Period 2 Day 1), which were separated by a washout period of 24 hours (+ up to 1 hour). In each period blood sampling for PK evaluation was performed before dosing (within 30 minutes) and at 10, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 120, 180, and 240 minutes post dose.

Study participants

54 healthy adult female premenopausal subjects entered the study and were randomised to either of the two treatment arms, AB (test-reference) or BA (reference-test), meaning they acted as their own control group [Sequence AB (n=28), Sequence BA (n=26)].

Of the 54 female subjects participating, 53 subjects were white and one subject was white-Asian. The mean age for all subjects was 29.2 years (range 18- 48 years), the mean weight was 62.1 kg (range 51.0 - 83.0 kg), the mean height was 164 cm (range 154- 183 cm), and the mean body mass index (BMI) was 23.0 kg/m^2 (range 19.1- 27.0 kg/m^2).

Treatments

- Treatment A (test): A single 20 µg/80 µL SC injection of RGB-10 (Gedeon Richter, batch No. E41002, expiration date; Jan 2015)
- Treatment B (reference): A single 20 µg/80 µL SC injection of Forsteo (Lilly France S.A.S., batch No. C142910F, expiration date: Feb 2015).

Test (RGB-10) was supplied as teriparatide 20 µg/80 µL SC solution for injection in a cartridge inserted in a reusable, multi-dose ServoPen Fix pen injector, manufactured by Ypsomed AG, Switzerland. One Movymia cartridge of 2.4 mL contains 600 micrograms of teriparatide (corresponding to 250 µg per mL).

In the course of the procedure, a dose accuracy test was performed comparing commercial pens of the reference product (Forsteo), as well as pens (ServoPen Fix) of the test product (RGB-10). Both the Forsteo pen and the ServoPen Fix were within the range of 80 ± 10 µL per dose, and hence can be seen as comparable.

Reference (Forsteo) was supplied as teriparatide 20 µg/80 µL SC solution for injection in a pre-filled pen. One Forsteo pre-filled pen of 2.4 mL contains 600 µg of teriparatide (corresponding to 250 µg per mL).

For both devices (i.e., ServoPen Fix and Forsteo pen) the same type of needle: BD Micro-Fine™+ Pen Needle (0.25 mm (31G), TW, 8 mm) was used.

Subjects received the subcutaneous injection in a semi-reclined or supine position, into the right side of the abdomen in period 1, into the left side of the abdomen in period 2.

Analytical Assay

The PK profiles of teriparatide were evaluated by means of teriparatide (RGB-10 and Forsteo) determination in human plasma samples using a validated enzyme-linked immunosorbent assay (ELISA). The lower limit of quantitation (LLOQ) to upper limit of quantitation (ULOQ) analytical range for teriparatide was 6.00 to 150 pg/mL. The method was validated with respect to accuracy, precision, linearity, sensitivity, specificity, and stability.

Data provided in the reports generally support the cross-validation of the ELISA to detect RGB-10 and Forsteo in human plasma. For the cross validation of the PTH(1-34) human plasma samples containing analyte are pre-treated with beads coated with goat anti-human PTH(39-84) (using the standard procedure outlined by the ELISA kit's manufacturers) it is noted that cross-reactivity with human PTH(1-84) is not

significant in the initial validation of this ELISA. All validations and samples have been pre-treated with the beads coated with anti-human PTH(39-84) in order to lower the LLOQ by reducing/removing cross reactivity of the assay with endogenous PTH. Since endogenous PTH is an interfering factor in the assay for PTH(1-34) and all samples are treated equally, this is acceptable.

PK parameters

Primary PK parameters

$AUC_{0\text{-}tlast}$ Area under the plasma concentration versus time curve to the last measurable concentration

C_{max} Maximum plasma concentration

Equivalence for the primary endpoints was to be concluded if the 94.12% CIs of the ratios of geometric least squares means (LSMs) (derived from the analyses on the natural log (ln)-transformed PK parameters $AUC_{0\text{-}tlast}$ and $C_{max)}$ of the test to the reference product were completely within the acceptance interval of 80.00-125.00 %.

Secondary PK parameters

t_{max} time to maximum concentration

$t_{½}$ apparent terminal elimination half-life

Other PK parameters

$AUC_{0\text{-}inf}$ Area under the plasma concentration versus time curve to infinity

$AUC_{\%extrap}$ Percent of area under the plasma concentration versus time curve to infinity extrapolated

t_{last} time to last measurable concentration

k_{el} apparent terminal elimination rate constant

CL/F apparent total clearance

V_z/F apparent distribution volume

Results

Disposition of subjects

Of the 54 healthy adult female premenopausal subjects entering the study and being randomised to either of the two treatment arms, 53 completed both periods (one subject withdrew consent for personal reasons), and 51 were included in the final PK-analysis set. One subject was excluded because of pre-dose concentrations >5% of C_{max} in both periods, and another subject was excluded because of too many missing blood draws in period 2 compromising the integrity of the PK parameters.

Primary PK-parameters ($AUC_{0\text{-tlast}}$, C_{max})

Table 2: Summary of Statistical Comparisons of Plasma Teriparatide Pharmacokinetic Parameters Following a Single 20 µg/80 µL sc Injection of RGB-10 and Forsteo (Treatment A Versus Treatment B)

	LSMs				
Parameters	Treatment A (RGB-10)	Treatment B (Forsteo®)	GMR%	94.12% CI	Intra-subject CV%
C_{max} (pg/mL)	83.192	90.179	92.25	85.51 - 99.52	19.37
$AUC_{0\text{-tlast}}$ (pg*hr/mL)	92.443	100.857	91.66	85.20 - 98.60	18.63
$AUC_{0\text{-inf}}$ (pg*hr/mL)	103.886	115.657	89.82	83.75 - 96.33	17.48
$t_{½}$ (hr)	0.654	0.715	91.39	83.28 - 100.29	23.38

Subjects 2, 22 and 54 were excluded from statistical analyses. Geometric least-squares means (LSMs) are calculated by exponentiating treatment LSMs derived from ANOVA. Geometric mean ratio (GMR)=100 * (test/reference); intra-subject CV was calculated as 100 x square root(exp[residual variance]-1).

$AUC_{0\text{-inf}}$: area under concentration-time curve from time zero to infinity; $AUC_{0\text{-last}}$: area under concentration-time curve from time zero to last quantifiable concentration; CI: confidence interval; C_{max}: maximum concentration; $t_{½}$: terminal half-life; t_{last}: time at last measurable concentration

Other PK-parameters

Table 3: Summary of Plasma Teriparatide Pharmacokinetic Parameters Following a Single 20 µg/80 µL sc Injection of RGB-10 and Forsteo (Treatment A and B)

Pharmacokinetic Parameters	Treatment A (N=51)[d]	Treatment B (N=51)[e]
$AUC_{0\text{-tlast}}$ (pg*hr/mL)[a]	91.8 (40.9)	99.0 (35.0)
$AUC_{0\text{-inf}}$ (pg*hr/mL)[a]	103 (37.8)	114 (29.7)
$AUC_{\%extrap}$ (%)[b]	10.9 ± 5.54	10.6 ± 5.15
C_{max} (pg/mL)[a]	82.4 (40.1)	89.2 (37.1)
t_{max} (hr)[c]	0.334 (0.166, 0.585)	0.417 (0.167, 0.667)
t_{last} (hr)[b]	2.49 ± 0.729	2.58 ± 0.707
$t_{1/2}$ (hr)[b]	0.701 ± 0.287	0.757 ± 0.285
k_{el} (1/hr)[b]	1.11 ± 0.331	1.03 ± 0.339
CL/F (L/hr)[b]	207 ± 83.2	183 ± 54.3
V_z/F (L)[b]	203 ± 96.1	198 ± 87.4

Treatment A: A single 20 µg/80 µL sc injection of RGB-10
Treatment B: A single 20 µg/80 µL sc injection of Forsteo®
a: Presented as GM (GCV%), GM: Geometric mean; GCV%: Geometric coefficient of variation
b: Presented as AM ± SD, AM: Arithmetic mean; SD: Standard Deviation
c: Presented as Median (Minimum, Maximum)
d: N = 50 for $AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, $t_{1/2}$, k_{el}, CL/F, V_z/F because k_{el} value could not be estimated for Subject 32
e: N = 49 for $AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, $t_{1/2}$, k_{el}, CL/F, V_z/F because k_{el} values could not be estimated for Subjects 32 and 41
Subjects 2, 22, and 54 were excluded from summary statistics for both treatments.

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).

Summary of trial

Title: A Randomised, Double-Blind, Single, 20 Microgram Fixed Dose, Two-Way Crossover Comparative Pharmacokinetic Study of RGB-10 and Forsteo in Two Stages, in Healthy Adult Female Subjects			
Study identifier	RGB-10-001		
Design	Single center, double-blind (via third-party), randomised, single, 20 µg/80 µL fixed dose, **2-way crossover** comparative PK study planned in 2 stages, in healthy adult female subjects. A second center was planned but did not dose any subjects. Following the completion of Stage 1, an interim analysis was performed using unblinded PK data from Stage 1, and a decision was made to consider the study complete.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2 periods of ca. 12 hours each; washout phase of 24 hours between both doses → 48 hours not applicable not applicable	
Hypothesis	Equivalence		
Treatments groups	RGB-10 (Treatment A / Test)	a single 20 µg/80 µL sc injection of RGB-10 (batch No. E41002) number randomized = 54	
	Forsteo (Treatment B / Reference)	a single 20 µg/80 µL sc injection of Forsteo (Lilly France S.A.S., batch No. C142910F) number randomized = (the same) 54	
Endpoints and definitions	Co-Primary endpoint	$AUC_{0\text{-}tlast}$	94.12% CIs of the LSM ratios derived from the analyses of the ln-transformed Area under the plasma concentration versus time curve to the last measurable concentration of test to reference formulation
	Co-Primary endpoint	C_{max}	94.12% CIs of the LSM ratios derived from the analyses of the ln-transformed Maximum measured plasma concentration of test to reference formulation
	Secondary endpoint	t_{max}	Non-parametric analysis of time of the maximum measured plasma concentration
	Secondary endpoint	$t_{1/2}$	Apparent terminal elimination half-life
Database lock	Not found		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol (Blood drawings for PK parameters lasted 4 hours in both periods)		
Descriptive statistics and estimate variability	Treatment group	RGB-10	Forsteo
	Number of subjects	51	51
	$AUC_{0\text{-}tlast}$ (pg*hr/mL) geometric mean	92.443	100.857

	C_{max} (pg/mL) geometric mean	83.192	90.179
	$t_{1/2}$ (hr) geometric mean	0.654 (39.24 min)	0.715 (42.9 min)
	t_{max} (hr) arithmetic mean	0.334 (20.04 min)	0.417 (25.02 min)
Effect estimate per comparison	Co-Primary endpoint $AUC_{0-tlast}$	Comparison groups	RGB-10 vs Forsteo
		Geometric mean ratio (%)	91.66
		94.12% CI	85.20-98.60
			Within 80.00-125.00%
	Co-Primary endpoint C_{max}	Comparison groups	RGB-10 vs Forsteo
		Geometric mean ratio (%)	92.25
		94.12% CI	85.51-99.52
			Within 80.00-125.00%
	Secondary endpoint $t_{1/2}$	Comparison groups	RGB-10 vs Forsteo
		Geometric mean ratio (%)	91.39
		94.12% CI	83.28-100.29
	Secondary endpoint t_{max}	Comparison groups	RGB-10 vs Forsteo
		Non parametric median	-0.075
		90% CI	-0.105; -0.007
		p-value	0.031
Notes	Although the primary efficacy parameters were within the predefined 80.00 to 125.00% range, there seems to be a slight difference of around 8% between the respective GMRs.		

2.4.2. Pharmacodynamics

For the information of the PD properties of teriparatide, the Applicant relied on the documentation of the reference product Forsteo.

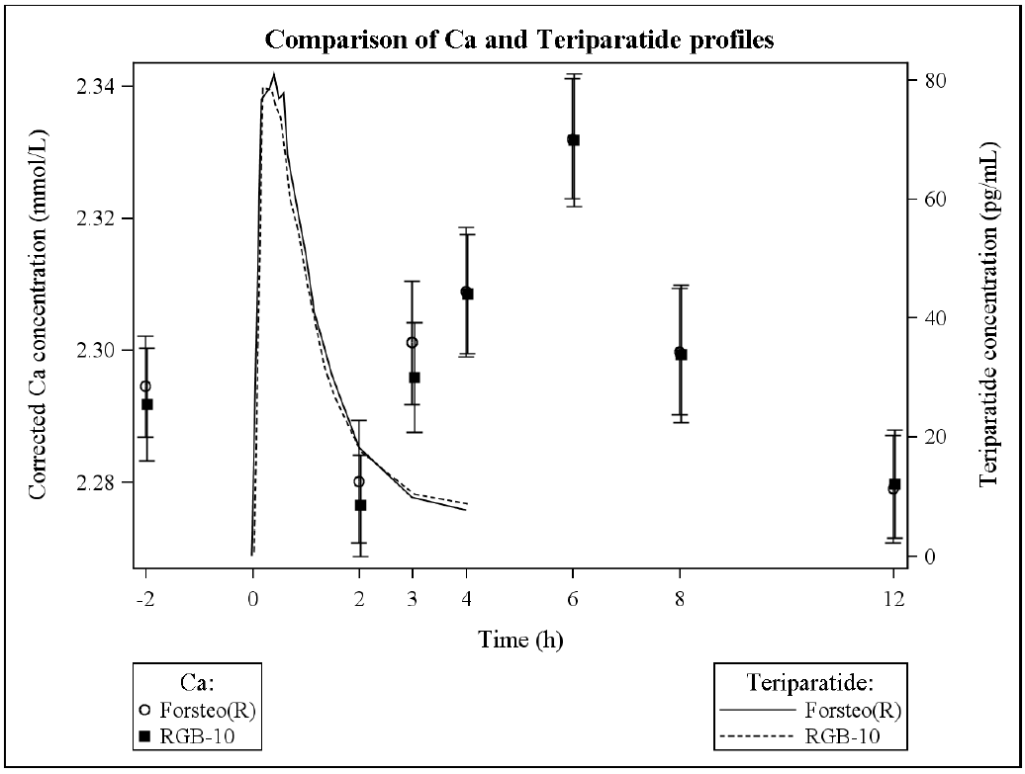
However, during the procedure, the applicant provided supportive data from the PK study, where increases in serum calcium upon teriparatide application were measured as part of the safety assessments and could be evaluated as a PD parameter.

Teriparatide is known to cause transient increases in calcium after each dose. This is observed in healthy volunteers and patients and is believed to be due to increased intestinal absorption and increased tubular reabsorption of calcium in response to teriparatide. The maximum calcium response is observed at approximately 4.25 hours in patients, with a median increase of 0.1mmol/L. The serum calcium concentration returns to normal by 16-24 hours after each dose.

During the comparative PK study (AA99812), serum calcium was measured at pre-dose and at 120, 180 and 240 minutes, and 6, 8 and 12 hours post-dose, as a safety endpoint. Calcium could also be analysed as a PD parameter. It is acknowledged that the available time-points are infrequent, and an equivalence margin was not pre-specified. However a comparable calcium response for RGB-10 and Forsteo would provide supportive evidence of similarity. The company was asked to provide comparative serum calcium concentration-time curves for RGB-10 and Forsteo. The analysis should include the PD parameters AUC, C_{max} and t_{max}. 95% confidence intervals should be provided.

Overlay-plot for serum calcium (mean ± SE) and mean teriparatide profiles

Figure 1:



Statistical analysis of all serum calcium PD parameters showed close similarity between RGB-10 and Forsteo® with GMRs very close to 100% for AUC and C_{max} and median difference close to zero for t_{max}. This, together with the high similarity between PK and PD profiles illustrated above support the conclusion of the two treatments having equivalent PK/PD relationships.

For further discussion of the serum calcium PD data from PK study (AA99812) see “Discussion on clinical pharmacology”, section “Pharmacodynamics”.

2.4.3. Discussion on clinical pharmacology

Pharmacokinetics

The choice of population and the design for the only clinical PK study of this abridged application are endorsed.

Since investigation of similarity aims at excluding significant differences between two substances, a study population as homogenous as possible is recommended. There is no data suggestive of a difference in PTH receptor density between osteoporotic and healthy individuals, and the effect of teriparatide was shown to be similar across a wide range of subjects ranging from healthy volunteers and women with chronic conditions (such as hypertension, heart failure and renal impairment) to osteopenic and osteoporotic patients displaying various disease severity. The exclusion of male subjects, although included in the indication, is also deemed acceptable since a biosimilar exercise does not need to establish the PK for each population anew.

Further to the demonstration of comparability between RGB-10 and the reference medicinal product Forsteo at the analytical and the non-clinical levels, the Applicant aimed at demonstrating therapeutic equivalence of RGB-10 to Forsteo in one comparative pharmacokinetic (PK) study in 54 healthy women. In view of the simple structure of teriparatide and referring to the Biosimilar Guidelines (CHMP/437/04 Rev 1: "In specific circumstances…" and EMEA/CHMP/BMWP/42832/2005 Rev1: "In exceptional cases…"), this is considered acceptable.

$AUC_{0\text{-tlast}}$ and C_{max} have been chosen as primary parameters. In this context, it is deemed acceptable, that the Applicant chose the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), stating "*In studies to determine bioequivalence after a single dose, the parameters to be analysed are $AUC_{(0\text{-}t)}$ … and C_{max}.",* for the selection of the primary parameters. Furthermore, both parameters are relevant and approved values for the comparison of bioequivalence and they are sensitive enough to show differences.

The secondary endpoints were $\mathbf{t_{max}}$ and $\mathbf{t_{1/2}}$.

The Applicant has pre-planned for a two-stage design, which allowed for stopping for equivalence at interim, as well as for a sample size reassessment. Regarding type I error control the testing procedure did foresee that as the first step in the initial stage 1 an interim analysis for equivalence was performed at the alpha level of 0.0294 (corresponding to a confidence interval of 94.12% coverage probability). According to this rule the trial was stopped after stage 1, concluding on equivalence.

The 94.12% confidence intervals for the geometric mean ratios of the primary endpoints ($AUC_{0\text{-tlast}}$ and C_{max}) of RGB-10 and Forsteo fell within the predefined equivalence margins of 80-125%, but 100%, i.e. unity was not included. Mean $AUC_{0\text{-tlast}}$ and C_{max} were around 8% lower following a single SC injection of RGB-10 compared to Forsteo. The same picture (non-inclusion of 100%) resulted from the additionally requested 90% CI of $AUC_{0\text{-tlast}}$ and C_{max}.

Based on EMA's Biosimilar guideline (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1):*"the interpretation of bioequivalence studies for biologicals is less straightforward than for small molecules. In the latter case the molecules are considered identical, whilst for biologicals, PK is used to detect possible differences in the interaction with the body between the originator and the biosimilar. This means that observing 90% CIs of ratios of biosimilar to reference product within a pre-specified, justified acceptance range may not, by itself, be sufficient. The location and the width of the confidence interval should also be taken into account in the interpretation of similarity. For example, statistically significant differences in 90% CIs within the justified acceptance range regarding relevant PK parameters would need to be explained and justified as not to preclude biosimilarity.",* a justification as to

why there are differences and why these differences should not change efficacy and safety for patients receiving RGB-10 instead of Forsteo was requested and provided during the procedure (see below).

The secondary endpoints, t_{max} and $t_{1/2}$ were also slightly below those of Forsteo.

T_{max} occurred during the first sampling time-point for 17 subjects after receiving the test product and 10 subjects after receiving the reference product. However the sampling commenced only 10 minutes after dosing. The sampling schedule was acceptable to CHMP (EMA/CHMP/SAWP/225300/2012) with the comment: *samples taken before 10 minutes will be of limited value due to the high variability*. During the d121 response, it was assessed as doubtful that an earlier sampling time-point (e.g. 5 minutes or 7.5 minutes) would have resulted in a significantly greater mean C_{max} for either test or reference product, given that the route of administration was subcutaneous rather than intravenous injection.

Any underestimation of mean C_{max} is more likely to affect the test product than the reference product, due to the increased number of observations affected. An underestimation of C_{max} would also lead to an underestimation of AUC. Any increase in mean C_{max} and AUC for the test product compared to the reference product would reduce the apparent difference in bioavailability between the test and reference product. It was agreed with the applicant that the addition of an earlier time-point would not have significantly affected results. If anything, the apparent difference in exposure between RGB-10 and Forsteo would have been reduced.

Also, with regard to the mode of action of teriparatide, it was questioned, whether the 8 % lower $AUC_{0\text{-tlast}}$ and C_{max} compared with the reference product may be relevant for the pharmacodynamic effects, as the skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. For this anabolic effect on bone, intermittent administration causing a high but short concentration spike of teriparatide is essential. Continuous administration of teriparatide induces preferential stimulation of osteoclastic activity over osteoblastic activity, leading to an increase in bone resorption and a decrease in bone strength, which resembles the pathophysiology of primary hyperparathyroidism.

Literature and discussion provided by the applicant during the procedure support that rather the intermittent course of teriparatide therapy as opposed to continuous exposure accounts for the anabolic effect of treatment.
While no definite estimation on the effect size of an “underexposure” of 8% (as compared with Forsteo) on the clinical outcome could be deduced, provided evidence points towards no/negligible effect: Data submitted for the approval of a single, non-weight corrected dose (20 µg) of Forsteo, which accounted for approx. 26% higher C_{max} values if teriparatide was given to patients with lower body weight, as well as authorisation of elective administration sites (either abdomen or thigh) causing 18% - 44% lower C_{max} values if teriparatide was given in the thigh instead of the abdominal wall, suggest that the observed difference is likely without meaningful clinical impact.

Concerning other endpoints, shorter t_{last} of RGB-10 and faster (apparent total plasma) Clearance (CL/F) compared to Forsteo, also could have led to the assumption that in vivo the organism is less exposed to RGB-10 than to Forsteo following the same dose.

The company argued that CL/F (apparent total plasma clearance) is a purely arithmetical value derived from dose (20 µg) and AUC and was of the opinion, that, due to the flip flop kinetics of teriparatide and an observed difference in $t_{1/2}$, rather a difference in absorption could be the driver of differences in exposure.

The applicant discussed the differences in the PK profiles from a statistical, device related, quality, bioanalytical and clinical perspective. The observed 8% difference in C_{max} and AUC while still being within the acceptance range of 80-125% was probably made visible (i.e. reaches statistical significance) due to the overestimation of the sample size for the first stage of the study. No major differences were identified by further analyzing the delivered volumes, active content, structure of the active substance and the PK assay. Therefore, any remaining differences between RGB-10 and Forsteo were considered sufficiently small not to preclude a positive B/R.

Pharmacodynamics

The EMA-Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, (EMEA/CHMP/BMWP/42832/2005 Rev1, 2014) states in section 5.2. Pharmacodynamic studies: "*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.*"

A limitation of the available PD marker Bone Mineral Density (BMD) and other biochemical markers of bone turnover, such as osteocalcin, bone-specific alkaline phosphatase, urine and serum N- or C-telopeptide of type I collagen and N-propeptide of type I procollagen, is that they are not considered very good surrogates for fracture risk reduction (see Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis, (CPMP/EWP/552/95 Rev.2)).

For teriparatide specifically, this has been documented in the literature: In a post hoc analysis of the Fracture Prevention Trial, the relationship between changes in lumbar spine BMD and vertebral fracture risk reduction with teriparatide treatment was assessed (Chen PJ Bone Miner Res 2006; 21:1785-1790). Teriparatide-mediated increases in lumbar spine BMD accounted for only 30-41% of the reduction in vertebral fracture risk.

Although it is recognised, that PD-markers might not be very sensitive in translating the full therapeutic (i.e. anti-fracture) effect of teriparatide, their evaluation could provide supportive data showing that the observed PK-differences do not directly translate into PD-differences.

Serum calcium measured during the comparative PK study (AA99812) was analysed as a PD parameter (see above, Figure 1, in section "Phamacodynamics").

In the analyses provided during the procedure, the 95% confidence intervals of the geometric mean ratio of the test/reference corrected calcium are within 99-101%. The mean corrected calcium concentration-time profiles are also comparable according to Figure 1. However it is noted that the 2 hour mean calcium is reduced compared to the -2 hour mean calcium.

The applicant was asked to explain the reason for the initial reduction in mean serum corrected calcium following administration of the test or reference product, as shown in Figure 1.

In their responses, the Applicant provided non-clinical and clinical literature (Parsons et al 1971, Frolik et al 2003, Borle 1968, "PDQ Physiology" by Uwe Ackermann, Maeda et al 2013, Forssman et al 2016) in order to explain the reason for the initial reduction in mean serum corrected calcium following administration of PTH. The underlying hypothesis is that parathyroid hormone increases calcium permeability of cell membranes, leading to calcium influx and consequent reduction in serum levels. Initial hypocalcaemia, around one hour post dose, was also observed in a clinical pharmacodynamic comparison of PTH(1-37) and teriparatide.

It was agreed with the applicant that the initial hypocalcaemia observed for RGB-10 and Forsteo is likely to be a real phenomenon based on the evidence presented, and that the initial 2-hour time point caught the tail end of the hypocalcaemic phase. Hence this issue was regarded resolved as well.

2.4.4. Conclusions on clinical pharmacology

The demonstration of clinical similarity is based on a comparative single-dose, cross-over PK study comparing single subcutaneous doses of RGB-10 and Forsteo. In principle, this was considered acceptable in the particular case of a small and simple biological such as teriparatide, if the PK study showed robust evidence for comparability.

The observed difference in C_{max} and AUC between RGB-10 and Forsteo likely became detectable (i.e. reached statistical significance) by an overestimation of the sample size for the first stage of the study (which is per se not a justification for the existence of a difference). Judging from available literature for Forsteo with regard to the impact of body weight and administration site on clinical outcomes, the clinical impact of the observed difference, however, was considered to be negligible.

No major differences were identified by further analyzing delivered volumes, active content, structure of the active substance and the PK assay.

Therefore RGB-10 and Forsteo were considered to be similar from a pharmacological perspective.

2.5. Clinical safety

Clinical safety data are only available from Study RGB-10-001.

Patient exposure

54 healthy female premenopausal volunteers were enrolled and received at least one dose of the test product. Subject 2 (Treatment Sequence AB) received RGB-10 only in Period 1 before withdrawing from the study due to personal reasons. Thus, only 53 of the enrolled subjects received a single dose of 20 µg teriparatide SC (Test and Reference product in a cross-over design) in each of the 2 study periods with a wash out period of 24 hours in between.

But all 54 enrolled subjects were included in the safety evaluation.

Adverse events

Experienced AE´s according to SOCs were:

Gastrointestinal disorders:

lower abdominal pain, dry lips, nausea, vomiting

General disorders and administration site conditions

asthenia, catheter site erythema/inflammation/pain, injection site erythema, vessel puncture site pain/swelling, “feeling hot”, fatigue

Investigations

decreased O_2 saturation

Metabolism and nutrition disorders

decreased appetite

Musculoskeletal and connective tissue disorders

back pain, limb discomfort, pain in extremity, myalgia

Nervous system disorders

dizziness, headache, paraesthesia, presyncope

Psychiatric disorders

nervousness

Reproductive system and breast disorders

dysmenorrhoea

Skin and subcutaneous tissue disorders

ecchymosis, papule

Vascular disorders

hypotension, peripheral coldness

Of the subjects dosed, (54 with RGB-10, 53 with Forsteo), 29 [54%] showed AEs after RGB-10, 33 [62%] after Forsteo.

Of the 127 treatment-emergent AEs (TEAEs) registered, 52 appeared after treatment with RGB-10, 75 after treatment with Forsteo. Of the 52 AEs after RGB-10, 42 were judged mild, 10 moderate; 33 were judged drug-related, 19 not. Of the 75 AEs after Forsteo, 56 were judged mild, 19 moderate; 40 were judged drug-related, 35 not.

In the main study, the most frequently reported treatment-emergent adverse events were nausea (10 subjects; 19% of subjects dosed), injection site erythema (9 subjects; 17%), dizziness (5 subjects; 9%), headache (5 subjects; 9%), vomiting (4 subjects; 7%) and presyncope (4 subjects; 7%) under RGB-10 treatment.

Under Forsteo the most frequently reported TEAEs were nausea (14 subjects; 26%), dizziness (11 subjects; 21%), headache (11 subjects, 21%), injection site erythema (6 subjects, 11%), vomiting (3 subjects; 6%) and presyncope (3 subjects; 6%).

The number of Adverse Events does not suggest a strong difference between treatments in terms of safety (if at all, trends point towards lower incidences of AEs under RGB-10 treatment).

However, due to the small study population and the short duration of treatment including the cross-over with (only) 1 day of wash-out in between, these results have to be regarded with caution.

Of the 15 (9 with RGB-10, 6 with Forsteo) injection site erythemae documented, none met the (predefined) criteria for Grade 1 classification for injection site reactions according to FDA Guidance, neither did the other AEs described at the injection sites. Although no European classification system has been used, it can be agreed that, these injection site erythemae can be regarded as minor.

Serious adverse events and deaths

No serious adverse event (SAE) or death occurred.

Laboratory findings

Mean results for serum chemistry, haematology, and urinalysis remained within reference range throughout the study with no remarkable observations in the change from baseline results.

Concerning deviations of laboratory values, most of them were isolated slight deviations from the normal ranges. Only very few values were striking, because more subjects were concerned:

Interesting was a decrease in LDH (in 14 subjects) from screening to post dose values. But this is not considered clinically relevant since no pathologies are known in this relation (besides from Vitamin C overdose, which is regarded unlikely).

Changes concerning (traces of) blood in the urine also appeared in several subjects, but these were expectable due to menstruation.

High urine calcium and low corrected calcium serum values were not only seen at screening but also post dose in several subjects. Obviously, the expected increase in total serum calcium 2 to 6 hours after teriparatide injection resulted only in slight elevations of the originally decreased corrected serum calcium values in some subjects. The slightly elevated urine calcium values are deemed expectable from teriparatide, but as some of them were pre-existent at screening already, not much weight is given to these slight changes, especially as they were seen with both treatments.

There were no laboratory adverse events reported in this study.

Since other laboratory parameters were not expected to change during the 3 days of the PK-study, haematology, urinalysis, serum chemistry (other than calcium), total cholesterol and triglycerides were only measured at screening, check-in and prior to discharge (for inclusion check and safety reasons). Hence, similar elaborate calculations, as were done for corrected calcium, vital signs and ECG values, would not be reasonable for values not expected to change during the short trial setting. Therefore, no further evaluation was finally requested.

Immunological events

No analysis of immunogenicity parameters has been performed, because the Applicant is of the opinion that a clinically relevant immunogenic potential of RGB-10 appears to be highly unlikely, as the immunogenic potential of Forsteo has proved to be negligible in the clinical studies for registration purposes as well as over the past ten years on the market.

Discontinuation due to AES

No discontinuations due to AEs occurred in PK-study RGB-10-001.

2.5.1. Discussion on clinical safety

Adverse events

The small size of the safety database makes any comparison of the respective safety profiles unreliable as the significance of numerical differences based on 54 subjects treated, moreover in a single–dose cross-over administration, is uncertain.

The type of AEs reported was in line with those listed in Forsteo SmPC, mostly nausea, dizziness, headache, injection site erythema, vomiting and presyncope.

In comparison with the most frequently registered undesirable effect listed in the reference SmPC, namely "pain in limb", only one subject with limb discomfort (2%) and 2 subjects with pain in extremity (4%) were registered in study RGB-10-001. This difference might possibly be attributable to the fact, that the administration of teriparatide in the RGB-10-001 study was limited to the abdomen.

Injection site erythema were seen more often in the RGB-10 group (9 vs 6 subjects, or 17 vs 11%), but all of the described erythema were very mild and thus this difference was regarded as of no relevance.

A history of sensitivity was an exclusion criterion in the comparative PK study because the ServoPen Fix pen injector used to administer RGB-10 may come into contact with latex during the manufacturing process. The applicant was asked to discuss whether a history of sensitivity to latex should be a contraindication for Movymia. The Applicant confirmed that the Movymia pen injector is free of latex traces. Therefore a history of sensitivity to latex does not need to be a contraindication.

Immunogenicity

According to the Applicant, the lack of immunogenicity concerns, characterising the past 12 years of market experience with Forsteo, might be the consequence of several different factors all reducing the risk of developing an immune response during teriparatide treatment. The fact of being a low molecular weight fully human molecule of microbial origin (i.e., lack of glycosylation) renders teriparatide less immunogenic compared to more complex biologicals. The continuous daily dosing regimen and the to some extent compromised immune system of the target population, either due to a certain degree of immunosenescence or as a result of sustained immunosuppressive treatment with systemic steroids, are thought to reduce the susceptibility of patients to immune-based adverse events. The Applicant sees the same conditions and circumstances applicable to RGB-10 as well.

While there are no concerns from a quality perspective, this issue is more complex from a non-clinical perspective. Although no neutralising antibodies were detectable in an immunogenicity study on rats, the incidence of antibody positive samples (95 screening positives with 34 confirmed positives in total) was higher for RGB-10 at all dose levels in comparison to Forsteo. Furthermore, Forsteo showed increasing antibody-titers with increasing dose while RGB-10 showed higher titers at the low dose group in comparison to its mid dose group.

While the overall incidence of antibody formation is quite low and the translatability of non-clinical immunogenicity data to humans is limited, an increased immunogenic capacity for RGB-10 cannot be entirely excluded.

The general immunogenic potential of teriparatide is considered low (small molecule, no glycosylation no posttranslational modifications, only 2,8% of antibody formation was registered after 12 month of treatment with Forsteo, target population of elder or glucocorticoid-treated patients might have a less reactive immune system). Nevertheless the lack of clinical characterisation of the immunogenicity of RGB 10 still presents a gap in the biosimilar exercise which needs to be addressed in an appropriate way, especially as some differences between RGB-10 and Forsteo could be seen in the PK endpoints, no clinical efficacy/safety (+ immunogenicity) study was conducted or is planned and the non-clinical study does not help to dispel remaining concerns.

With respect to this issue, the Applicant proposed to provide the immunogenicity data of a Japanese efficacy/safety study RGB1023031 comparing RGB-10 with Forteo (teriparatide; Japan). This study is ongoing and is carried out by the Japanese partner of the Applicant. The Applicant has submitted a study protocol (RGB1023O31) version 1.1 (04/03/2016) for this phase 3 clinical study: *A comparative study to evaluate the similarity of RGB-10 to Forteo in patients with osteoporosis at high risk of fracture.*

It is a multi-centre, randomized, active-controlled, parallel group comparative efficacy and safety study, conducted in Japan. The study population consists of patients with primary osteoporosis at high risk of fracture. Subjects will be randomised 1:1 to RGB-10 or Forteo, 20 µg daily subcutaneously for 52 weeks. Anti-teriparatide antibody testing will be conducted. If anti-teriparatide antibody is positive, neutralising activity will be determined.

The design of this study is adequate to provide meaningful comparative efficacy and safety data, including immunogenicity data. Inclusion in the RMP was considered appropriate. The applicant's estimated timelines are acceptable.

The proposal of submitting supportive immunogenicity data from a large phase III study to provide additional data on immunogenicity was deemed acceptable.

2.5.2. Conclusions on clinical safety

Based on the limited amount of safety data available and the cross-over design of the PK-study the confirmatory assessment of similarity on the safety level largely relies on the demonstration of comparability on the physicochemical, biological and non-clinical level, which supports biosimilarity between the two products.

A plan for post-marketing evaluation of immunogenicity was laid out by the Applicant. Immunogenicity data from an ongoing Japanese efficacy/safety study comparing RGB-10 and Forteo (teriparatide; Japan) will be provided after its completion. A detailed study protocol was provided with the responses to the D180 LoOI.

Taken together it is agreed that the safety profile of Forsteo and RGB-10 can be considered comparable, and is therefore acceptable.

2.6. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Hypercalcaemia Orthostatic hypotension
Important potential risks	Osteosarcoma (potential risk from non-clinical finding) Non-uraemic calciphylaxis
Missing information	Immunogenicity

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
RGB-10 Phase III Clinical study RGB1023O31: A comparative study to evaluate the similarity of RGB-10 to Forteo® in patients with osteoporosis at high risk of fracture Category 3.	Providing immunogenicity data during treatment with Movymia/Terrosa Furthermore assessing the clinical relevance (efficacy or safety consequences) of anti-teriparatide antibody formation.	Missing Information of Immunogenicity	Started in Q1 2016	Planned: 2018/2019

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Hypercalcaemia	*Appropriate labelling:*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Text in SmPC: Contraindication concerning pre-existing hypercalcaemia in ***Section 4.3.*** Warning in ***Section 4.5*** concerning a potential interaction with digitalis. It is highlighted that teriparatide should be used with caution in patients taking digitalis. Hypercalcaemia greater than 2.76 mmol/L is listed as an uncommon adverse reaction and Hypercalcaemia greater than 3.25 mmol/L is listed as a rare adverse reaction in ***Section 4.8.*** ***Section 4.9*** includes delayed hypercalcaemia as an expected effect of overdose. *Prescription-only medicine*	
Orthostatic hypotension	*Appropriate labelling:* **Text in SmPC:** Warnings and precautionary measures are included in ***Section 4.4*** concerning orthostatic hypotension. Warning in ***Section 4.7*** concerning transient, orthostatic hypotension or dizziness. It is highlighted that patients should refrain from driving or the use of machines until symptoms have subsided. It is stated in ***Section 4.9*** of the SmPC that effects of overdose might include the risk of orthostatic hypotension. *Prescription-only medicine.*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Potential Risk		
Osteosarcoma (potential risk from non-clinical finding)	*Appropriate labelling:* **Text in SmPC:** The treatment duration is limited to 24 months in ***Section 4.2*** and ***Section 4.4***. Use is contraindicated in patients with Paget's disease of the bone, skeletal malignancy or prior radiation of the skeleton (***Section 4.3***). Information concerning pre-clinical findings is included in ***Section 5.3***. *Prescription-only medicine.*	None
Non-uraemic calciphylaxis	*Prescription-only medicine* Movymia/Terrosa is a medicinal product subject to special medical prescription legal status. It is used under continuous monitoring by a specialist after specialist/hospital diagnosis.	None
Missing Information		
Immunogenicity	*Appropriate labelling:* **Text in SmPC:** It is stated in ***Section 4.8*** that in a large clinical trial, antibodies that cross-reacted with teriparatide were detected in 2.8% of women receiving Forsteo®. It is also emphasised that there was no evidence of hypersensitivity reactions, allergic reactions, effects on serum calcium, or effects on Bone Mineral Density response in connection with	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Forsteo®. *Prescription-only medicine.*	

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. 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.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Movymia (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. Benefit-Risk Balance

3.1. Favourable effects

The drug substance and drug product control strategies were provided during the procedure to a sufficient extent. The provided data indicate that the manufacturing process is capable of delivering a product of consistently high quality, for which similarity to the reference product could be demonstrated.

The comparability programme itself is not very extensive, but acceptable in light of the simple molecular structure of RGB-10 (34 amino acids without disulfide bonds) and its expression in E.coli (no glycosylation, no posttranslational modifications).

Results of receptor binding and cell-based functional assays suggestive of comparable performance are shown, and comparative non-clinical PD studies as well as toxicological studies were also conducted, although the latter are not considered having sufficient discriminatory power to identify clinically relevant differences.

The only clinical data to support biosimilarity are from a comparative PK study; no clinical PD or efficacy data are submitted. This simplified approach was accepted by CHMP and the comparative PK study was conducted in accordance with CHMP advice; data from this study is considered pivotal for this application.

3.2. Uncertainties and limitations about favourable effects

The main concern arising from the development program of RGB-10 was the observed difference in PK parameters: the point estimates of the GMRs of AUC and C_{max} showed ~8% lower values for RGB-01 compared with Forsteo, while the 94.12% CIs for the ratios of AUC and C_{max} are contained within the acceptance range of 80-125%. This was seen as indicating a slight PK underexposure of RGB-10 compared with Forsteo and the applicant was asked to perform a thorough root cause analysis for these PK differences.

The company approached the problem from different angles and provided a comprehensive discussion.

Referring to quality, comparison of active substance content and dose accuracy tests excluded a difference in administered dose. State of the art tests revealed structural similarity of the active ingredient. Identical composition excludes absorption differences, and subtle differences in the impurity profile, anyhow resulting in the same degradation kinetics, were not seen as possible reasons for the observed PK differences.

Regarding the PK results the applicant argued that an overestimation of the sample size for the first stage of the study (due to smaller than expected intra-subject CV%) may have contributed to making the small differences in C_{max} and AUC detectable (reaching statistical significance). This argument was basically accepted (though it is not per se a justification for the existence of a difference). Further, a slight underestimation of C_{max} of RGB-10 seems likely based on differences in accuracy of PK parameter estimates since t_{max} was observed at the first sampling time point more often for RGB-10 than for Forsteo (17 vs 10 cases).

The potential clinical impact of the observed PK differences was also discussed, even if considered only of secondary importance in a biosimilar development. Judging from available literature for Forsteo, the impact of the observed difference on clinical outcomes is likely to be negligible: For Forsteo it has been shown that considerable differences in C_{max} (around 3 to 5 times higher than the difference between C_{max} of RGB-10 and Forsteo in the PK study) can occur with the single fixed dose (20 µg) in low body weight subjects and also between the different application sites (abdominal wall or thigh), without consequences for clinical outcomes.

No PD and/or efficacy data were submitted and this was initially questioned in view of the PK results. However, teriparatide is known to cause transient increases in calcium after each dose, and in the comparative PK study serum calcium had been measured at several time-points as a safety endpoint. Upon CHMP request the applicant compared the serum calcium concentration-time curves for RGB-10 and Forsteo: Calcium profiles over time appear comparable, providing some support for the clinical similarity of RGB-10 and Forsteo. An initial decrease in corrected serum calcium observed in both groups was explained as presumably due to PTH induced increase in calcium permeability of cell membranes leading to calcium influx and consequent reduction in serum levels; this is also in line with provided literature data. Moreover, when considering the need for clinical data, it was taken into account that teriparatide is a relatively simple peptide molecule and RGB-10 is produced in the same cell line as the reference product, without glycosylation or any post-translational changes.

Taken together the applicant provided sufficient evidence in favour of biosimilarity between RGB-10 and Forsteo.

3.3. Uncertainties and limitations about unfavourable effects

No immunogenicity testing was incorporated in the PK study nor would this have been considered meaningful.

Although no neutralising antibodies were detectable in an immunogenicity study in rats, the incidence of antibody positive samples was higher for RGB-10 in comparison to Forsteo. However, the overall incidence of antibody formation was quite low and the translatability of non-clinical immunogenicity data to humans is limited, and the general immunogenic potential of teriparatide is considered low. The structural simplicity of teriparatide and the widely demonstrated biosimilarity on the analytical level provide reassurance that the remaining risk of relevant differences in clinical immunogenicity is sufficiently small to be characterised post marketing. A plan outlining how immunogenicity could be characterised was provided by the applicant and is part of the risk management plan. The company will inform post marketing on the immunogenicity outcome of an ongoing Japanese efficacy/safety study comparing RGB-10 and Forsteo.

3.4. Balance of benefits and risks

For a biosimilar, the benefit-risk balance is derived from the reference product, provided the totality of evidence collected from the physicochemical and biological characterisation and the non-clinical and clinical data package supports the comparability of the two products, which CHMP considered to be the case.

3.5. Conclusions

The overall Benefit/Risk balance of Movymia 20 µg/80 µL solution for injection is positive.

4. Recommendations

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

Movymia is indicated in adults.

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

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

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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 theRMP.

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.