10 November 2022
EMA/923811/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kauliv

International non-proprietary name: teriparatide

Procedure No. EMEA/H/C/004932/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

List of abbreviations

AA	Amino acid
ADA	Anti-drug antibody
AEs	Adverse Events
AEX	Anion exchange chromatography
ALT	Alanine transaminase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AS	active substance
AST	Aspartate aminotransferase
AUC	Area Under the Curve
$AUC_{0\text{-}120\ min}$	AUC from zero (predose) to time of 120 minutes
$AUC_{0\text{-}180\ min}$	AUC from zero (predose) to time of 180 minutes
$AUC_{0\text{-}90\ min}$	AUC from zero (predose) to time of 90 minutes
$AUC_{0\text{-}t}$	AUC from time 0 to last quantifiable concentration
$AUC_{0\text{-}\infty}$	AUC from time 0 to infinity
$\%AUC_{0\text{-}t}$	Percentage AUC(0-∞) extrapolated
BLQ	Below Limit of Quantitation
cAMP	Cyclic Adenosine Mono Phosphate
CEX	Cation exchange chromatography
CFB	Change From Baseline
CI	Confidence Interval
CL/F	Clearance
CPP	Critical process parameter
CQA	Critical quality attribute
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
Da	Dalton(s)
DLP	Data Lock Point
DNA	deoxyribonucleic acid
DoE	Design-of-Experiment
DP	Drug product
E. coli	*Escherichia coli*
EMA	European Medicines Agency
EOPC	End of production cell(s)
EU	European Union
EURD	European Union Reference Date
FDA	Food and Drug Administration
FP	finished product
FTIR	Fourier transform infrared spectroscopy
GCP	Good Clinical Practice
GMP	Good manufacturing practice
HCP	host cell protein
HC DNA	host cell DNA
IMAC	Immobilized metal affinity chromatography
INN	international nonproprietary name
IPC	In-process control
IPTG	Isopropyl β-D-1-thiogalactopyranoside
KPA	Key performance attribute

KPP	Key process parameter
L	Liter(s)
LCA	limit of in-vitro cell age
LS	Least Square
MAA	Marketing Authorisation Application
MCB	Master cell bank
MD	Mean Difference
MeSH	Medical Subject Headings
MIA	Manufacture and importation authorization
MO	Major Objection
MS	mass spectrometry
MW	Molecular weight
NOR	Normal operating range
OC	Other concern
OR	Odds Ratio
OOS	out-of-specification
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PP	Process parameter
PPA	Process performance attribute
PPQ	Process performance qualification
PSUR	Periodic Safety Assessment Report
PTH	Parathyroid Hormone
PV	process validation
QP	Qualified person
RCTs	Randomised Clinical Trials
RH	relative humidity
RP	Relative potency
RP-HPLC	Reverse phase high performance liquid chromatography
RT	Reference-test
SEC	size exclusion chromatography
SD	Standard Deviation
SE	Standard Error
TEAE	Treatment-Emergent Adverse Event
TR	Test-reference
ULOQ	Upper limit of quantitation
ULN	Upper limit of normal
US	United States
UV	ultraviolet spectrometry
Vz/F	Apparent Volume of distribution
WCB	Working cell bank
µL	Microliter

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Strides Pharma Cyprus Ltd. submitted on 14 September 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Kauliv, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2017.

The applicant applied for the following indication:

Kauliv is indicated in adults.

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

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

1.2. Legal basis, dossier content <and multiples>

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, a clinical bioequivalent study with the reference medicinal product Forsteo and with appropriate own applicant's non-clinical and clinical data.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: FORSTEO 20 micrograms / 80 microliters solution for injection in pre-filled pen
- Marketing authorisation holder: Eli Lilly Nederland B.V., The Netherlands
- Date of authorisation: (10-06-2003)
- Marketing authorisation granted by:
  - Union

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

1.3. Information on Paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
25 June 2015	EMEA/H/SA/3102/1/2015/III	Walter Janssens, Juha Kolehmainen
20 July 2017	EMEA/H/SA/3102/1/FU/1/2017/III	Juha Kolehmainen, Peter Kiely, Elmer Schabel

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

Quality:

- Overall approach to demonstrate biosimilarity of Stelis Teriparatide [rh PTH (1-34)] biosimilar with the reference products Forsteo (Lilly Nederland B.V.) and Forteo (Lilly USA).
- Acceptability of the studies for physicochemical characteristics, biological assays and stability to establish biosimilarity.
- Adequacy of the manufacturing process and the specifications for the active substance and the finished product.
- Proposal on the comparability exercise strategy
- Specifications for the active substance and drug product.
- Overall approach to establish Quality comparability, including test for product related impurities.
- Extractable study, container closure system and the approach not to conduct a formal leachability study.
- Coverage of the generic kit for detecting host cell proteins (HCPs) in the in-process samples.
- Development of two presentations for the product, reusable pen and disposable pen.
- Manufacturing development plans.

Multidisciplinary Question on Quality and Non-clinical:

- Overall non-clinical in vitro data package.

Multidisciplinary Questions on Quality and Clinical:

- Use of a single assay, and the acceptability of the chosen assay method, to measure rh PTH(1-34) concentrations in the PK studies.

- Acceptability of the approach to use one assay for the detection of anti-teriparatide antibodies in the Phase I and Phase III studies to support a MAA.
  Method and validation of the PK assay for Teriparatide [rh PTH (1-34)] as part of the proposed pivotal Phase-I study.

Multidisciplinary Questions on Quality and Non-clinical and Clinical:

- Acceptability of the reduced clinical program with the proposed pivotal Phase 1 PK bioequivalence study in healthy volunteers, together with the proposed quality comparability exercise, including complementary in-vitro assays, for MAA. Development of the re-usable pen and the disposable pen with the respective cartridges.

Clinical:

- Acceptability of the proposed phase I study design to demonstrate PK similarity between Stelis Teriparatide [rh PTH(1-34)] and FORSTEO®, in particular with regards to the population, primary endpoints and sample size.
- Adequacy of the phase I study to support initiation of the phase III study and MAA with Stelis Teriparatide [rh PTH(1-34)] batches produced using a scaled up manufacturing process at a new site.
- Acceptability of the phase III study design to demonstrate similarity in terms of efficacy, PD and safety including immunogenicity, primary endpoint and sample size calculation.
- Timing of the primary analysis of the phase 3 data. Agreement was sought to seek MA for all indications currently approved for the EU reference product FORSTEO® by extrapolating the safety and efficacy comparability conclusion from the proposed phase III study.
- Acceptability of an alternative option to demonstrate biosimilarity/ comparability on the basis of physicochemical and functional assays as well as phase I study for MAA.
- Geographic distribution of planned patient recruitment.
- Acceptability of the proposed 3-way pivotal Phase-I PK safety and tolerance study to demonstrate biosimilarity with Forsteo® RMP with regards to the primary and secondary endpoints, selection of gender and demography /region of the patients and sample size to establish PK equivalence for MAA.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Agnes Gyurasics

The application was received by the EMA on	14 September 2020
The procedure started on	1 October 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2020

The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 December 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 January 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 January 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 October 2021
The following GMP inspection were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at two sites located in India ‘’Stelis Biopharma Pvt Ltd. (Unit-I), Plot no.293, Bommasandra Jigani link Road, Jigani Industrial Area, Anekal Taluk, Bengaluru – 560 105, India’’ and ‘’ Stelis Biopharma Pvt Ltd. (Unit-II), Plot no.: 2-D1, Obadenahalli, Doddaballapura, 3rd Phase, Industrial area, Doddaballapura Taluk, Bengaluru Rural District – 561 203, India’’, was carried out in March 2022. The outcome of the inspection carried out was issued on 13th June 2022	26 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	2 December 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	10 December 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	16 December 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 June 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	6 July 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 July 2022
The CHMP agreed on 2nd list of outstanding issues in writing to be sent to the applicant on	21 July 2022
The applicant submitted the responses to 2nd CHMP List of Outstanding Issues on	11 October 2022

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to 2nd List of Outstanding Issues to all CHMP and PRAC members on	26 October 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to 2nd List of Outstanding Issues to all CHMP and PRAC members on	3 November 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kauliv on	10 November 2022

2. Scientific discussion

2.1. About the product

	Kauliv
Dosage form and strength:	cartridge containing 3 mL of teriparatide solution for injection [250µg/mL]
Procedure:	Biosimilar application
Therapeutic class or indication:	ATC code: H05AA02
Proposed dosage range:	20µg/80µL dose

Kauliv was developed as biosimilar product to the European reference product Forsteo (Eli Lilly) solution for injection in pre-filled pen, containing 20µg / 80µL of recombinantly produced teriparatide. It is proposed for the same indications and dosages as approved for the reference product. The marketing authorisation for the reference product Forsteo was granted to Eli Lilly by the European Union in June 2003 (via the Centralised Procedure, marketing authorisation number EU/1/03/247/001-002). As part of the global product development approach, the finished product was also developed to be equivalent to the reference listed drug (RLD) Forteo 20 micrograms / 80 mL solution for injection in pre-filled pen, marketed in the United States by Lilly USA.

Kauliv is provided in a cartridge containing 3 mL of drug product solution. It is intended for use with the re-usable Kauliv pen. The pen is manufactured by Owen Mumford.

Pack sizes are 1 cartridge / pack and 3 cartridges / pack.

Therapeutic indications, posology, and route of administration proposed for Kauliv are identical to those for Forsteo. Forsteo is currently 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.

Forsteo is available as a pre-filled pen of 2.4 mL, containing 600 micrograms of teriparatide corresponding to 250 micrograms per mL; each dose of 80 microlitres contains 20 micrograms of teriparatide. The recommended dose of Forsteo is 20 micrograms administered once daily, the maximum total duration of treatment should be 24 months, and the 24-month course should not be repeated over a patient's lifetime. Patients should receive supplemental calcium and vitamin D supplements if dietary intake is inadequate.

Kauliv is a sterile, colourless, clear, isotonic solution formulated in a multi-dose cartridge presentation (28 doses) and is loaded into a reusable pen device for delivering the intended dose of 80 uL. The biologically active ingredient of Kauliv is teriparatide which is a key regulator of the concentrations of calcium, phosphate, and active vitamin D metabolites in blood and modulates cellular activity in bone resulting in bone remodelling and maintenance of the bone structure. Teriparatide is the biologically

active 34-amino acid N-terminal fragment and analogue of the 84-amino acid native parathyroid hormone PTH (1-84). It belongs to the pharmacotherapeutic group of calcium homeostasis, parathyroid hormones and analogues, ATC-code H05AA02.

Physiological actions of parathyroid hormone include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. The biological actions of PTH and teriparatide are mediated through binding to specific high-affinity cell-surface receptors known as the PTH-1 receptors. Teriparatide and the 34 N-terminal amino acids of PTH bind to these receptors with the same affinity and have the same physiological actions on bone and kidney

2.2. Quality aspects

2.2.1. Introduction

The finished product Kauliv is presented as solution for injection containing 250 micrograms/ml of teriparatide as active substance.

Other ingredients are: mannitol, glacial acetic acid, anhydrous sodium acetate, metacresol, diluted hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

The product is available in a 3 ml cartridge (intended for 28 doses) to be used with a re-usable pen.

2.2.2. Active Substance

2.2.2.1. General information

The active substance (INN: teriparatide) is a recombinant is a linear polypeptide molecule expressed in *E. coli*. It is a truncated analogue of native human parathyroid hormone, PTH (1-84), consisting of the biologically active 34-amino acid N-terminal fragment (rhPTH [1-34]) of human PTH (1-84). rhPTH (1-34) has a molecular weight (MW) of 4118 Daltons (Da). It crystallises as a slightly bent, long helical dimer. It does not contain any disulphide bridges, glycosylation or other post-translational modifications. Information on the physiochemical properties of rhPTH (1-34) have been provided. Teriparatide has been developed as a biosimilar to the reference product, the EU-approved Forsteo and the US-approved Forteo (Eli Lilly).

2.2.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls
Teriparatide active substance (AS) is manufactured and released at Stelis Biopharma Pvt Ltd, Plot no.293, Bommasandra Jigani link Road, Bengaluru, India (referred to as Unit-I). The Master cell bank (MCB) and Working cell bank (WCB) sites were stated. A Major Objection (MO) has been raised concerning the EU GMP compliance of the sites involved in AS manufacture including future WCB manufacture, raw material and in-process testing. The sites have been inspected by EU authorities and their GMP compliance was confirmed. In the response to the MO, EU GMP certificates of compliance for Stelis Biopharma manufacturing sites, where the activities of active substance manufacturing including future WCB manufacture, raw material and in-process testing take place was also submitted. The QP declaration has been appropriately updated to cover the claimed manufacturing activities.

Teriparatide is recombinantly expressed as PTH fusion protein by *E. coli* cells with a tag having an enzyme cleavage site. The tag is used to ease purification of fusion protein during purification. The fusion protein is a soluble protein thereby avoiding any refolding step.

The teriparatide AS upstream manufacturing process is a conventional fed batch process starting with the inoculum build-up, comprising two stages of culture expansion from shake flask (seed 1) followed by fermentation (seed II) and IPTG-induced production of PTH fusion protein in a fed batch production.

After cell harvest the downstream process starts with cell lysis, followed by centrifugation and hollow fibre filtration. The filtrate containing the teriparatide fusion protein is subjected to purification by a series of chromatography steps. Teriparatide AS is buffer-exchanged and stored in PETG bottles at -20°C.

Process parameter (PPs) for each step including their classification as critical (CPP), key (KPP) and non-critical (non-CPP) were provided in separate tables. The description of the manufacturing process contains the essential information including classification of CPPs/KPPs/non-CPPs and presented in relevant dossier sections. Harvest criteria for cell culture purity and cell age have been defined. In-process controls (IPCs) and tests are included in the downstream process description. However the preliminary IPC acceptance criteria for cell lysis efficiency should be revised once data is generated from 20 (or other suitable number) commercial scale batches (REC). Bioburden control during the downstream process is performed and respective IPCs have been established. Neither re-processing nor re-filtration is foreseen in the manufacture of teriparatide.

Control of materials
The generation of the cell substrate is well described. The cloning strategy of the expression plasmid has been adequately described. The DNA and protein sequence as well as a schematic of the final expression plasmid are included in the dossier. The Applicant provided the requested information on alignment of amino acid sequence of the PTH fusion protein with the nucleotide sequence of cloned cDNAs encoding human PTH, available published patents, the sequence of native PTH and the product sequence of the innovator company.

A two-tiered banking system consisting of a master cell bank (MCB) and a working cell bank (WCB) has been established A dual storage system for the MCB and WCB is also in place The generation of MCB/WCB is described.

The characterisation testing program of MCB and WCB is considered adequate to identify relevant phenotypic and genotypic characteristics. As regards stability of MCB and WCB under the proposed storage conditions, the Applicant provided the requested stability protocol for MCB and WCB testing. The retest period and test parameters are deemed adequate.

End of production cell banks have been prepared from process validation batches executed at the intended commercial scale. As requested, information on viability was provided. Cell identity has been confirmed by 16sRNA analysis.

The raw materials used for cell culture and purification are listed in the dossier. Where applicable, reference is made to compendial monographs. No raw materials derived from human and/or animal sources are used in the process. As requested, the applicant has provided information on resin materials and filters, and revised the dossier accordingly. Respective CoAs have been submitted.

Control of critical steps and intermediates
Critical steps during the upstream and downstream manufacturing of teriparatide AS have been identified and in-process controls (IPCs) have been presented. Attributes monitored for controlling the critical steps during upstream and downstream processing were listed together with their acceptance

criteria and are found to be in agreement with information provided in section 3.2.S.2.2. CPPs along with respective control ranges for each manufacturing step have been included in section 3.2.S.2.4 . Acceptable definitions of critical quality attributes (CQAs) of teriparatide AS have been provided.

No process intermediates are reported in sections 3.2.S.2.2 and 3.2.S.2.4. However, hold times have been defined for cases of urgent need and maximum holding times between different manufacturing steps have been provided. Results of hold time studies sufficiently support the proposed holding times and conditions.

Process validation and/or verification
Process validation follows a traditional 3 batches/NOR approach based on process characterisation. Three consecutive teriparatide AS batches manufactured at the intended commercial scale have been included in the process validation campaign and subsequently released according to Ph. Eur. specifications meeting the pre-defined acceptance criteria for all parameters.

According to the applicant, the process parameters (CPP/KPP/NPP) and critical quality attributes (CQA) at each stage have been monitored as per the process validation protocol and process control strategy. All evaluated critical and key process parameters and performance attributes for the upstream/downstream process were found to be within the normal operating and expected ranges. Selected non-critical process parameters were also verified to be within the specified ranges. Each lot met in-process limits, demonstrating consistent operations. All relevant CPPs and CQAs related to teriparatide AS and its manufacture have been verified in the process validation campaign. Based on that, suitability and robustness of the teriparatide AS manufacturing process is considered to be confirmed.

Column resin and membrane life-times have also been demonstrated. In general, the studies confirmed that resins and filters perform consistently over the defined life spans. An acceptable, full-scale verification protocol for column/membrane lifetime has been provided.

Intermediate holding times and storage conditions have been validated based on evaluation of protein concentration and purity using scale-down models.

Shipping qualification studies demonstrated suitability of the selected shipping configuration.

Manufacturing process development
Various manufacturing site transfers have been taken place from early manufacturing process development towards the proposed commercial AS process and the proposed commercial site starting with the establishment of process consistency at Stelis. Subsequently, the manufacturing process was transferred to the GMP facility for manufacture of GMP batches for non-clinical and pilot PK study followed by transfer to the GMP manufacturing facility for scalability and additional process optimisation. The final manufacturing process was subsequently transferred including downscaling to the proposed commercial site at Stelis Unit-I. Of note, site transfer to the proposed commercial manufacturing site at Stelis Unit-I has been completed prior to initiation of pivotal clinical trial and process validation.

According to the applicant, operational parameters have been optimised throughout development. The manufacturing processes used to produce the AS materials that have been employed in pre-clinical and clinical studies have been clearly described. It has been clarified at which stage specific parameters have been optimised.

The manufacturing processes used for the production of pre-clinical and clinical materials have been directly compared with the proposed commercial process and differences have been outlined following a MO raised in this regard. Process changes have been identified and evaluated by the applicant taking into consideration ICH Q5E requirements. Summarising, the provided data are considered acceptable

to demonstrate comparability between the AS manufacturing processes used for production of pre-clinical material and clinical/commercial material and thus the MO has been resolved.

According to the applicant, a structured approach for performing and elaborate process characterisation studies for upstream and downstream manufacturing process has been followed. A thorough risk analysis of the manufacturing process, which involved the identification and evaluation of all risks based on historical data, development reports, batch summaries, manufacturing records, relevant technical reports and literature reviews has been conducted. Risk assessment (report provided), Ishikawa analysis, Cause and Effects (C&E) analysis and a failure mode and effects (FMEA) analysis were used to identify potential failure modes and to link these to the manufacturing steps and parameters as well as to classify CPPs the respective reports are available. Based on the outcome of risk assessment, process parameters have been classified in accordance with ICH.

A brief summary of process characterisation studies for each unit operation including study type and ranges for each tested parameter, CQA impacted, classification as CPP or non-CPP, along with corresponding NORs and PAR is included in the dossier. Linkage of CPPs to CQAs has been sufficiently described, CQAs have been explicitly defined and named along with a rationale for designating these as CQAs. CQAs are generally determined by a risk assessment of product quality attributes and their impact on safety and efficacy using information from clinical, non-clinical, and toxicological studies as well as prior knowledge. A list of all CQAs defined for teriparatide AS has been included in the dossier.

Overall, the applicant's strategy to control the process is considered acceptable. A risk assessment for identification of material attributes and process parameters with the potential for having an effect on CQAs as required by ICH Q11 has been provided. Critical process parameters and CQAs applied for the commercial process were identified during process development. Respective supportive information/ reports have been provided.

Characterisation
Recombinant teriparatide consists of 34 amino acids without disulfide bonds. Due to its expression in E. coli cells glycosylation or posttranslational modifications are not part of its structure. Noteworthy that the peptide is expressed as a fusion protein >18 kDa.

The initially presented information regarding the AS characterisation was not satisfactory since it was mainly based on batch comparability. Also, there were some contradicting results in other parts of the dossier and literature data. Therefore a MO was raised requesting comprehensive additional information on the characterisation of teriparatide.

In the response state-of-the-art analytical standard techniques have been applied for characterisation of relevant physicochemical and biological quality characteristics of teriparatide. The characterisation studies have been performed using batches manufactured with the proposed commercial manufacturing process also representative for clinical trial material. The primary structure amino acid sequence analysis, and secondary and higher structure was studied by employing state of the art analytical techniques and presented in the dossier. The biologic function of teriparatide was confirmed by a cell based (UMR-106) bioassay (in-house, USP).

Impurities
Product related substances have been addressed. Approximately ten individual substances were detected, which were mainly composed of oxidised, deamidated or succinimide intermediates. Forced degradation studies were submitted which did not reveal any impurities other than those already known.

Process related substances have been monitored at the level of each unit operation to demonstrate clearance, data provided on the removal of process related impurities are considered sufficient.

A MO was raised during the procedure concerning the removal and clearance of process-related impurities. For most of the impurities appropriate clearance could be demonstrated and there is no necessity to include parameter and acceptance criteria into the AS/FP specification. For the specific Tag impurity, the discrepancy between the reported maximum level Tag impurity in AS batches and the calculated Tag impurity in the finished product has now also been clarified. Furthermore, to determine Tag impurity in the AS more sensitively than with current LC-MS method, a new ELISA test has been developed. The new test method is sufficiently described and appropriately validated and the AS specification has been accordingly updated with an acceptance criterion. Justification for the proposed limit was based on method performance data and on batch data from clinical and process validation batches. Studies on the removal of process related impurities confirmed the clearance of process-related impurities. Summarising the provided data, Tag impurity has been demonstrated to be constantly below quantitation limit in both clinical and process validation batches manufactured with the commercial scale. The MO on process related impurities and specifically the introduction of an adequate test parameter and acceptance criterion for process-related Tag impurity is considered resolved.

Container closure system
Teriparatide bulk AS is stored in sterile Polyethylene Terephthalate Glycol (PETG) bottles with High Density Polyethylene (HDPE) screw caps. The PETG bottles and the HDPE closure comply with EP 3.2.2.1. The risk of leachables from the container closure system has been investigated and is negligible.

2.2.2.3. Specification

The AS release and shelf life specifications has been presented in the relevant dossier sections that include tests for physical characteristics (physical appearance, pH), identity (peptide mapping, RP-HPLC), purity (assay related substances, purity, process related impurities), potency (bioassay) and safety related tests (bioburden, bacterial endotoxins).

The proposed specification for release of the AS is covering the relevant quality attributes of teriparatide. The provided specification contains identity and content by RP-HPLC, purity by RP-HPLC and SE-HPLC, identity by peptide mapping, potency (and bio-identity) by in-vitro bioassay, endotoxins, bioburden, HCP, hcDNA and acetronitrile content. The justification for the specification has been based largely on the teriparatide monographs of Ph. Eur. and/or USP and have been father tightened during the procedure based on clinical/PV batch data (including clinical, process validation and additional batches taken for addressing EMA queries). The shelf life specifications acceptance criteria for process-related impurities remained slightly higher than the release specification but comply with monograph limits which is considered acceptable. Control of Tag impurity is implemented into the active substance specification with an acceptable limt.

Analytical procedure
The information on the analytical methods used was insufficient initially and a MO was raised requesting sufficiently detailed narrative descriptions for each analytical method and structured inclusion in the dossier in view of product lifecycle management of potential. Likewise, consistent information on validation of analytical procedures was requested. Following the response to the MO, all analytical methods have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Adequate validation data was provided in summary tables. Method verification was provided for compendial test methods. MO was consequently resolved. The in-vitro potency is determined based on the stimulation of adenylate cyclase activity in the rat osteosarcoma cell line. Activation of the PTH receptor initiates a cascade event which triggers an

intracellular rise in cAMP concentration. This increase was determined and compared with the USP RS using commercially available cAMP ELISA kit.

Reference standards of materials
The applicant has established an internal reference standard (IRS). The identification name, date of manufacture and the analytical test methods for which the RS is intended to be used, as well as the AS batches used for the RS production were provided. A protocol for preparing reference materials was provided.

Batch analyses
Batch analysis data have been provided including the data generated from the process validation batches. The process validation batches were manufactured at the intended commercial scale in Stelis Unit-1. All batches met the specification at the time of measurement. All process verification lots met the proposed commercial specification.

2.2.2.4. Stability

Stability data have been provided comprising data for 24 months long-term (-20 ± 5°C) storage and six month accelerated storage (5± 3°C) with three primary stability batches manufactured at commercial scale. Stability at both long-term and accelerated temperature conditions are in accordance with ICH requirements.

Supportive stability data were presented for process validation batches for 24 months at -20°C and 6 months at 5°C.

Samples were tested for Physical appearance, identity, assay, purity, potency, bacterial endotoxin and bioburden. OOS was observed at an intermediate timepoint and was attributed to the method execution. However, no confirmed OOS results were reported during the analysis of subsequent time points. All parameters were within the specification limits. The results for related impurities indicate that the method is suitable and accurate for estimating related impurities. In addition, the method has been revalidated to demonstrate the suitability of the method for commercial batch release.

Data of forced degradation studies of teriparatide including acidic pH, alkali pH, oxidative stress and thermal degradation were presented. The parameters protein content, related compounds, HMWs and impurity identification were considered as critical quality attributes. The study on the forced degradation of the active substance teriparatide resulted in the expected degradation products (various deamidation, oxidation and succinimide intermediates). The data provided confirm the statement that the forced degradation studies resulted mainly in the already known deamidated and oxidized impurities as well as succinimide intermediates. Photostability study was performed on the finished product. This is considered acceptable

Overall, the stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period.

2.2.3. Finished Medicinal Product

2.2.3.1. Description of the product and pharmaceutical development

Kauliv finished product (FP) is a sterile, colourless, clear, isotonic solution for injection presented in a cartridge as a multi-dose presentation (28 doses) containing 250 µg teriparatide (r-DNA origin) as

active ingredient per mL of solution. Each cartridge contains 3.0 ml of solution. The cartridge is to be loaded onto a reusable pen device to deliver a total of 28 doses (each dose containing 20 µg per 80 microliter) of teriparatide.

The FP solution is filled in a glass cartridge that is closed with a bromobutyl rubber stopper and a combiseal with bromobutyl bilayer on the product-contacting side.

The cartridge is intended for use with the re-usable pen device developed for Kauliv. The user is required to install a 3 ml cartridge of teriparatide into the cartridge holder, reassemble the cartridge holder and pen body, and attach a sterile needle prior to each injection. The priming dose (P) and a single dose of drug (D) is dialled using the dose knob, at the non-needle end of the device. The dose is then delivered by pressing a release button on the side of the device.

Figure 01: Representative image of Kauliv™ Pen

Pharmaceutical Development

Kauliv was developed as biosimilar to Forsteo. The qualitative composition of proposed biosimilar product is the same as that of the reference medicinal product Forsteo except for minor differences in the quantity of two components: sodium acetate and glacial acetic acid. All excipients used are specified according to Ph. Eur.

The influence of manufacturing process setup, like order of excipient addition, nitrogen sparging, etc. and parameters like pH, temperature, mixing duration on the teriparatide bulk drug product solution was investigated. Based on these results, the manufacturing process was designed. Compatibility studies with the product solution and the sterile filters were performed and support suitability of the selected materials.

Several site transfers occurred during manufacturing process development, up to the final upscale and transfer to the site where the commercial process is intended to take place. The outcome of the comparability exercise indicated that the process and the finished products manufactured at the site used to manufacture material for the pivotal clinical studies and the site to be used for commercial FP manufacture were highly comparable.

Container closure system

The FP primary packaging system consists of a 3 mL siliconised glass cartridge, closed with a bromobutyl plunger stopper and a combi-seal with bilayer (cream bromo butyl + polyisoprene). The information on the primary packaging components is deemed sufficient.

Extractables/ leachables studies have been performed with the rubber stopper, the combi-seal, and the pre-siliconised glass cartridge. Few substances were identified in the extractable studies above the AET, amongst others inorganic ions. These potential leachables were further investigated in FP samples that had undergone 3 months storage under accelerated conditions. None of the substances identified as potential leachable could be confirmed in the FP samples. The suitability of the container closure system in terms of compatibility is considered satisfactorily demonstrated.

Compatibility with the pen device was demonstrated in terms of pen functionality with Kauliv cartridges. Overall, the information provided on compatibility of the pen device with the FP in cartridges is considered satisfactorily shown.

Kauliv is a sterile injection containing metacresol to ensure sterility over the in-use period of 28 days. Preservative efficacy was tested, using in-use stability study samples. Container closure integrity was investigated and found to be confirmed.

2.2.3.2. Manufacture of the product and process controls

The FP manufacture is performed at Stelis Biopharma Pvt Ltd. (Unit-II), Plot no.: 2-D1, Obadenahalli, Doddaballapura, 3rd Phase, Industrial area, Doddaballapura Taluk, Bengaluru Rural District –561 203, India.

Batch release takes place at Fairmed Healthcare GmbH, Maria-Goeppert-Strabe-3, 23562 Luebeck, Germany.

A MO has been raised concerning the EU GMP compliance of the site involved in finished product manufacture. The site has been inspected by EU authorities and its GMP compliance was confirmed. In the response to the MO, EU GMP certificate of compliance was provided.

The manufacturing process of the FP includes of the following steps: preparation of buffers and solutions, addition of AS, compounding of the formulated bulk, and filling into cartridges**.**

While the FP manufacturing process is a straightforward fill-finish process, it is considered to be a non-standard manufacturing process. The manufacturing process description is acceptable. Batch size was clearly stated. Process parameters and in-process tests are stated with their classification as critical or non-critical and acceptable ranges.

Sterilisation of the primary packaging is part of the FP manufacturing and its description is included with a satisfactory level of detail in the relevant chapters of section P.3.3. Satisfactory information on the validation of the sterilisation cycles for glass vials and plunger stoppers is included in P.3.5.

The information provided in filter validation studies supports the use of the sterilization filters.

Four commercial scale batches have been manufactured for process validation, executed at the intended commercial site. Overall, the four runs were executed successfully, resulting in FP batches compliant with the FP specification. Media fill runs reflecting the conditions of the finished product manufacturing process were successfully performed.

2.2.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form for physical characteristics (physical appearance, pH, osmolality extractable volume), identity (RP-HPLC), purity (assay related substances, purity, meta-cresol content) , potency (bioidentity) and safety related tests(sterility, particulate matter, bacterial endotoxins).

In the initial submission the specification was based on essential parameters of the USP finished product monograph for teriparatide solution for injection. A MO was raised requesting the acceptance criteria for assay, purity and impurities (by RP-HPLC and SEC) to be appropriately revised to account for the requirements of ICHQ6B and an Article 10(4) application (biosimilar). In their response to the MO the Applicant established limits based on the EU reference product analytical data and taking into account their own manufacturing process capability. Specifications have been set based on the nonclinical, clinical and stability data sets and the limits were tightened during the procedure in line with batch data. Overall the parameters and the corresponding limits are acceptable and the MO was resolved.

Identity is confirmed by RP-HPLC in comparison to reference standard, and relative potency also confirming identity is quantified by a cell-based assay. RP-HPLC is used for assay, and a second RP-HPLC procedure is applied for determination of purity and selected impurities. Purity in terms of size variants is addressed by SEC. Pharmaceutical particulars are covered: physical appearance, extractable volume, osmolality, particulate matter, sterility and bacterial endotoxins.

During the procedure, a MO was raised in relation to the absence of a comprehensive nitrosamine risk evaluation on potential risk factors for nitrosamine formation in the active substance, finished product solution and primary packaging process. In response, the applicant provided a risk evaluation concerning the presence of nitrosamine impurities, applying the principles outlined in the "Assessment report Procedure under Article 5(3) of Regulation EC (No) 726/2004" (EMA/369136/2020)". Since the AS is being manufactured by fermentation process using *E. coli* bacteria, the presence of N-nitroso amine impurities is scientifically not possible. No risk was identified. In addition, batch analysis using a verified method confirmed nitrosamine impurities to be below the detection limits of the specified batch samples. Therefore, no additional control measures are deemed necessary. The MO was considered resolved.

Analytical procedures
The information on the analytical methods used was initially insufficient and a MO was raised requesting sufficiently detailed descriptions for each analytical method and structured inclusion in the dossier in view of product lifecycle management of potential. Likewise, consistent information on validation of analytical procedures was requested. Following the response to the MO all analytical methods have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Adequate validation data was provided in summary tables. Method verification was provided for compendial test methods. MO was consequently resolved.

Reference standards
The specification and the results of the in-house teriparatide reference standard qualification and shelf-life determination have been submitted. The in-house standard is calibrated against the EP CRS. Information on the metacresol reference material used for quantification of metacresol in the FP is provided.

Batch analyses
Release data have been provided for 15 batches. These comprise development/ pilot clinical trial batches, pivotal clinical trial batches, and commercial scale (PV) batches. All batches comply with the proposed specification.

2.2.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (5 ± 3°C) and for up to 6 months under accelerated conditions (25°C / 60% RH) according to the ICH guidelines were provided. These batches have been manufactured at a development site, but could be accepted as primary stability batches since comparability between these batches and commercial batches manufactured at the proposed site is considered demonstrated. The stability batches were packed in the primary packaging proposed for marketing.

Samples were tested for stability indicating parameters covering physical characteristics, identity, purity, potency and safety related tests. Of note that for one batch an OOS result was obtained with respect to main peak purity after 24 months of storage at real-time conditions. The OOS was investigated and a root cause identified (delay in sample analysis, storage of sample at room temperature); therefore, no concerns derive from it.

Additional stability data were presented for the 4 process validation batches for up to 24 months under long term conditions (5 ± 3ºC) and for up to 6 months under accelerated conditions (25ºC / 60% RH). All data comply with the specification. Data on visible particles have been generated after 29 months of storage. These confirm absence of visible particles, and support the conclusion that visible particles are absent over the entire shelf-life; this is accepted. Under accelerated conditions, OOS results have been reported for purity by RP-HPLC for some samples after 6 months storage. This is in line with

expectations as teriparatide is sensitive to temperature, and supports the proposed storage conditions (5 ±3ºC)

Photostability study was performed demonstrating that teriparatide solution is light sensitive, but sufficiently protected when packed in cartons.

An in-use stability study was performed with two batches of Kauliv. The results complied with the specification and support the claimed in-use stability of 28 days. Additionally, the stability of the product during the real use scenario of 28 days at 2-8°C was established by a simulated in-use stability study. The preservative efficacy and sterility were also done at the end of 28 day period.

Based on available stability data, the proposed shelf-life of 24 months with the storage conditions (*Store in a refrigerator (2°C – 8°C); Do not freeze; Keep the cartridge in the outer carton in order to protect from light);* as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.2.3.5. Biosimilarity

The Applicant performed an analytical comparability study to evaluate similarity of Kauliv to Forsteo (EU), Forteo (US) and Forteo (India) on the quality level. As the pivotal clinical PK study was performed (amongst others) with Forsteo (EU), the summary of the results is focused on the comparability of Kauliv to the EU sourced Forsteo. Information on comparability to Forteo (US) and Forteo (India) are not considered relevant and hence, are not discussed in the context of this application.

Multiple batches of Stelis Teriparatide finished product were compared with multiple batches of EU sourced Forsteo. The similarity report was presented in the form of the overlay of spectrums/chromatograms (wherever possible), tables containing observed results, statistical analysis (wherever possible; especially for quantitative results), equivalence tests and the result summary. Forsteo samples sourced from the EU were treated as a reference for all the similarity experiments.

The following quality attributes were investigated:

Category	Attribute	Method	Approach to establish analytical similarity
Physicochemical Attributes	Content (Purity and Quantity)	Assay by RP-HPLC	Data table, Graphical Overlay, Quality Ranges (established by Reference Product) and Statistical Equivalence Test
	Aggregates	SEC-UV by HPLC	Data table, Graphical Overlay, Quality Ranges (established by RMP)
		SEC-MALS by HPLC	Data table, Quality Ranges (established by Reference Product)
		Dynamic light scattering (DLS)	Data table, Quality Ranges (established by RMP)
	Metacresol	RP-HPLC	Data table, Graphical Overlay, Quality Ranges (established by RMP)
	Peptide mass finger printing	LC-MS/MS	Data table, Graphical Overlay, Quality Ranges (established by RMP)
	Amino Acid sequence	Peptide Mapping by LC MS/MS (N-terminal sequencing)	Data table
Structural Attributes	Conformation Secondary and Higher Order Structure	Intact molecular mass by LC-MS	Data table, Graphical Overlay, Quality Ranges (established by RMP)
		Capillary Iso Electric Focusing	Data table, Graphical Overlay, Quality Ranges (established by RMP)
		Far UV Circular Dichroism (CD)	Data table, Graphical Overlay, Quality Ranges (established by RMP)
		Near UV Circular Dichroism (CD)	Data table, Graphical Overlay, Quality Ranges (established by RMP)
		Fourier transform infrared spectroscopy	Data table, Graphical Overlay, Quality Ranges (established by RMP)
		Extrinsic Fluorescence	Data Table and Graphical Overlay
		Intrinsic Fluorescence	
		1D 1H nuclear magnetic resonance (NMR), and 2D [1H-1H] Nuclear Over Hauser Effect Spectroscopy (NOESY)	
Functional attributes	*In-vitro* Bioassay	Rat Osteosarcoma (UMR106) cell line	Data Table
		Human cell-based Bioassay (cAMP hunter Teriparatide bioassay in CHOK1 cells)	Data Table
Receptor binding	PTH Receptor Binding Kinetics	Surface plasma resonance	Graphical Overlay and Data Table
Impurity determination	Molecular Weight	Capillary Electrophoresis (CE)-SDS	Data table, Graphical Overlay, Quality Ranges (established by Reference Product)
	Product Related Impurities	RP-HPLC and LC-MS	Graphical Overlay and Data Table
	rhPTH (1-30)	RP-HPLC	Data table, Graphical Overlay, Quality Ranges (established by Reference Product)
	Succinimide (30)	RP-HPLC	
	Single Max Impurity	RP-HPLC	
	Total Impurity	RP-HPLC	
	Deamidation	RP-HPLC	
Other Attributes	pH	Measurement of pH	Data table, Quality Ranges (established by Reference Product)
	Physical Appearance	Visual	Evaluation
	Aggregates	Analytical ultracentrifugation (AUC)	Data table, Quality Ranges (established by Reference Product)
	Charge Variants	Cation Exchange Chromatography	Data table, Graphical Overlay, Quality Ranges (established by Reference Product

The primary structure of test and reference products was investigated by intact mass, peptide mass fingerprinting and peptide mapping with MS and MS/MS confirming the sequence. Secondary structure was investigated by far UV CD, FTIR, NMR. Test and reference product were found to be identical in

terms of primary structure and similarity with respect to secondary structure could be confirmed. Likewise, analysis of charged variants and the determination of the isoelectric point did not reveal differences. Size variants were comprehensively investigated by SEC, SEC-MALS, DLS and AUC. In both products, only minor amounts of HMWs were detected. In most cases, the monomer content was near 100%.

Related substances were investigated by RP-HPLC. Numerical values for all test and reference product batches included in the study are stated peak-wise (RRT). Acceptance criteria for similarity were not clearly pre-defined in terms of impurities. However, in the Applicant's own data evaluation, impurities were compared based on quality ranges. Stelis teriparatide FP displays a similar impurity profile as Forsteo. RP-HPLC data support the similarity claim.

The teriparatide content of Kauliv and Forsteo was determined using RP-HPLC in comparison to the in-house reference standard. It is acknowledged that the actually measured content of teriparatide in both products was compared. In this respect, the products are deemed comparable.

Potency of Kauliv and the RMP Forsteo was compared by a cell-based assay using UMR-106 cells. The products could not be directly compared, but each relative to the identical reference standard, which is acceptable. The potency results show similar biological activity.

Size-related variants are comparable between test and reference product. Kauliv might contain product-related impurities emerging from the Tag fusion protein, called "precursor" in the Applicant's risk assessment. Residual Tag may pose a risk for immunogenicity and might alter the safety profile of Kauliv in comparison to the reference product. The potential presence /desired absence of the precursor-related impurities has been addressed in the analytical similarity study by making reference to the data on process validation/ depletion of impurities. It can be concluded that the levels of Tag impurities are well controlled. Comparative degradation studies under accelerated/ stress conditions were performed; they support the similarity claim.

Statistics
Overall, the Applicant missed to present an appropriately justified statistical evaluation approach for the analytical similarity study. It is noted that most of the data were evaluated based on quality ranges. The statistical evaluation as proposed by the Applicant does not add any relevant information; however, the data provided allow for an overall conclusion on similarity.

Conclusion
Considering the uncertainty deriving from the initially presented inadequate information about the analytical methods used for the AS and FP a MO had been raised since the missing information precluded a definite conclusion on biosimilarity. However following the resolution of the MOs relating to the analytical methods and their validation as well as the responses to all the issues raised as other concerns with regards to biosimilarity, the MO on the biosimilarity conclusion was resolved and biosimilarity of Kauliv to reference product Forsteo can be concluded. The precursor-related impurities are present at very low levels, not jeopardizing analytical similarity.

2.2.3.6. Adventitious agents

None of the materials used in the manufacturing process contain any material human or animal origin. There is no risk form TSE or viral contamination.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The teriparatide active substance upstream manufacturing process is a conventional fed batch process. In the downstream process the AS is subjected to multiple purification steps. The description of the manufacturing process contains essential information. The information on control of critical steps and intermediates is considered acceptable. A minor unresolved quality issue, having no impact on the Benefit/Risk ratio of the product, pertains to revising the preliminary IPC acceptance criteria for cell lysis efficiency. This point is put forward and agreed as recommendation for future quality development.

Characterisation of the active substance has been performed using state-of-the-art analytical techniques. Process validation follows a traditional approach. Information on the removal and clearance of process related substances is considered acceptable. For the control of the process-related Tag impurity specifically, a new ELISA analytical method has been implemented into the AS specification together with an adequate acceptance criterion. The AS specification is mainly based on the Ph. Eur. Monograph and is acceptable.

All MOs raised during the procedure in relation to the AS, pertaining to the GMP compliance of the proposed manufacturing sites, the removal of process related impurities including Tag impurity, the comparison of manufacturing processes used for pre-clinical and clinical materials with the proposed commercial process, the characterisation of teriparatide and the deficiencies of analytical procedures, have been resolved by the applicant providing all the requested information and updating the dossier accordingly.

The finished product composition was developed to be biosimilar to Forsteo. The finished product manufacturing process is straight-forward, consisting of compounding steps, sterile filtration and an aseptic fill- and finish process.

The description of the analytical procedures applied for finished product control and respective validation summaries for the analytical procedures are acceptable. The finished product specifications for release and shelf-life is deemed acceptable. An overall acceptable systematic risk assessment with respect to nitrosamines has been provided. The claimed shelf-life for the finished product was substantiated by appropriate data.

All MOs raised in relation to the FP, pertaining to the GMP compliance of the proposed manufacturing sites, the deficiencies of analytical procedures, the initially proposed specifications, the risk evaluation concerning the presence of nitrosamine impurities, and the initial uncertainty in concluding biosimilarity, have been resolved by the applicant providing all the requested information and updating the dossier accordingly.

Biosimilarity of Kauliv to reference product Forsteo can be concluded. From the information provided on the Tag impurity, it can be concluded that the precursor-related impurities are present at very low levels, not jeopardizing analytical similarity.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Following the substantial updated information provided during the procedure and the respective dossier updates, the results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to revise the acceptance criterion for PTH value used for control of cell lysis efficiency at step 6, once the data from sufficient number of batches.

2.3. Non-clinical aspects

2.3.1. Pharmacology

The active ingredient of Kauliv is recombinant teriparatide consisting of the first 34 N-terminal amino acids (molecular weight of 4117.7 Da) of the native human 84-amino acid hormone PTH. Kauliv has been developed as biosimilar to the European reference product Forsteo with Eli Lilly Nederlands B.V. as the Marketing Authorisation Holder. The non-clinical programme for the development of Kauliv focused on the investigation of comparability and aimed at the demonstration of similarity between Kauliv and the reference medicinal product Forsteo.

The Kauliv nonclinical development program is based on two vitro cell-based potency assays (UMR-106 and CHO-K1 cell-based bioassays) and receptor-binding studies using surface plasmon resonance (SPR).

The following table provides an overview of the presented studies.

Table 1: ***Summarizes the functional biosimilarity methods***

Method employed	Critical quality attributes	Impact	Effect
UMR-106 cell-based assay – In house	Biological activity and receptor binding	Altered or lost biological activity	Efficacy
UMR-106 cell-based assay – USP			
Saos-2 cell-based assay			
CHO-K1 cell-based assay			
Receptor Binding	Binding affinity to PTH R1		

In the cell-based potency assays cAMP levels were measured. Potencies of Kauliv and the reference product Forsteo were expressed as relative potencies compared to a reference teriparatide standard. The Applicant did not compare Kauliv and the reference product Forsteo directly, i.e. head-to-head in one experiment due to plate layout restrictions. The Applicant was asked for more detailed information and, although not completely in line with the guidelines, the reasoning of the Applicant was considered acceptable. Furthermore, the Applicant was asked to justify the deviation from the applicable guideline by comparing only a single concentration (EC50) and not a set of concentrations covering the range where potential differences are most sensitively detected. In response the The Applicant showed that the obtained dose dependent response is symmetrical with distinct upper and lower asymptotes and a linear range, meaning that the horizontal shift in EC50 value is a true representation of relative potency with respect to standard.

The summary of mean and SD of relative potency (RP) data results compared to USP reference standard for EU Forsteo® lots and Kauliv lots are summarized in the below tables:

*Table 2****: Comparative evaluation of mean RP and SD for EU Forteo and Kauliv batches (IH Bioidentity method)***

Batches	Mean RP	SD
EU Forsteo (n = 6)	1.09	0.07
Kauliv lots (n=9)	1.04	0.11

*Table 3**: Comparative evaluation of mean RP and SD for EU sourced Forteo® and Kauliv batches (USP Bioidentity method)***

Batches	Mean RP	SD
EU Forsteo (n = 7)	0.93	0.08
Kauliv lots (n=7)	0.89	0.07

*Table 4**: Comparative evaluation of mean RP and SD for EU sourced Forteo and Kauliv batches (CHO-K1 cell-based method)***

Batches	Mean RP	SD
EU Forsteo® (n = 10)	0.88	0.12
Kauliv lots (n=11)	0.91	0.07

Additionally, Mean and SD of EC_{50} values for Forsteo® and Kauliv have also been summarized in the below table:

*Table 5**: EC50 Comparison of Mean and SD for EU sourced Forsteo® and Kauliv batches. (USP Identity method)***

Batches	EC 50	SD
Mean of EU Forsteo® lots (N=7)	0.145	0.038
Mean of Kauliv batches(N=7)	0.124	0.045

Relative potencies determined for Kauliv were in both cell lines within the mean ± 2 SD of the reference product Forsteo. The Applicant bases the evaluation of the results of the biosimilarity studies on Mean ± Standard deviations of the EU reference product Forsteo and different values of up to ± 3 SD are provided. No clear rationale or guideline was provided by the Applicant for the application of this type of comparison. The Applicant was asked to justify. In response the Applicant justified the statistical analysis of the biosimilarity results. To accommodate for the natural variations in the manufacturing processes and also variability arising from analytical instruments, 90% confidence intervals were used with reference ranges established using mean +/-3 standard deviations (which covers 99% of the reference range).

Neither study documentations nor raw data could be found in the initially submitted dossier. The Applicant was asked to provide the original experimental study documentations of the functional in-vitro cell-based studies including all raw data as well. The Applicant submitted raw data files but these raw data did not enable a full understanding of the following of the calculations of the in-vitro relative potency values stated in the non-clinical overview. In response to requests the Applicant provided initially missing information on how the relative potency values stated in the non-clinical overview were derived in detail.

In addition to the above cell-based platforms, the binding kinetics of Kauliv to the PTH1 receptors was evaluated using SPR (surface plasmon resonance). The KD values calculated are considered beingwere within mean ± 2 SD of the reference product Forsteo and, therefore, considered similar.

*Table 6**: Mean and SD of KD for EU sourced Forsteo and Kauliv batches***

Batches	Mean KD (µM)	SD
Mean of EU Forsteo® lots (N=12)	12.4	1.71
Mean of Kauliv lots (N=11)	12.0	1.08

From a non-clinical point of view the in-vitro data provided by the Applicant indicate that both products, Kauliv and Forsteo, are functionally comparable. Nevertheless, these in-vitro data are only a part of the exercise of demonstration of biosimilarity between Forsteo and Kauliv. Therefore, the final decision, whether Kauliv and Forsteo may be considered biosimilar is to a large part dependent on the Quality assessment of the product (please, see Quality assessment report for details).

2.3.2. Pharmacokinetics

No non-clinical studies investigating pharmacokinetics of Kauliv have been provided. This is considered acceptable considering the type of application (Biosimilar). Pharmacokinetics of teriparatide are well known.

2.3.3. Toxicology

The Applicant has performed 28 day repeated dose toxicity studies with daily subcutaneous administration of Kauliv in rats and rabbits in order to comply with Non-European regulative requirements. As stated in the applicable guideline *in vitro* assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals. The repeated dose toxicity studies performed by the Applicant are not considered relevant in order to assess biosimilarity of the product under review to the reference product.

The highest doses administered in the studies (5.2 µg/kg/day in rabbits and 10.3 µg/kg/day in rats) are reported as NOAELs. No skin reactions different from the vehicle control group are reported for Kauliv treated animals.

2.3.4. Ecotoxicity/environmental risk assessment

The active substance is a peptide, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, teriparatide is not expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

In line with the type of application procedure the data package submitted is very limited.

Cell based in vitro potency assays and surface plasmon resonance measurements performed in order to demonstrate biosimilarity of Kauliv to the reference product Forsteo indicate that receptor binding and triggering of intracellular second messenger (cAMP) response of Kauliv and Forsteo are similar.

Based on results from repeated dose toxicity studies in rats and rabbits which are not considered relevant from biosimilarity point of view, there are no non-clinical concerns regarding local toxicity of Kauliv.

The wording of SmPC sections 4.6 and 5.3 is in line with that of the reference product Forsteo.

2.3.6. Conclusion on the non-clinical aspects

Results of the very limited data package supports biosimilarity from non-clinical point of view, although the final decision regarding biosimilarity of Kauliv to Forsteo depends on the Quality assessment of the product.

From non-clinical point of view there is no objection against marketing authorisation of the product under review.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

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

- **Tabular overview of clinical studies**

The Applicant has provided results from 2 clinical PK/PD studies, a pivotal 3-way comparative PK/PD study between Kauliv and the EU reference product Forsteo as well as the US comparator Forteo and a 2-way pilot PK/PD study conducted between Kauliv and the reference product Forsteo. The clinical trials are summarised in the tables below.

*Table 7**: Overview Pharmacokinetic Studies***

Pivotal Study PTH/CT1-002/R5

Type of Study and Test product(s)	**Study identifier Location of Study report**	**Study Objectives**	**Dosage Regimen Route of Administration Duration; Investigational Product(s)**	**Healthy Subjects or Diagnosis of Patients Number of Subjects**	**Study Status Type of Report**	**Study design and duration of treatment**

PK pivotal PK study: A single center, randomised, double blind, 3-treatment, 3-period, single-dose, cross over, comparative Phase-I study to evaluate pharmacokinetics, safety, tolerability, and pharmacodynamics (PK/PD) of Kauliv [rh-PTH (1-34)] with Forsteo and Forteo (teriparatide, Eli Lilly) in healthy volunteers following subcutaneous single dose administration of 20 µg Teriparatide.	Protocol No: PTH/CT1-002/R5	Protocol No: PTH/CT1-002/R5 Primary objective: • To evaluate the pharmacokinetics of Kauliv [rh-PTH (1-34)] in comparison with the reference products Forsteo (EU) and Forteo (US) marketed by Eli Lilly. Secondary objective: • To evaluate safety and tolerability of Kauliv [rh-PTH (1-34)] in comparison with the reference products Forsteo (EU) and Forteo (US) marketed by Eli Lilly. • To evaluate transient effects of Kauliv [rh-PTH (1-34)] in comparison with the reference products Forsteo (EU) and Forteo (US) marketed by Eli Lilly, on baseline corrected ionised serum calcium concentrations.	Single-dose, subcutaneous injection into abdomen. 1 week washout between periods Test product: Kauliv [rh-PTH (1-34)] [teriparatide, Stelis Biopharma Pvt. Ltd., India] Reference product: Forsteo (EU) and Forteo (US) marketed by Eli Lilly.	78 healthy subjects of both genders, age between 18 and 45	Study completed Final clinical study report	Double-blind, randomised, balanced, 3-treatment, 6-sequence, 3-period, single dose, cross-over comparative phase I study. Single dose, 3 periods

Pilot Study PTH/CT1-001/R0

Type of Study and Test product(s)	**Study identifier Location of Study report**	**Study Objectives**	**Dosage Regimen Route of Administration Duration; Investigational Product(s)**	**Healthy Subjects or Diagnosis of Patients Number of Subjects**	**Study Status Type of Report**	**Study design and duration of treatment**

PK pilot study: A randomised, double-blind, 2-treatment, 2-period, single-dose, cross-over, comparative study to evaluate pharmacokinetics, safety and tolerability of Kauliv (rh-PTH [1-34]) (teriparatide, Stelis Biopharma Pvt. Ltd., India) with Forsteo (teriparatide, Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands) in healthy volunteers following subcutaneous administration of a single dose of 20 mcg Teriparatide	PTH/CT1-001/R0	Primary objective: To evaluate the PK of Kauliv in comparison with the reference formulation sourced from the EU (Forsteo, Eli Lilly Nederland BV, The Netherlands). Secondary objective: To evaluate safety and tolerability of Kauliv in comparison with the reference formulation sourced from the EU (Forsteo, Eli Lilly Nederland BV, The Netherlands). Exploratory objective: To evaluate transient effects of Kauliv in comparison with the reference formulation sourced from the EU (Forsteo, Eli Lilly Nederland BV, The Netherlands) on serum ionised calcium and endogenous intact PTH (1-84) concentrations.	Single-dose subcutaneous injection of 20 µg teriparatide into either side of anterior abdominal wall/thigh, alternating between opposite sites in the 2 periods 28 days washout between periods Test product: Kauliv [rh-PTH (1-34)] [teriparatide, Stelis Biopharma Pvt. Ltd., India] Reference product: Forsteo marketed by Eli Lilly.	30 healthy subjects of both gender, age between 18 and 45	Study completed Final clinical study report	Randomised, double-blind, 2-treatment, 2-period, single-dose, cross-over, comparative study. Single dose, 2 periods

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

In addition to the physicochemical, structural, and biological characterisation and the nonclinical data, the Applicant has provided results from 2 clinical PK/PD studies (see above).

The Applicant has not provided data from dedicated studies to characterise the PK of teriparatide. Information on general PK properties of teriparatide are based on the published documentation of the reference medicinal product Forsteo. This is considered acceptable for a biosimilar product.

The volume of distribution for teriparatide is approximately 1.7 L/kg. The half-life is approximately 1 hour when administered subcutaneously, which reflects the time required for absorption from the injection site.
No metabolism or excretion studies have been performed with teriparatide, but the peripheral metabolism of parathyroid hormone is believed to occur predominantly in liver and kidney.
Teriparatide is eliminated through hepatic and extra-hepatic clearance (approximately 62 L/hr in women and 94 L/hr in men).
No differences in teriparatide pharmacokinetics were detected with regard to age (range 31 to 85 years). Dosage adjustment based on age is not required.

For the current biosimilar MAA, in addition to the physicochemical, structural, and biological characterisation and the nonclinical data, the Applicant has provided results from 2 clinical PK/PD studies, a pivotal 3-way and a 2-way pilot PK/PD study.

Pivotal Study PTH/CT1-002/R5

The pivotal trial compared PK, PD, and safety aspects of the test product Stelis Teriparatide with the EU reference product Forsteo and the US reference product Forteo in a 3-period, single-dose, cross-over design; the 3 treatment periods were separated by a washout period of at least 1 week.

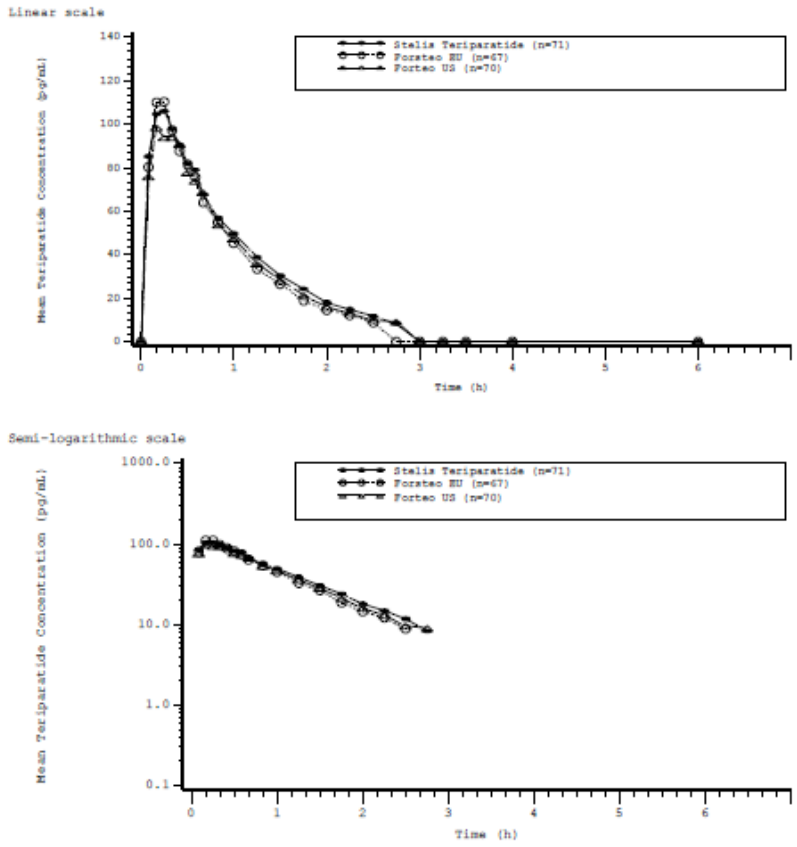
The design including the washout period of ≥1 week and the chosen study population are considered acceptable. Aspects regarding the treatments used in the study have been reported and the chosen reference product is endorsed.
The study objectives and the chosen endpoints are in general adequate for the assessment of biosimilarity between test and reference product. Aspects of immunogenicity have not been investigated in this trial. PK and PD sampling time points are considered adequate.
The sample size has been calculated by customary methods, using valid assumptions and is considered in line with current guidance and approved products.
Randomisation and blinding are considered adequate; blind of study subjects to the device used was maintained.
For the determination of teriparatide concentrations in human serum samples, an automated system together with a commercially available kit (IDI iSYS Immunoanalyzer Automated Chemiluminescence Method) was used. It is stated that anti-PTH(1-34) antibodies are used in this kit which have been derivatised to act either as capture or detection antibodies. The assay was validated with respect to the relevant parameters, i.e. accuracy and precision (intra-, inter-assay), dynamic range (~8 - 400 pg/mL). The LLOQ was determined to be 8 pg/mL. Selectivity experiments were limited to analysis of blank samples, 9 out of 10 were below LLOQ. Interference with human blood was observed and corresponds to the instructions for use from the kit supplier. The kit manufacturer states that interference with native PTH (1-84) is as low as 4%. Specificity for teriparatide (PTH 1-34) was demonstrated by analysis of PTH(1-84) spiked samples at various concentrations. No interference occurred at PTH (1-84) levels of 15.6, 164, and 557 pg/mL (all results < LLOQ). Thus, interference of the teriparatide quantification assay with native PTH can be excluded.
For measuring serum ionised calcium standard diagnostic methods have been used.
As regards statistical methods, the standard approach for bioequivalence analysis was followed in accordance with the relevant EMA guideline for primary analysis. The influence of outliers and potential unreliable PK parameters was adequately assessed by sensitivity analyses. For PD analysis, EU standard for equivalence analysis is 95% CI, but this was provided as well. A document called Statistical Analysis Plan Final 1.0 dated 12 July 2018 has been found in the dossier.

As per protocol 78 healthy subjects were randomised to 1 of the 6 treatment sequence groups and 68 out of 78 (87.2%) subjects completed the study; AEs (5/10; 50.0%) accounted for the most common cause for premature withdrawal. Nine (9) subjects discontinued the study early; of these, all but 1 subject received at least 2 treatments.
Information on study amendments has been provided; as regards sample size and subject enrolment it is stated that there have been 5 protocol revisions.
Overall, there was a higher than expected number of haemolysed samples. According to the Applicant thorough root cause analysis was undertaken, but no single root cause could be identified; it is hypothesised that this is an artefact due to the high frequency of PK sample collections.
Groups were sufficiently balanced with regard to demographic and other baseline characteristics except that 53 out of 78 subjects were female (67.9%). Since all subjects served as her / his own control, this is not considered to influence the PK / PD results.

Overall, 6.4% of subjects missed a Kauliv, 5.1% a Forsteo, and 1.3% a Forteo dose.
The most commonly reported concomitant medications were anilides and there was a significant difference in anilides use between prior and post first dose (3/78, 3.8% prior first dose; 15/78, 19.2% post first dose).

Arithmetic mean plasma concentration-time profiles and PK parameters of teriparatide were comparable between the 3 products investigated. Median t_{max} was approximately 0.250 hours, geometric mean $t_{1/2}$ ranged between 0.7834 and 0.8541 hours, and CL/F and Vz/F were also comparable across treatments. Stelis Teriparatide generally had the lowest GCV% across all treatments.

*Figure 02**: Mean Teriparatide Concentration-time Profiles for all Treatments on Linear and Semi-logarithmic Scales (Pharmacokinetic Analysis Set)***



Note: 'n' is the number of subjects who contribute data to the summary statistics for the respective treatment.
Source: Figure 14.2.1

*Table 8: **Geometric Mean (GCV%) Teriparatide Pharmacokinetic Parameters by Treatment (Pharmacokinetic Analysis Set)***

Parameter	Treatment					
	n	Stelis Teriparatide	n	Forsteo®	n	Forteo®
$AUC_{(0-\infty)}$ (pg*h/mL)	64	130.6 (27.0)	60	115.9 (31.9)	61	120.6 (31.3)
$AUC_{(0-t)}$ (pg*h/mL)	71	117.6 (31.9)	66	106.7 (37.0)	67	109.0 (36.2)
$AUC_{(0-90min)}$ (pg*h/mL)	63	90.54 (29.6)	61	84.24 (34.9)	62	87.12 (36.4)
$AUC_{(0-120min)}$ (pg*h/mL)	64	102.9 (29.1)	53	98.10 (32.4)	57	93.84 (32.4)
$AUC_{(0-180min)}$ (pg*h/mL)	37	124.5 (30.0)	24	123.7 (28.4)	31	110.1 (33.9)
C_{max} (pg/mL)	71	108.7 (35.1)	66	106.6 (38.5)	67	103.6 (38.0)
t_{max} (h) [a]	71	0.250 (0.083, 0.833)	66	0.234 (0.083, 0.667)	67	0.250 (0.083, 0.667)
λ_z (1/h)	64	0.8116 (33.4)	60	0.8848 (43.6)	61	0.8161 (45.6)
$t_{1/2}$ (h)	64	0.8541 (33.4)	60	0.7834 (43.6)	61	0.8494 (45.6)
CL/F (L/h)	64	153.1 (27.0)	60	172.6 (31.9)	61	165.9 (31.3)
V_z/F (L)	64	188.7 (42.2)	60	195.1 (47.3)	61	203.2 (51.8)
$\%AUC_{ex}$	70	9.793 (48.2)	66	10.16 (54.1)	67	10.39 (54.6)

Abbreviations: λz = apparent terminal rate constant, $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity, AUC_{0-t} = area under the concentration-time curve from time 0 to the last quantifiable concentration, $AUC_{0-90min}$ = area under the concentration-time curve in the sampled matrix from zero (predose) to time of 90 minutes, $AUC_{0-120min}$ = area under the concentration-time curve in the sampled matrix from zero (predose) to time of 120 minutes, $AUC_{0-180min}$ = area under the concentration-time curve in the sampled matrix from zero (predose) to time of 180 minutes, C_{max} = peak plasma concentration, obtained directly from the observed concentration versus time data, CL/F = apparent systemic clearance after extravascular study drug administration, GCV% = geometric coefficient of variation, $t_{1/2}$ = terminal elimination half-life, t_{max} = time to C_{max}, Vz/F = apparent volume of distribution after extravascular study drug administration a Median (range)
Source: Table 14.2.2

Numerous subjects had missing data due to missing or haemolysed samples at various time points of the PK profile. No specific handling for PK parameter exclusion based on missing data was performed for the planned primary analysis.

Multiple subjects had quantifiable predose concentrations >5% of C_{max}. The Applicant argues that most likely haemolysis has led to these detectable pre-dose concentrations and that there is a lack of evidence of PTH(1-84) interference on the teriparatide assay.

The 90% CIs as well as the 95% CIs of the geometric LS mean ratios for the primary analysis including only subjects with evaluable paired PK/PD data for each of the treatment comparisons the PK parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were within the predefined acceptance limits for the definition of biosimilarity of 80.00% to 125.00% for Stelis Teriparatide versus Forsteo, Stelis Teriparatide versus Forteo, and Forsteo versus Forteo.
However, geometric mean ratios for the primary PK endpoints AUC_{0-inf} and AUC_{0-t} do not pass through unity. The observed AUC for the test product Kauliv is approximately 11% higher than the reference product. It is hypothesised that this may be due to the higher number of missing or haemolysed samples in the reference group.

Table 9: ***Statistical Comparison of Key Pharmacokinetic Parameters (Method 1) (Pharmacokinetic Analysis Set)***

Parameter (unit)	Treatment	n	LS Mean	Pair	Ratio (%)	90% CI	95% CI
$AUC_{(0-\infty)}$ (pg*h/mL)	Stelis Teriparatide	52	127.5	Stelis Teriparatide/ Forsteo®	111.07	(105.96, 116.44)	(104.97, 117.53)
	Forsteo®	52	114.8				
	Stelis Teriparatide	54	133.8	Stelis Teriparatide/ Forteo®	110.93	(104.32, 117.97)	(103.05, 119.42)
	Forteo®	54	120.6				
	Forsteo®	50	114.9	Forsteo®/ Forteo®	96.77	(90.42, 103.57)	(89.21, 104.98)
	Forteo®	50	118.8				
$AUC_{(0-t)}$ (pg*h/mL)	Stelis Teriparatide	61	117.3	Stelis Teriparatide/ Forsteo®	110.26	(103.77, 117.16)	(102.53, 118.57)
	Forsteo®	61	106.4				
	Stelis Teriparatide	63	117.9	Stelis Teriparatide/ Forteo®	108.80	(101.73, 116.36)	(100.39, 117.91)
	Forteo®	63	108.3				
	Forsteo®	58	106.6	Forsteo®/ Forteo®	98.43	(92.18, 105.10)	(90.99, 106.47)
	Forteo®	58	108.3				
C_{max} (pg/mL)	Stelis Teriparatide	61	110.6	Stelis Teriparatide/ Forsteo®	100.40	(95.20, 105.87)	(94.21, 106.99)
	Forsteo®	61	110.1				
	Stelis Teriparatide	63	110.1	Stelis Teriparatide/ Forteo®	105.55	(99.83, 111.60)	(98.74, 112.83)
	Forteo®	63	104.3				
	Forsteo®	58	107.8	Forsteo®/ Forteo®	100.75	(94.57, 107.33)	(93.40, 108.68)
	Forteo®	58	107.0				

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity, AUC_{0-t} = area under the concentration-time curve from time 0 to the last quantifiable concentration, CI = confidence interval, C_{max} = peak plasma concentration, LS mean = least squares mean Notes: Results based on linear model with fixed effects for treatment, period, sequence, and subjects nested within sequence. Subjects who completed both periods and who provided valid PK parameter data for both periods were included for the statistical analysis.
Source: Table 14.2.3.1

The sensitivity analysis of the 90% and 95% CIs supported the primary findings. Confidence intervals of the geometric mean ratios for the $AUC_{0\ t}$ and C_{max} were also within the predefined acceptance limits of 80.00% to 125.00% for all treatment comparisons and were passing through unity, indicating that the missing samples might have impacted the 90% and 95% confidence intervals of the geometric mean ratios for PK parameters not passing through unity.

For the partial areas $AUC_{0-90min}$, $AUC_{0-120min}$, and $AUC_{0-180min}$ for both methods, the 90% and 95% CIs of the geometric mean ratios for the primary PK endpoints were within the predefined acceptance limits of 80.00% to 125.00% with the exception of $AUC_{0-180min}$ for the Stelis Teriparatide versus Forteo comparison using method 1 (90% CI: 105.23, 125.18; 95% CI: 103.30, 127.52).

Table 10: ***Statistical Comparison of Other Pharmacokinetic Parameters – Method 1 (Pharmacokinetic Analysis Set)***

Parameter (unit)	Treatment	n	LS Mean	Pair	Ratio (%)	90% CI	95% CI
$AUC_{(0\text{-}90min)}$ (pg*h/mL)	Stelis Teriparatide	51	89.66	Stelis Teriparatide/ Forsteo®	108.57	(103.43, 113.96)	(102.44, 115.07)
	Forsteo®	51	82.58				
	Stelis Teriparatide	53	90.94	Stelis Teriparatide/ Forteo®	108.92	(102.74, 115.48)	(101.55, 116.83)
	Forteo®	53	83.50				
	Forsteo®	51	85.87	Forsteo®/ Forteo®	100.28	(93.87, 107.12)	(92.65, 108.54)
	Forteo®	51	85.63				
$AUC_{(0\text{-}120min)}$ (pg*h/mL)	Stelis Teriparatide	44	103.8	Stelis Teriparatide/ Forsteo®	106.98	(102.32, 111.86)	(101.41, 112.86)
	Forsteo®	44	96.98				
	Stelis Teriparatide	49	101.2	Stelis Teriparatide/ Forteo®	109.93	(104.09, 116.11)	(102.96, 117.38)
	Forteo®	49	92.07				
	Forsteo®	42	99.08	Forsteo®/ Forteo®	102.22	(95.22, 109.73)	(93.87, 111.30)
	Forteo®	42	96.93				
$AUC_{(0\text{-}180min)}$ (pg*h/mL)	Stelis Teriparatide	16	143.4	Stelis Teriparatide/ Forsteo®	108.19	(99.57, 117.55)	(97.77, 119.72)
	Forsteo®	16	132.5				
	Stelis Teriparatide	19	123.4	Stelis Teriparatide/ Forteo®	114.77	(105.23, 125.18)	(103.30, 127.52)
	Forteo®	19	107.5				
	Forsteo® Forteo®	14	118.6	Forsteo®/ Forteo®	103.90	(89.53, 120.58)	(86.58, 124.70)
		14	114.1				

Abbreviations: $AUC_{0\text{-}x}$ = area under the concentration-time curve from time 0 to time x, CI = confidence interval, LS mean = least squares mean
Notes: Results based on linear model with fixed effects for treatment, period, sequence, and subjects nested within sequence. Subjects who completed both periods and who provided valid PK parameter data for both periods were included for the statistical analysis.
Source: Table 14.2.3.3

Using method 2, which included subjects who had at least 1 dose with any evaluable data, statistical analysis results were comparable to those seen with method 1 for the primary and secondary PK parameters, both for the full data set and excluding outliers.

The intra-subject CV% was generally acceptable for all primary PK parameters ranging between 14.1% to 22.7% for method 1 and 17.7% to 21.2% for method 2. The inter-subject CV% for all primary PK parameters ranged between 36.2% to 52.4% for method 1 and 25.1% to 31.5% for method 2. Since all subjects served as her / his own control the high inter-subject coefficient of variation is not considered to influence the interpretation of the results.

Supportive data pilot study PTH/CT1-001/R0

Supportive data are available from the pilot single-centre, 2-period, 2-sequence, cross-over study PTH/CT1-001/R0 comparing PK and PD aspects of Stelis Teriparatide with Forsteo.

The overall design of this study including the wash-out period of 4 weeks and the main inclusion and exclusion criteria are considered acceptable.
Objectives are adequate to investigate PK / PD biosimilarity. Primary and secondary PK endpoints are

considered appropriate and exploratory PD endpoints are also endorsed. The measurement of teriparatide

antibodies as a safety endpoint is considered to be of limited value as the study includes only a single administration of the test product followed by the reference product or vice versa; however, the wash-out period of 4 weeks is considered adequate in this regard.
PK sample time-points every 5 minutes during the first study phase would have been more appropriate considering the rapid absorption of teriparatide.
The sample size is limited to 30 subjects. Randomisation including stratification by injection site and blinding are considered adequate; subjects were blinded to the device used.
According to the Applicant, the analytical method used to determine teriparatide concentrations was identical to that used in the pivotal trial.
The Applicant used a commercially available kit together with commercially available controls to analyse intact PTH concentrations in plasma. Validation data have been provided.
As in the pivotal trial, standard methods for measuring serum ionised calcium have been used.
According to the study protocol, for safety data anti-drug antibodies and neutralising antibodies needed to be assessed. For the assessment of ADA analytical method ALM172 was developed and validation data have been provided. As no antibodies to teriparatide have been detected the assay for detecting neutralising antibodies has not been applied despite the Applicant's statement that immunogenicity results were presented for neutralising antibodies.
Descriptive statistics have been applied.

Thirty (30) subjects were enrolled and randomised to 2 treatment sequences, TR and RT (15 subjects each). A total of 12 subjects in sequence TR and 13 in sequence RT completed the study as per protocol; the most common reason for discontinuation was withdrawn consent (4 subjects, 2 per sequence).
Data from only 8 out of 30 subjects were included in the primary analysis; 12 subjects had at least one evaluable exposure parameter and 8 had results for $AUC_{0\text{-}inf}$ in both treatment periods and were included in the primary analysis, 28 subjects had evaluable exposure parameters in at least one treatment period and were included in the secondary analysis.

The protocol amendment and the reported protocol deviations are not considered to have influenced the study results.The study included more male (66.7%) than female (33.3%) subjects; the mean (SD) age was 26 (6) years. Demographics and baseline characteristics were sufficiently balanced between groups.

Teriparatide was rapidly absorbed following administration of both test and reference product with a median t_{max} of 10 minutes for both treatments. Elimination was rapid with a geometric mean $t_{1/2}$ of approximately 1 hour. More than 80% of $AUC_{0\text{-}inf}$ was generally characterised for both treatments. Geometric mean teriparatide C_{max} was dependant on the site of administration, 48% and 85% higher when injected in the abdominal wall than the thigh in the test and the reference groups, respectively, while $AUC_{0\text{-}inf}$ did not appear to be meaningfully impacted by injection site. The upper range of t_{max} was shorter following administration into the abdominal wall compared to the thigh, which might explain the higher C_{max} with this route of administration.

*Table 11: **Geometric Mean (GCV%) Teriparatide Pharmacokinetic Parameters by Treatment and Injection Site***

Treatment/ Injection Site	Statistic	$AUC_{(0\text{-}Inf)}$ (pg*h/mL)	$AUC_{(0\text{-}t)}$ (pg*h/mL)	C_{max} (pg/mL)	t_{max}[a] (h)	$t_{1/2}$ (h)	λ_z (1/h)	CL/F (L/h)	V_z/F (L)	$\%AUC_{(0\text{-}t)}$ (%)
Stelis Teriparatide/ Pooled	n	12	14	14	14	12	12	12	12	12
	Geomean	78.23	75.60	89.2928	0.167	0.8303	0.8348	255.6	306.3	88.04
	GCV%	34.1	44.8	57.4	(0.0830, 0.333)	47.5	47.5	34.1	50.7	7.6
Stelis Teriparatide/ Abdominal Wall	n	6	7	7	7	6	6	6	6	6
	Geomean	81.00	85.20	121.5751	0.0830	0.6585	1.053	246.8	234.6	91.83
	GCV%	41.5	56.5	48.5	(0.0830, 0.167)	34.1	34.1	41.5	49	3.6
Stelis Teriparatide/ Thigh	n	6	7	7	7	6	6	6	6	6
	Geomean	75.55	67.09	65.5826	0.167	1.047	0.6621	264.7	399.9	84.40
	GCV%	28.9	30.1	44.8	(0.0830, 0.333)	48.2	48.2	28.9	35.3	8.5
Forsteo®/ Pooled	n	25	28	28	28	25	25	25	25	25
	Geomean	97.66	85.29	89.1039	0.167	0.9428	0.7350	204.8	278.6	87.53
	GCV%	34.2	41.8	43.4	(0.0830, 0.667)	54.4	54.5	34.2	68.6	11.8
Forsteo®/ Abdominal Wall	n	12	14	14	14	12	12	12	12	12
	Geomean	100.5	86.94	108.2407	0.167	0.7682	0.9017	199.0	220.6	90.60
	GCV%	31.4	36.7	46.8	(0.0830, 0.333)	49.9	49.9	31.4	61.5	8.6
Forsteo®/ Thigh	n	13	14	14	14	13	13	13	13	13
	Geomean	95.07	83.68	73.3504	0.167	1.139	0.6086	210.4	345.7	84.79
	GCV%	37.8	47.9	28.8	(0.0830, 0.667)	51.4	51.5	37.7	67.2	13.7

Abbreviations: $AUC_{0\text{-}inf}$=area under the concentration-time curve from time 0 extrapolated to infinity, $AUC_{0\text{-}t}$=area under the concentration-time curve from time 0 to the last quantifiable concentration, CL/F=apparent clearance; C_{max}=peak plasma concentration, GCV%=geometric coefficient of variation, t_{max}=time to peak plasma concentration, $t_{1/2}$=half-life; $\%AUC_{0\text{-}t}$= percent of area measured by $AUC_{0\text{-}t}$ relative to the extrapolated $AUC_{0\text{-}inf}$, Vz/F=apparent volume of distribution; λz= elimination rate constant
[a] Median (range)

Source: Table 14.2.1.2.Statistical comparisons included only subjects with sufficient quantifiable concentrations to calculate exposure parameters. Geometric mean teriparatide $AUC_{0\text{-}inf}$ was 10% (primary analysis; n = 8/30) lower following Stelis Teriparatide administration compared to Forsteo; the 90% CI bounds were 80.80% to 100.45% and the intra-subject variability ranged from 9.9% to 15.1%. The geometric mean teriparatide C_{max} was 13% (primary analysis; n = 12/30) higher after treatment with Stelis Teriparatide compared to Forsteo; the 90% CI bounds were 91.63% to 139.49%, outside the predefined acceptance range.

*Table 12: **Primary Statistical Comparison of Key Pharmacokinetic Parameters in the Pilot Study***

Parameter (unit)	Site of Injection	Treatment	n	LS Mean	Ratio (%)	90% CI
$AUC_{0\text{-}inf}$ (pg*h/ml)	Pooled	Stelis Teriparatide Forsteo	8 8	87.72 97.37	90.09	(80.80, 100.45)
	Abdominal Wall	Stelis Teriparatide Forsteo	4 4	96.75 112.8	85.76	(65.05, 113.07)
	Thigh	Stelis Teriparatide Forsteo	4 4	72.46 77.77	93.17	(73.85, 117.54)
$AUC_{0\text{-}t}$ (pg*h/ml)	Pooled	Stelis Teriparatide Forsteo	12 12	87.42 89.29	97.91	(87.39. 109.69)
	Abdominal Wall	Stelis Teriparatide Forsteo	6 6	92.71 93.42	99.24	(76.96, 127.99)
	Thigh	Stelis Teriparatide Forsteo	6 6	67.35 71.84	93.74	(80.59, 109.04)
C_{max} (pg/ml)	Pooled	Stelis Teriparatide Forsteo	12 12	104.5383 92.4631	113.06	(91.63, 139.49)

Parameter (unit)	Site of Injection	Treatment	n	LS Mean	Ratio (%)	90% CI
	Abdominal Wall	Stelis Teriparatide Forsteo	6 6	131.3303 114.6749	114.52	(81.12, 161.69)
	Thigh	Stelis Teriparatide Forsteo	6 6	88.6546 62.4418	141.98	(117.35, 171.79)

Thirteen (13) out of 29 subjects had either no quantifiable postdose concentrations or limited consecutive or intermittently quantifiable concentrations following Stelis Teriparatide treatment and PK parameters were not determined. The cause was investigated and according to the Applicant, the most possible reason was incomplete or null dosing of the test product Stelis Teriparatide probably due to ineffective priming of the device used in this study although according to the study report test and reference products were administered by trained study centre staff.

For pen device / human factors assessment please see assessment of Quality aspects.

2.4.2.2. Pharmacodynamics

The Applicant has not provided data from dedicated studies to characterise the PD properties of teriparatide. Available information is based on the documentation of the reference medicinal product Forsteo. This is considered acceptable for a biosimilar product.

Endogenous PTH, an 84-amino acid peptide, plays a central role in calcium and phosphate metabolism in bone and kidneys. Its physiological effects include stimulation of bone formation by directly affecting osteoblasts and by increasing renal tubular reabsorption of calcium and excretion of phosphate as well as indirectly increasing intestinal absorption of calcium via its effects on 1,25-dihydroxycholecalciferol production. Teriparatide is the active fragment (1-34) of endogenous human PTH.
Teriparatide and PTH mediate their biological effects via specific, G-protein-dependent, high-affinity membrane cell-surface receptors which are expressed on osteoblasts and renal tubular cells. Both molecules exert similar physiological effects on bone and kidneys. These effects lead to increases in bone strength of the spine, hip, and peripheral anatomic sites as well as a decreased fracture risk. The stimulation of bone resorption and formation is dose dependant.
Treatment with teriparatide increases 1,25-dihydroxycholecalciferol concentrations and decreases 25-hydroxycholecalciferol concentrations. This effect may contribute to the biological effects of teriparatide, for example, to stabilise calcium balance by increasing intestinal calcium absorption and renal calcium conservation.

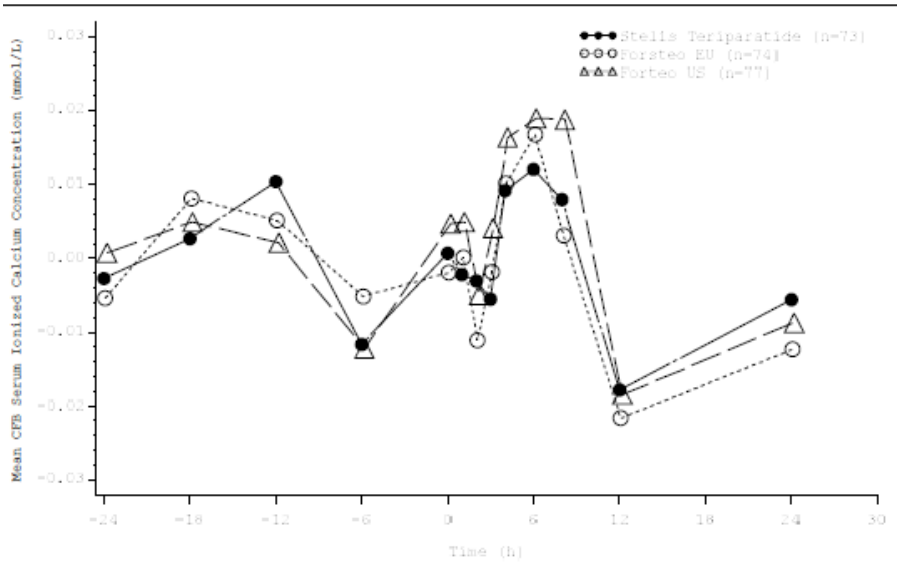
Pharmacodynamic information with the applied medicinal product has been provided from the pivotal and the pilot PK/PD comparability studies; both included secondary endpoints to assess PD similarity between Kauliv and the EU reference product Forsteo after a single 20 µg dose of teriparatide. For the pivotal study PTH/CT1-002/R5 observed and change from baseline ionised serum calcium concentrations have been reported, while for the pilot study PTH/CT1-001/R0 PD parameters were observed and change from baseline serum ionised calcium as well as endogenous intact PTH (1-84) and change from baseline concentrations were observed.

For methods as well as participant flow, conduct of the studies, and baseline data please see Pharmacokinetics above.

Pivotal Study PTH/CT1-002/R5

In the pivotal trial PTH/CT1-002/R5 the mean observed serum ionised calcium concentrations briefly decreased with trough values around 2 to 3 hours postdose before transiently increasing for all products. The observed mean change from baseline (CFB) and percent CFB concentration-time profiles were comparable across treatment arms.

Figure 03: ***Mean Change-from-baseline Serum Ionised Calcium Concentration-time Profiles for Each Day -1 and Day 1 Serial Sample Collection (Pharmacodynamic Analysis Set)***



Notes: CFB = change-from-baseline. Baseline is the average value of measurements on Day -1 and the Day 1 predose measurement in each treatment period. 'n' is the number of subjects who contribute data to the summary statistics for the respective treatment.
Source: Figure 14.2.6.1

Table 13: ***Mean (SD) Change-from-baseline Ionised Calcium Pharmacodynamic Parameters on Day 1 by Treatment (Pharmacodynamic Analysis Set)***

Parameter	Treatment					
	n	Stelis Teriparatide	n	Forsteo®	n	Forteo®
$AUC_{(0-t)}$ (mmol*h/L)	72	-0.1198 (0.8752)	73	-0.1934 (0.7160)	77	-0.07633 (0.7975)
C_{max} (mmol/L)	73	0.034 (0.034)	74	0.035 (0.023)	77	0.042 (0.031)
t_{max} (h) [a]	73	6.000 (1.000, 24.233)	74	6.000 (1.000, 24.667)	77	6.000 (1.000, 24.467)
C_{min} (mmol/L)	73	-0.053 (0.075)	74	-0.058 (0.075)	77	-0.050 (0.067)
t_{min} (h) [a]	73	8.000 (1.000, 24.100)	74	6.017 (1.000, 24.050)	77	12.000 (1.000, 24.300)

a Median (range)
Source: Table 14.2.8

The 90% and 95% CIs of the comparisons for AUC_{0-t} and C_{max} were tight and within the predefined acceptance limits of 80.00% to 125.00%. Intra-subject variability for observed serum ionised calcium PD parameters ranged from 1.1% to 1.9% and inter-subject variability from 1.3% to 2.8%.

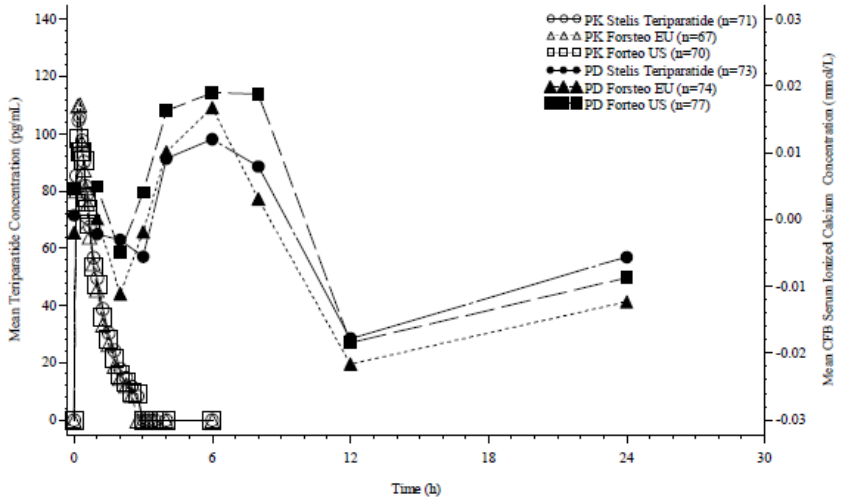
*Table 14: **Statistical Comparison of Serum Ionised Calcium Pharmacodynamic Parameters between Treatment Groups- Method 1 (Pharmacodynamic Analysis Set***

Parameter (unit)	Treatment	n	LS Mean	Pair	Ratio (%)	90% CI	95% CI
$AUC_{(0-t)}$ (mmol*h/L)	Stelis Teriparatide	68	29.56	Stelis Teriparatide/ Forsteo®	100.14	(99.66, 100.63)	(99.56, 100.72)
	Forsteo®	68	29.51				
	Stelis Teriparatide	71	29.58	Stelis Teriparatide/ Forteo®	99.93	(99.40, 100.47)	(99.29, 100.58)
	Forteo®	71	29.60				
	Forsteo®	72	29.52	Forsteo®/ Forteo®	99.77	(99.35, 100.19)	(99.26, 100.27)
	Forteo®	72	29.59				
C_{max} (mmol/L)	Stelis Teriparatide	70	1.271	Stelis Teriparatide/ Forsteo®	99.85	(99.51, 100.18)	(99.45, 100.25)
	Forsteo®	70	1.273				
	Stelis Teriparatide	72	1.271	Stelis Teriparatide/ Forteo®	99.46	(99.05, 99.87)	(98.96, 99.95)
	Forteo®	72	1.278				
	Forsteo®	73	1.272	Forsteo®/ Forteo®	99.53	(99.22, 99.85)	(99.16, 99.91)
	Forteo®	73	1.278				

Abbreviations: AUC_{0-t} = area under the concentration-time curve from time 0 to the last quantifiable concentration, CI=confidence interval, C_{max} = peak serum concentration, LS mean = least squares mean
Notes: Results based on ANCOVA model with fixed effects for treatment, period, sequence, subject within sequence, and a continuous covariate for baseline value (per period). Subjects who completed both periods and who have evaluable PD parameter data for both periods were included for the statistical analysis.
Source: Table 14.2.9.1

Pharmacokinetics of teriparatide and mean CFB serum ionised calcium concentrations indicated an indirect response relationship.

*Figure 04: **Mean Change-from-baseline Serum Ionised Calcium Concentration and Mean Teriparatide-time Profiles for Day 1 Sample Collection (PK Analysis Set/PD Analysis Set)***



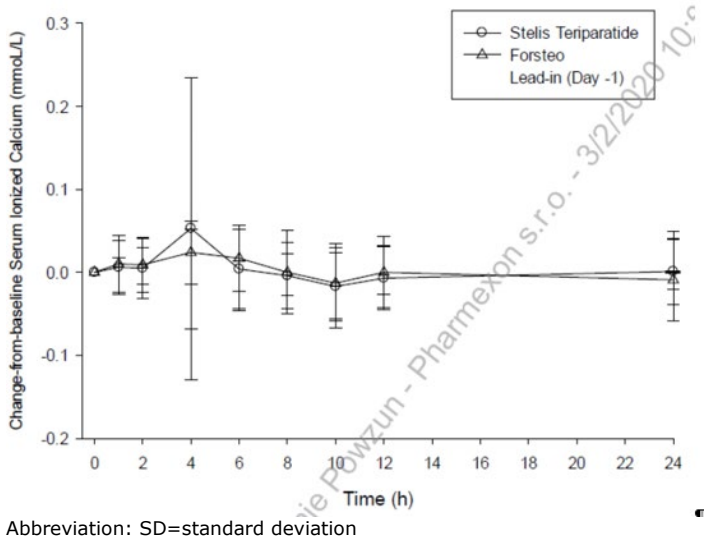
Notes: CFB = change-from-baseline. Baseline is the average value of measurements on Day -1 and the Day 1 predose measurement in each treatment period. 'n' is the number of subjects that contribute data to the summary statistics for the respective treatment.
Source: Figure 14.2.7

Pilot Study PTH/CT1-001/R0

In the pilot study PTH/CT1-001/R0 all PD analyses were carried out using the PD analysis set including all subjects irrespective of whether they had quantifiable postdose concentrations of teriparatide or quantifiable predose concentrations >5% of C_{max}.

Serum ionised calcium concentrations increased transiently after dosing with both Stelis Teriparatide and Forsteo and peaked at 4 hours post-dose, while concentrations on lead-in Day -1 appeared relatively flat. Serum ionised concentrations remained higher than lead-in concentrations through 6 hours postdose. Serum ionised calcium concentrations appeared higher after treatment with Stelis Teriparatide then with Forsteo, but median concentrations were comparable between treatments.

*Figure 05**: Mean (±SD) change from baseline (pre-dose baseline) concentration – time profile for serum ionised calcium.***



Abbreviation: SD=standard deviation
Source: Figure 14.2.6.

*Table 15**: Geometric Mean (GCV%) Serum Ionised Calcium Pharmacodynamic Parameters***

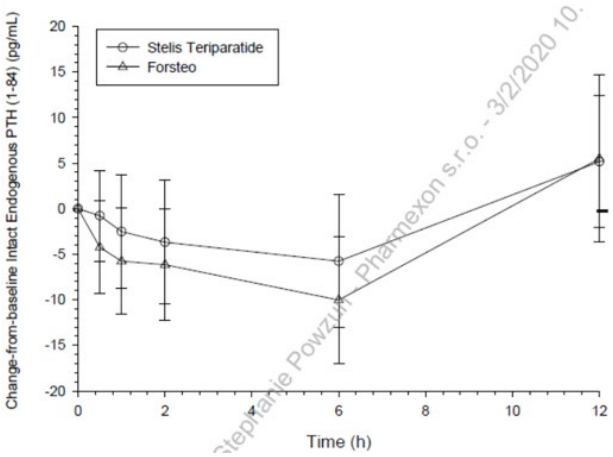
		Observed					Change-from-Baseline[a]	
Treatment/ Injection Site	**Statistic**	C_{avg} (mmol/L)	C_{max} (mmol/L)	C_{min} (mmol/L)	t_{max}[b] (h)	t_{min}[b] (h)	DC_{max} (mmol/L)	DC_{min} (mmol/L)
Lead-in Day -1	n	30	30	30	30	30	30	30
	Geomean	1.242	1.271	1.184	4.00	5.00	0.031	0.010
	GCV%	1.8	1.6	5.9	(0.00, 23.67)	(0.00, 23.67)	52.7	0.0
Stelis Teriparatide	n	28	28	28	28	28	28	28
	Geomean	1.262	1.325	1.225	4.00	8.00	0.044	0.019
	GCV%	2.1	10.8	2.7	(0.00, 24.03)	(0.00, 24.00)	143.4	191.9
Forsteo®	n	27	27	27	27	27	27	27
	Geomean	1.258	1.294	1.220	4.00	10.00	0.032	0.039
	GCV%	1.6	1.9	3.3	(0.00, 12.00)	(0.00, 24.05)	80.1	617.5

Abbreviations: C_{avg}=average concentration, C_{max}=peak plasma concentration, C_{min}=minimum concentration, DC_{max}=maximum increase of concentration, DC_{min}=minimum increase of concentration, GCV%=geometric coefficient of variation, geomean = geometric mean, t_{max}=time to peak plasma concentration, t_{min}=time to minimum concentration
[a] Baseline was predose baseline
[b] Median (range)
Source: Table 14.2.2.5.

Concentrations of intact endogenous PTH in plasma were partially suppressed after treatment with both Stelis Teriparatide and Forsteo for up to 6 hours postdose. The observed decrease in intact endogenous PTH was greater with Forsteo than Stelis Teriparatide treatment; mean and median C_{min} following Stelis Teriparatide treatment were 18.57 pg/ml and 17.2 pg/ml compared to 16.48 pg/ml and 16.1 pg/ml with Forsteo, respectively.

Overall, the degree of suppression of plasma concentrations of intact endogenous PTH was highly variable in this study.

Figure 06: ***Mean (±SD) change from baseline concentration profiles for intact, endogenous PTH (1-84) following Stelis Teriparatide and Forsteo administration***



Abbreviations: SD=standard deviation, PTH=parathyroid hormone
Source: Figure 14.2.11.

Table 16: ***Median (Range) Observed Endogenous PTH (1-84) Plasma Pharmacodynamic Parameters***

Treatment	Statistic	Observed	
		C_{min} (pg/mL)	t_{min} (h)
Stelis Teriparatide	n	28	28
	Mean	18.57	3.554
	Median	17.2	2.00
	Range	6.8, 35.7	0.00, 12.00
Forsteo®	n	27	27
	Mean	16.48	3.834
	Median	16.1	6.00
	Range	7.7, 27.9	0.50, 6.00

Abbreviations: Cmin=minimum concentration, PTH=parathyroid hormone, tmin=time to minimum concentration
Source: Table 14.2.1.4.

2.4.3. Discussion on clinical pharmacology

In addition to the physicochemical, structural, and biological characterisation and the nonclinical data, the Applicant has provided results from 2 clinical PK/PD studies, a pivotal 3-way comparative study between Kauliv and the EU reference product Forsteo as well as the US comparator Forteo and a pilot 2-way study comparing Kauliv with Forsteo. The primary objective of these studies was the comparison of the PK profiles of Kauliv and the reference product. PD comparison (i.e. ionised calcium) was a secondary endpoint. This is acceptable.

In both studies, teriparatide concentrations in human serum samples were measured using an automated system together with a commercially available kit (IDI iSYS Immunoanalyzer Automated Chemiluminescence Method). The assay was validated with respect to the relevant parameters. Interference with human blood was observed and corresponds to the instructions for use from the kit supplier. Interference of the teriparatide quantification assay with native PTH can be excluded.

For measuring serum ionised calcium standard diagnostic methods have been used.

For the pivotal trial the design including the wash-out period of ≥1 week and the chosen study population, reference product, study objectives, and endpoints are in general adequate for the assessment of biosimilarity between test and reference product. Aspects of immunogenicity have not been investigated in this pivotal trial.
As regards statistical methods, the standard approach for bioequivalence analysis was followed in

accordance with the relevant EMA guideline for primary analysis. The influence of outliers and potential unreliable PK parameters was adequately assessed by sensitivity analyses.
As per protocol 78 subjects were randomised to 1 of the 6 treatment sequence groups and 68 out of 78 (87.2%) completed the study; AEs (5/10; 50.0%) accounted for the most common cause for premature withdrawal.
Groups were sufficiently balanced with regard to demographic and other baseline characteristics.
Overall, 6.4% of subjects missed a Kauliv, 5.1% a Forsteo, and 1.3% a Forteo dose.
The most commonly reported concomitant medications were anilides and there was a significant difference in anilides use between prior and post first dose.
Arithmetic mean plasma concentration-time profiles and PK parameters of teriparatide were comparable between the 3 products investigated.
Numerous subjects had missing data due to missing or haemolysed samples at various time points of the PK profile; the number of haemolysed samples was higher than expected. According to the Applicant thorough root cause analysis was undertaken, but no single root cause could be identified; it is hypothesised that this is an artefact due to the high frequency of PK sample collections. No specific handling for PK parameter exclusion based on missing data was performed for the primary analysis.
Multiple subjects had quantifiable predose concentrations >5% of C_{max}. The Applicant argues that most likely haemolysis has led to these detectable pre-dose concentrations and that there is a lack of evidence of PTH(1-84) interference on the teriparatide assay.
The 90% CIs as well as the 95% CIs of the geometric LS mean ratios for the primary analysis of the PK parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were within the predefined acceptance limits, but geometric mean ratios for the primary PK endpoints AUC_{0-inf} and AUC_{0-t} do not pass through unity. The observed AUC for the test product Kauliv is approximately 11% higher than the reference product. It is hypothesised that this may be due to the higher number of missing or haemolysed samples in the reference group. Sensitivity analyses supported the primary findings as did analyses using method 2, which included subjects who had at least 1 dose with any evaluable data.

The supportive data from the pilot single-centre, 2-period, 2-sequence, cross-over study PTH/CT1-001/R0 are limited by the high number of subject without quantifiable teriparatide concentrations. Thirty (30) subjects were enrolled and randomised, but data from only 8 out of 30 subjects were included in the primary analysis. Thirteen (13) out of 29 subjects had either no quantifiable postdose concentrations or limited consecutive or intermittently quantifiable concentrations following Stelis Teriparatide treatment and PK parameters were not determined. The cause was investigated and according to the Applicant, the most possible reason was incomplete or null dosing of the test product Stelis Teriparatide probably due to ineffective priming of the device used in this study although according to the study report, test and reference products were administered by trained study centre staff. In the pilot study geometric mean teriparatide AUC_{0-inf} was 10% lower following Stelis Teriparatide administration compared to Forsteo (90% CI 80.80% to 100.45%); geometric mean teriparatide C_{max} was 13% higher with Stelis Teriparatide compared to Forsteo (90% CI 91.63% to 139.49%).

As regards pharmacodynamic parameters in the pivotal trial PTH/CT1-002/R5 observed, mean CFB, and percent CFB concentration-time profiles were comparable across treatment arms; mean observed serum ionised calcium concentrations briefly decreased with trough values around 2 to 3 hours postdose before transiently increasing for all products. Pharmacokinetics of teriparatide and mean CFB serum ionised calcium concentrations indicated an indirect response relationship.

In the pilot study PTH/CT1-001/R0 serum ionised calcium concentrations increased transiently after dosing with both Stelis Teriparatide and Forsteo and peaked at 4 hours post-dose, while concentrations on lead-in Day -1 appeared relatively flat. Concentrations were higher with Stelis Teriparatide then with Forsteo, but median concentrations were comparable.

Concentrations of intact endogenous PTH in plasma were partially suppressed after treatment with both Stelis Teriparatide and Forsteo for up to 6 hours postdose; the decrease was greater with Forsteo than Stelis Teriparatide treatment. Overall, the degree of suppression of plasma concentrations of intact endogenous PTH was highly variable in this study.

2.4.4. Conclusions on clinical pharmacology

In the pivotal study, the 90% CIs as well as the 95% CIs of the geometric LS mean ratios for the primary analysis of the PK parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were within the predefined acceptance limits, but geometric mean ratios for the primary PK endpoints AUC_{0-inf} and AUC_{0-t} did not pass through unity. The observed AUC for the test product Kauliv is approximately 11% higher than the reference product Forsteo. This difference is unlikely to be clinically relevant, which is supported by similar changes in serum ionised calcium. Therefore, the PK/PD data support biosimilarity.

2.4.5. Clinical efficacy

The Applicant has not provided data from dedicated studies to inform on the efficacy of teriparatide. Information on the efficacy of teriparatide is based on the documentation of the reference medicinal product Forsteo. This is considered acceptable for a biosimilar product.

Risk factors for osteoporosis

Independent risk factors, e.g. low BMD, age, previous fracture, family history of hip fractures, high bone turnover, and low body mass index should be considered in order to identify women and men at increased risk of osteoporotic fractures who could benefit from treatment.

Premenopausal women with glucocorticoid-induced osteoporosis should be considered at high risk for fracture if they have a prevalent fracture or a combination of risk factors that place them at high risk for fracture (e.g. low bone density, sustained high dose glucocorticoid therapy, high underlying disease activity, low sex steroid levels).

Postmenopausal osteoporosis

The pivotal study included 1,637 postmenopausal women (mean age 69.5 years). At baseline, 90% of the patients had one or more vertebral fractures and on average vertebral BMD was 0.82 g/cm^2 (equivalent to a T-score of -2.6). All patients were offered 1,000 mg calcium and at least 400 IU vitamin D per day. Results from up to 24 months (median 19 months) treatment with Forsteo demonstrated statistically significant fracture reduction (see table below); to prevent one or more new vertebral fracture, 11 women had to be treated for a median of 19 months. After a median of 19 months of treatment, bone mineral density (BMD) had increased in the lumbar spine and total hip, respectively, by 9% and 4% compared with placebo (p<0.001).

*Table 17**: Results Pivotal Study Postmenopausal Women***

Fracture Incidence in Postmenopausal Women:			
	Placebo (N = 544) (%)	Teriparatide (N = 541) (%)	Relative risk (95% CI) vs. placebo
New vertebral fracture (≥1) [a]	14.3	5.0 [b]	0.35 (0.22, 0.55)

Multiple vertebral fractures (≥2) [a]	4.9	1.1 [b]	0.23 (0.09, 0.60)
Non-vertebral fragility fractures [c]	5.5%	2.6% [d]	0.47 (0.25, 0.87)
Major non-vertebral fragility fractures[c] (hip, radius, humerus, ribs and pelvis)	3.9%	1.5% [d]	0.38 (0.17, 0.86)

Abbreviations: N = number of patients randomly assigned to each treatment group; CI = Confidence Interval.
[a] The incidence of vertebral fractures was assessed in 448 placebo and 444 teriparatide patients who had baseline and follow-up spine radiographs.
[b] p≤0.001 compared with placebo
[c] A significant reduction in the incidence of hip fractures has not been demonstrated
[d] p≤0.025 compared with placebo.

In a post-treatment follow-up study, 1,262 postmenopausal women from the pivotal trial were enrolled. The primary objective was to collect safety data of teriparatide. During this observational period, other osteoporosis treatments were allowed and additional assessment of vertebral fractures was performed. During a median of 18 months following discontinuation of teriparatide, there was a 41% reduction (p=0.004) compared with placebo in the number of patients with a minimum of one new vertebral fracture.

In an open-label study, 503 postmenopausal women with severe osteoporosis and a fragility fracture within the previous 3 years (83% had received previous osteoporosis therapy) were treated with teriparatide for up to 24 months. At 24 months, the mean increases from baseline in lumbar spine, total hip, and femoral neck BMD were 10.5%, 2.6%, and 3.9% respectively. The mean increases in BMD from 18 to 24 months were 1.4%, 1.2%, and 1.6% at the lumbar spine, total hip, and femoral neck, respectively.

A 24-month, randomised, double-blind, comparator-controlled phase 4 study included 1,360 postmenopausal women with established osteoporosis; 680 subjects were randomised to teriparatide and 680 to oral risedronate 35 mg/week. At baseline, the women had a mean age of 72.1 years and a median of 2 prevalent vertebral fractures; 57.9% of patients had received previous bisphosphonate therapy and 18.8% took concomitant glucocorticoids during the study. The 24-month follow-up was completed by 1,013 (74.5%) patients. The mean (median) cumulative dose of glucocorticoid was 474.3 (66.2) mg in the teriparatide and 898.0 (100.0) mg in the risedronate arm. The mean (median) vitamin D intake in the teriparatide and in the risedronate arm were 1,433 IU/day (1,400 IU/day) and 1,191 IU/day (900 IU/day), respectively. For those subjects who had baseline and follow-up spine radiographs, the incidence of new vertebral fractures was 28/516 (5.4%) in teriparatide- and 64/533 (12.0%) in risedronate-treated patients (relative risk [95% CI] = 0.44 [0.29-0.68], P<0.0001). The cumulative incidence of pooled clinical fractures (clinical vertebral and non-vertebral fractures) was 4.8% in teriparatide and 9.8% in risedronate-treated patients (hazard ratio [95% CI] = 0.48 [0.32-0.74], P=0.0009).

Male osteoporosis

In a clinical trial in men with hypogonadal (defined as low morning free testosterone or elevated FSH or LH) or idiopathic osteoporosis 437 patients (mean age 58.7 years) were enrolled. Baseline spinal and femoral neck BMD mean T-scores were -2.2 and -2.1, respectively. At baseline, 35% of patients had a vertebral fracture and 59% had a non-vertebral fracture.

All patients were offered 1,000 mg calcium and at least 400 IU vitamin D per day. Lumbar spine BMD significantly increased by 3 months. After 12 months, BMD had increased in the lumbar spine and total hip by 5% and 1%, respectively, compared with placebo. However, no significant effect on fracture rates was demonstrated.

Glucocorticoid-induced osteoporosis

The efficacy of teriparatide in men and women (N=428) receiving sustained systemic glucocorticoid therapy (≥5 mg prednisone for ≥3 months) was demonstrated in the 18-month primary phase of a 36 month, randomised, double-blind, comparator-controlled study (alendronate 10 mg/day). Twenty-eight percent (28%) of patients had one or more radiographic vertebral fracture at baseline. All patients were offered 1,000 mg calcium and 800 IU vitamin D per day.

This study included postmenopausal women (N=277), premenopausal women (N=67), and men (N=83). At baseline, the postmenopausal women had a mean age of 61 years, mean lumbar spine BMD T-score of −2.7, median prednisone equivalent dose of 7.5 mg/day, and 34% had one or more radiographic vertebral fractures; premenopausal women had a mean age of 37 years, mean lumbar spine BMD T-score of −2.5, median prednisone equivalent dose of 10 mg/day, and 9% had one or more radiographic vertebral fractures; and men had a mean age of 57 years, mean lumbar spine BMD T-score of −2.2, median prednisone equivalent dose of 10 mg/day, and 24% had one or more radiographic vertebral fractures.

Sixty-nine percent (69%) of the patients completed the 18-month primary phase. At the 18 month endpoint, teriparatide significantly increased lumbar spine BMD (7.2%) compared with alendronate (3.4%) ($p<0.001$). Teriparatide compared with alendronate increased BMD at the total hip (3.6% versus 2.2%, $p<0.01$), as well as at the femoral neck (3.7% versus 2.1%, $p<0.05$). In patients treated with teriparatide, lumbar spine, total hip, and femoral neck BMD increased between 18 and 24 months by an additional 1.7%, 0.9%, and 0.4%, respectively.

At 36 months, analysis of spinal X-rays from 169 alendronate and 173 teriparatide treated patients showed that 13 (7.7%) patients in the alendronate and 3 (1.7%) patients in the teriparatide group ($p=0.01$) had experienced a new vertebral fracture. In addition, 15 of 214 patients (7.0%) in the alendronate and 16 of 214 patients in the teriparatide group (7.5%) had experienced a non-vertebral fracture ($p=0.84$).

In premenopausal women, the increase in BMD from baseline to the 18 month endpoint was significantly greater in the teriparatide compared with the alendronate group at the lumbar spine (4.2% versus −1.9%; $p<0.001$) and total hip (3.8% versus 0.9%; $p=0.005$). However, no significant effect on fracture rates was demonstrated.

Supportive data

The Applicant conducted a literature search and refers to the data of studies, meta-analyses, and international clinical guidelines to support the efficacy of teriparatide in different patient populations.

Guidelines

The referred guidelines were released by the American College of Rheumatology and The International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis.

The International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis published guidance for the diagnosis and management of osteoporosis in 2013 with an update in 2019 that includes new information on the evaluation of bone microstructure in facture risk assessment, the role of FRAX® and Fracture Liaison Services in secondary fracture prevention, long-term effects on fracture risk of dietary intakes, and increased fracture risk on stopping drug treatment. It states that treatment with teriparatide has been shown to significantly reduce the risk of vertebral and also non-vertebral fractures. There is no convincing evidence that

teriparatide reduces hip fractures, but this may reflect an absence of evidence, not an evidence of absence. Thus, the recommendation for its use in high-risk people is particularly strong in patients with vertebral fractures. The recommended dose is 20 mcg of teriparatide, given as a subcutaneous injection. Treatment with PTH has been studied when given for 18 to 24 months and beneficial effects on non-vertebral fracture with teriparatide have been shown to persist for up to 30 months after stopping teriparatide. Although studies in rats have indicated an increased incidence of osteosarcoma with long-term administration of very high doses of teriparatide, these findings have not been considered relevant for patients treated with very much lower doses of teriparatide.

The American College of Rheumatology considers that in women older than 40 years at low to moderate risk of fractures, if bisphosphonate treatment is not appropriate, teriparatide should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D [Buckley L, 2017]. These recommendations were echoed by Swiss experts [Meier C, 2014].

Publications

The Applicant provided an extensive overview of the available literature data to support the efficacy of teriparatide treatment. The literature included systematic reviews and meta-analyses, published pivotal clinical trials, pivotal clinical trials in postmenopausal osteoporosis, other published clinical trials in postmenopausal osteoporosis, premenopausal osteoporosis, patients at high risk of fracture, synopsis of papers on cyclicity and length of administration, and on clinical trials in non-approved indications. The study populations included postmenopausal women with osteoporosis, men with primary or hypogonadal osteoporosis, and patients receiving long-term glucocorticoid therapy. The referred meta-analyses were mainly based on a general, non-selected population of women and men with osteoporosis.

The observed efficacy related endpoints were lumbar spine and femoral neck BMD, total body bone mineral content, vertebral or non-vertebral fracture risk, clinical vertebral and non-vertebral fragility fractures, back pain, hip fracture, and health-related quality of life in various combinations throughout the different studies.

The studies compared teriparatide treatment to placebo and/or to one or more of the following treatments: alendronate sodium, raloxifene and calcium and vitamin D alone, oestrogens and oestrogen/progestin, calcitonin, vitamin D analogues, denosumab, zoledronic acid, and oral bisphosphonates in various settings.

Overall, the results of the provided studies are positive regarding the efficacy of teriparatide treatment.

The Applicant provided a summary of the **Human Factor activities** undertaken by Owen Mumford Ltd. (OM), during development of the Rutland Autopen. These included two internal readability studies (with 6 adult subjects per each), an external readability study, a device verification summary study, two Stelis reusable pen formative usability studies, and a Stelis reusable pen summative usability study.

The Rutland Autopen is a reusable injection pen, designed for sc. use of teriparatide Stelis injection for the treatment of osteoporosis. The drug will be contained within a standard 3 ml cartridge.

The device delivers a single priming dose of 20 µl and an injection dose of 80 µl. Intended users of the device are HCPs, self-injecting patients, and caregivers.

Internal readability studies were conducted by OM with two iterations of the modified Instructions for Use (IFU) to verify that it is readable and supports the user to carry out the intended use steps. Further testing was conducted by Stelis Biopharma.

During the internal readability study, two participants dialled past P in error while priming the device, all participants successfully injected a dose in each scenario. Three (3) participants (2 in Study 1, 1 in Study 2) expressed a concern that they were not sure any liquid had been injected.

Summative usability test

The objective of this test was to show that the intended users, who are patients with osteoporosis (probable manual dexterity restrictions in their hands, arms, and fingers and/or reduced visual acuity, User group 2) and Healthcare Professionals who specialise in osteoporosis (User Group 1) can safely and effectively use the Teriparatide Stelis Reusable Pen Injector and the accessories (Dose Selector Adaptor and Release Button Extension) in the intended use environment supported by the IFU.

Both user groups were tested in a simulated environment, which looks like a HCP office for User Group 1 and a home for User Group 2. User Group 1 was planned to inject teriparatide into a skin pad attached to an observer, whereas User Group 2 was intended to inject into a skin pad attached to themselves, this later simulated a self-injection process. A training session was also included into this summative user test study.

Formative usability study report

The objective of this test was to show that the intended users, who are patients with osteoporosis (probable manual dexterity restrictions in their hands, arms, and fingers and/or reduced visual acuity, but experienced in self-injecting; User group 2), patients with osteoporosis, non-experienced in self-injecting (User Group 3), and Healthcare Professionals who specialise in osteoporosis (User Group 1) can safely and effectively use the Teriparatide Stelis Reusable Pen Injector and the accessories (Dose Selector Adaptor and Release Button Extension) in the intended use environment supported by the IFU.

All user groups were tested in a simulated environment, which meant a HCP office for User Group 1 and a home for User groups 2 and 3. User Group 1 was planned to inject sterile water into a skin pad attached to an observer, whereas User Group 2 and 3 were intended to inject into a skin pad attached to themselves, this latter simulating a self-injection process. A training session was also included into this formative user test study. The number of subjects was 6, 6, and 5 for User Groups 1, 2, and 3, respectively. Note that all subjects in the HCP group (group 1) were rheumatology nurses.

In total, the 17 study participants in this Formative Usability Test performed 697 tasks, of which 653 tasks were performed successfully (with 4 close calls and 8 tasks performed with difficulty). Forty-four (44) tasks were performed with use errors.

Critical and high-risk tasks most frequently performed with use error were as follows:

- 6/17 study participants did not know they had to store this pen injector in the fridge (Critical task).
- 5/17 study participants did not dial to the 'D' for dose as intended and did something else (High risk task).
- 4/17 study participants did not inspect the cartridge for cloudiness (Critical task).

It is worth noting also that there were clear differences in usability performance between self-injection experienced (User Group 2) and self-injection naive (User group 3) subjects.

Supplementary formative usability study report

The study participants in this supplementary Formative Usability Study were patients with Osteoporosis over the age of 65-85 (theoretical intended users of the Stelis Teriparatide Reusable Pen Injector and

the accessories (Dose Selector Adaptor & Release Button Extension) as intended, in the intended use environment supported by the IFU.

The demographic of these study participants was targeted at age 65-85, which was more extreme than that recorded in the previous Formative Usability Study. Five (5) study participants were recruited, with some who had manual dexterity problems and a lack of visual acuity. They were all aged between 65-70 years old to represent an older intended use population.

Critical and high-risk tasks most frequently performed with use error were as follows:

- 3/5 study participants were not able to dial to the 'P' as required in the task (high risk task).
- 3/5 study participants were not able to dial to the 'D' as required in the task (high risk task).
- 2/5 study participants (one reiterated the same use error twice) were not able to remove the needle (critical task).

Comparison of the results of the two formative usability studies shows that a high percent of subjects was not able to dial the 'D' as required for dose delivery and/or 'P' as required for priming despite the device design enhancement between the two formative studies. Note that during the first readability study some subjects had doubt whether the dose was delivered successfully or not. It is also worth noting that during the pilot PK study 13 of 29 subjects received inadequate teriparatide doses, and this finding were explained by incorrect priming by the Applicant.

Nevertheless, it seems that the design of the Stelis Reusable Teriparatide Pen Injector is acceptable from a technological viewpoint. The reason why some volunteers could not properly administer the injection is due to misunderstanding the instructions. In the light of these results, particular attention should be paid to the text of the PI to avoid dose administration errors.

2.4.6. Discussion on clinical efficacy

The Applicant has not provided data from dedicated studies to inform on the efficacy of teriparatide. Instead, reference is made to the available documentation of the reference medicinal product Forsteo. This is considered acceptable since a scientific bridge to the reference product has been established by demonstrating highly similar physicochemical, structural, and biological characteristics and equivalent pharmacokinetic profiles.

2.4.7. Conclusions on the clinical efficacy

A dedicated efficacy study is not needed to establish biosimilarity of a teriparatide to the reference product.

2.4.8. Clinical safety

The Applicant has not provided data from dedicated studies to inform on the safety of teriparatide. Safety information for teriparatide is primarily based on the documentation of the reference medicinal product Forsteo. In addition, safety data of the pivotal and the pilot single-dose PK/PD studies have been provided. In general, this is considered acceptable for a biosimilar product. However, immunogenicity data are only available for the early pilot study where antibody induction has been assessed; no immunogenicity data are available for the pivotal trial.

2.4.8.1. Patient exposure

The safety assessment of the pivotal trial included 78 subjects; the safety analysis set included all subjects who received at least one dose during the study. The number of subjects who received Stelis Teriparatide was slightly lower (n = 73) than numbers in the Forsteo (n = 74) or Forteo (n = 77) groups. Two (2) subjects withdrew from the study, 1 was lost to follow-up, 1 did not complete the period 3 dosing period due to a family emergency, and 1 experienced AEs of elevated AST and CK.

In the pilot study 29 (96.7%) out of the 30 subjects received treatment with 20 µg Stelis Teriparatide and 28 (93.3%) with Forsteo; 13 (43.3%) subjects in sequence TR and 14 (46.7%) in sequence RT received treatment in both periods. Two (2) subjects in sequence TR and 1 in sequence RT were withdrawn from the study after period 1 without receiving the treatment in period 2.

2.4.8.2. Adverse events

In the pivotal trial the majority of subjects (65/78 subjects, 83.3%) experienced at least 1 adverse event and in 45 out of 78 subjects [57.7%; Stelis Teriparatide 24/73 (32.9%); Forsteo 18/74 (24.3%); Forteo 20/77 (26.0%)] these were considered related to study drug. Most of the adverse events assessed as related to study drug were mild in severity and resolved.

Moderate related adverse events were reported for 3/73 subjects (4.1%) after Stelis Teriparatide and 1/77 (1.3%) after Forteo; mild related adverse events were reported for 21/73 (28.8%) of subjects after Stelis Teriparatide, 18/74 (24.3%) after Forsteo, and 19/77 (24.7%) after Forteo. No severe adverse event was considered related to study drug; a severe adverse event of enzyme level increased, not considered related, was experienced by 1/77 subject (1.3%) after Forteo.

The most commonly reported AEs overall were headache [26/78 (33.3%); Stelis Teriparatide 10/73 (13.7%); Forsteo 6/74 (8.1%); Forteo 15/77 (19.5%)] and upper respiratory tract infection [12/78 (15.4%); Stelis Teriparatide 3/73 (4.1%); Forsteo 4/74 (5.4%); Forteo 5/77 (6.5%)].

In the pilot Study PTH/CT1-001/R0 at least one adverse events occurred in 19/30 (63.3%) subjects, 13/29 on Stelis Teriparatide and 13/28 (46.4%) on Forsteo. The incidence of adverse events (16/30, 53.3%) reported as possibly or probably related to study drug was comparable between groups. No serious adverse events were reported. Mild adverse events were reported in 19 (63.3%) subjects and moderate adverse events in 2 (6.7%) subjects; these events were equally distributed across groups. No severe adverse events or adverse events leading to permanent discontinuation of study drug were reported and no subject died during the study.

Overall, the available data do not indicate relevant differences in adverse event profiles between test and reference products and did not identify any new or unexpected safety findings.

Pooled safety data did also not identify significant differences in adverse event profiles between test and reference products. Details are summarised in the following tables.

*Table 18**: Display of all treatment-emergent adverse events in the PK studies (Pilot & Pivotal)***

System organ class / Preferred term	**Number of subjects (pilot study) n=30**	**Number of subjects (pivotal study) n=78**	**Total number of subjects in both studies n=108**
Number of subjects with TEAE	19 (63.3%)	65 (83.3%)	84 (77.8%)
Gastrointestinal disorders	4(13.3%)	19 (24.4%)	23 (21.3%)
Abdominal discomfort	1 (3.3%)		1 (0.9%)
Dyspepsia	1 (3.3%)		1 (0.9%)
Nausea	1 (3.3%)	10 (12.8%)	11 (10.2%)
Vomiting	1 (3.3%)		1 (0.9%)
Abdominal pain		4 (5.1%)	4 (3.7%)

General disorders and administration site conditions	12 (40%)	14 (17.9%)	26 (24.1%)
Injection site erythema	12 (40.0%)		12 (11.1%)
Catheter site pain		7 (9.0%)	7 (6.5%)
Infections and infestations	4 (13.30%)	14 (17.9%)	18 (16.7%)
Upper respiratory tract infection	1 (3.3%)	12 (15.4%)	13 (12.0%)
Gastroenteritis	1 (3.3%)		1 (0.9%)
Injury, poisoning and procedural complications	1 (3.3%)		1 (0.9%)
Arthropod bite	1 (3.3%)		1 (0.9%)
Musculoskeletal and connective tissue disorders	2 (6.7%)	6 (7.7%)	8 (7.4%)
Muscle twitching	1 (3.3%)		1 (0.9%)
Myalgia	1 (3.3%)	3 (3.8%)	4 (3.7%)
Nervous system disorders	5 (16.7%)	44 (56.4%)	49 (45.4%)
Headache	4 (13.3%)	26 (33.3%)	30 (27.7%)
Dizziness	1 (3.3%)	8 (10.3%)	9 (8.3%)
Dizziness Postural		8 (10.3%)	8 (7.4%)
Lethargy	1 (3.3%)		1 (0.9%)
Presyncope		9 (11.5%)	9 (8.3%)
Syncope		3 (3.8%)	3 (2.8%)
Dysgeusia		2 (2.6%)	2 (1.9%)
Migraine		2 (2.6%)	2 (1.9%)
Respiratory, thoracic and mediastinal disorders	2 (6.7%)		2 (1.8%)
Nasal congestion	2 (6.7%)		2 (1.9%)
Cardiac disorders		11 (14.1%)	11 (10.2%)
Postural orthostatic tachycardia syndrome		10 (12.8%)	10 (9.3%)
Palpitations		2 (2.6%)	2(1.9%)
Vascular disorders		3 (3.8%)	3 (2.8%)
Orthostatic hypotension		2 (2.6%)	2 (1.9%)

*Table 19**: Display of comparative all treatment-emergent adverse events in the PK studies (Pilot & Pivotal)***

System organ class / Preferred term	**Kauliv N = 102; n (%)**	**Forsteo N = 102; n (%)**	**Forteo N = 77; n (%)**
Number of subjects with TEAE	56 (54.9%)	44 (43.1%)	33 (42.9%)
Gastrointestinal disorders	8 (7.8%)	8 (7.8%)	7 (9.1%)
Abdominal discomfort	1 (1.0%)		
Dispepsia		1 (1.0%)	
Nausea	4 (3.9%)	5 (4.9%)	2 (2.6%)
Vomiting	1 (1.0%)		
Abdominal pain	1 (1.0%)	1 (1.0%)	2 (2.6%)
General disorders and administration site conditions	18 (17.6%)	10 (9.8%)	2 (2.6%)
Injection site erythema	9 (8.8%)	7 (6.9%)	
Catheter site pain	4 (3.9%)	2 (2.0%)	1 (1.3%)
Infections and infestations	6 (5.9%)	6 (5.9%)	6 (7.8%)
Upper respiratory tract infection	4 (3.9%)	6 (5.9%)	5 (6.5%)
Gastroenteritis	1 (1.0%)		
Injury, poisoning and procedural complications	1 (1.0%)		
Arthropod bite	1 (1.0%)		
Musculoskeletal and connective tissue disorders	2 (2.0%)	6 (5.9%)	1 (1.3%)
Muscle twitching		1 (1.0%)	
Myalgia	1 (1.0%)	3 (2.9%)	
Nervous system disorders	26 (25.5%)	18 (17.6%)	21 (27.3%)
Headache	12 (11.8%)	9 (8.8%)	15 (19.5%)
Dizziness	2 (2.0%)	4 (3.9%)	4 (5.2%)
Dizziness Postural	2 (2.0%)	3 (2.9%)	3 (3.9%)
Lethargy		1 (1.0%)	
Presyncope	6 (5.9%)		3 (3.9%)
Syncope	3 (2.9%)		
Dysgeusia			2 (2.6%)

Migraine	2 (2.0%)		
Respiratory, thoracic and mediastinal disorders	1 (1.0%)	1 (1.0%)	
Nasal congestion	1 (1.0%)	1 (1.0%)	
Cardiac disorders	4 (3.9%)	5 (4.9%)	4 (5.2%)
Postural orthostatic tachycardia syndrome	4 (3.9%)	5 (4.9%)	3 (3.9%)
Palpitations			2 (2.6%)
Vascular disorders	2 (2.0%)	1 (1.0%)	
Orthostatic hypotension	2 (2.0%)		

2.4.8.3. Immunological events

As for methods please see Pharmacokinetics above.

So far, information on immunogenicity is limited to the pilot study, no antibody measurement has been included in the pivotal study.

Apparent discrepancies concerning actual levels of Tag impurity in Stelis Teriparatide batches have been clarified during the assessment and the Applicant has presented a control strategy for constantly and adequately controlling this impurity at a sufficiently low level by routine testing of the finished product.
The new ELISA-based method was able to consistently show that Tag impurity levels in active substance and finished product are acceptable and significantly lower than the previously proposed limit.
Furthermore, the Applicant estimated the amount of the total non-product related proteinaceous impurities to be below the level of 100 ppm conventionally considered for total non-product related proteinaceous impurities suggesting an acceptable immunogenicity risk from protein impurities.
The Applicant has also performed a quality risk assessment to evaluate the safety risk associated with the tag impurity based on the residual level in the product, prior literature knowledge on the impurity components, clinical information, and the clearance profile during the manufacturing process. Based on this risk evaluation the Applicant considered that the risk from impurity in the drug product is low, adequately controlled, and does not pose a safety concern.
It is therefore agreed that the potentially remaining tag impurity is not likely to pose an immunogenicity related safety concern in patients.

2.4.8.4. Post marketing experience

According to the Applicant, there is currently no post-marketing data available; the medicinal product has not been marketed in any country. However, extensive post-marketing data exist for the reference product Forsteo first licensed in the EU in 2003 for which biosimilarity of the applied medicinal product is claimed by the Applicant.

2.4.9. Discussion on clinical safety

The Applicant has not provided data from dedicated studies to inform on the efficacy and safety of teriparatide. Safety information for teriparatide is primarily based on the documentation of the reference medicinal product Forsteo. In addition, safety data of the pivotal and the pilot single-dose PK/PD studies have been provided. In general, this is considered acceptable for a biosimilar product. However, immunogenicity data are only available for the early pilot study where antibody induction has been assessed; no immunogenicity data are available for the pivotal trial.

Overall, the available data do not indicate clear differences in adverse event profiles between test and reference products in the PK/PD studies and no new or unexpected safety findings have been identified, but interpretation is limited by the single treatment and low number of subjects included. However, for a biosimilar teriparatide, bridging to the safety experience gained with the reference product is generally possible based on analytical / functional and PK similarity.

The only issue was the potential presence of tag in Kauliv, which may theoretically increase immunogenicity. According to the quality assessment, process related impurities potentially affecting immunogenicity can be sufficiently controlled at very low levels and adequate justification that remaining tag will not be of concern has been provided.

2.4.10. Conclusions on the clinical safety

Sufficient evidence has been provided to conclude on a similar safety profile of Kauliv compared to the reference product Forsteo.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None

2.5.4. Conclusion

The CHMP considers that the risk management plan version 2.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

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

2.6.2. Periodic Safety Update Reports submission requirements

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

2.7. Product information

2.7.1. 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.*

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kauliv (teriparatide) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Kauliv was developed as biosimilar product to Forsteo (Eli Lilly), containing 20µg/80µL of recombinantly produced teriparatide. It is provided in a cartridge containing 3 mL of drug product solution and intended for use with the re-usable Kauliv pen.

Therapeutic indications, posology, and route of administration proposed for Kauliv are identical to those for Forsteo. Forsteo is currently 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 Applicant performed an analytical comparability study to evaluate similarity of Kauliv to Forsteo (EU), Forteo (US), and Forteo (India) on the quality level. In addition, a comparative clinical PK/PD study was performed to support the application. As the pivotal clinical PK study was performed (amongst others) with Forsteo (EU), the summary of the results is focused on the comparability of

Kauliv to the EU sourced Forsteo. Information on comparability to Forteo (US) and Forteo (India) are not considered relevant and hence, disregarded in the context of this application.

A total of 10 batches of Stelis Teriparatide drug product were compared with 9 batches of EU sourced Forsteo. The similarity report is presented in the form of the overlay of spectrums/chromatograms, tables containing observed results, statistical analysis, equivalence tests, and the result summary.

The following quality attributes were investigated, partially by orthogonal analytical methods: Intact mass, primary and secondary structure, teriparatide content, charge variants, related substances by RP-HPLC and SEC, metacresol content, and biological activity (cell-based assays and binding kinetics).

3.2. Results supporting biosimilarity

The analytical data provided support analytical similarity. Precursor-related impurities are present at very low levels, not jeopardising analytical similarity.

As regards pharmacokinetic and pharmacodynamic comparability in the pivotal study PTH/CT1-002/R5, the 90% CIs as well as the 95% CIs of the geometric LS mean ratios for the primary PK parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} and the secondary PD parameters (ionised calcium) AUC_{0-t} and C_{max} were within the predefined acceptance limits.

3.3. Uncertainties and limitations about biosimilarity

Teriparatide used for Kauliv is expressed as fusion protein with a tag. The tag impurity can potentially pose a increased risk for immunogenicity. However, the Applicant presented data confirming that the amount of precursor is controlled at very low levels.

3.4. Discussion on biosimilarity

From a quality point of view, analytical similarity can be concluded; data have been presented confirming that the precursor that might pose a risk for increased immunogenicity of the biosimilar product is controlled at very low levels.

3.5. Extrapolation of safety and efficacy

Biosimilarity has been established for Kauliv to the reference product Forsteo, as such this applies to all indications licensed for Forsteo.

3.6. Additional considerations

None

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, biosimilarity of Kauliv to reference product Forsteo and therefore a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

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

Kauliv is indicated in adults.

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

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

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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

An updated RMP should be submitted:

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