26 February 2026
EMA/77774/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zandoriah

International non-proprietary name: teriparatide

Procedure No. EMEA/H/C/006688/0000

Note

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

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List of abbreviations

AS	Active substance
AUC0-inf	The area under the plasma concentration-time profile; calculated from time 0 to infinity
AUC0-t	The area under the serum concentration versus time curve from time 0 to last determined concentration
BET	Bacterial endotoxin
CAMP	Cyclic adenosine 3,5-monophosphate
cAMP	Cyclic adenosine monophosphate
CCIT	Container closure integrity test
CD	Circular Dichroism
CE-SDS	Capillary sodium dodecyl sulphate gel electrophoresis
CEX	cation exchange (chromatography)
CFU	Colony forming unit
CI	confidence interval
cIEF	Capillary isoelectric focusing
CIP	clean-in-place (CIP)
CL/F	Apparent Total Clearance
Cmax	Maximum Serum Concentration
CPP	Critical process parameter
CQA	Critical quality attribute
CTD	Common technical document
CV	column volumes
DL	Detection limit
DoE	Design of Experiment
DP	drug product
DS	drug substance
EU	Endotoxin unit
ESI	Electrospray ionisation
FBS	Foetal bovine serum
FDS	Formulated Drug Substance
FDS	Filtered Drug Substance
FFDS	Filtrated Formulated Drug Substance
FMEA	Failure Mode and Effects Analysis
GMP	Good Manufacturing Practice
GM	Geometric Mean
HCP	Host cell protein
HMW	High Molecular Weight species
icIEF	I Imaged capillary isoelectric focusing
ICP-OES	inductively coupled plasma optical emission spectroscopy
INN	international non proprietary name
IPC	In-process control
IPQC	in-process quality control
iPTH	Intact Parathyroid Hormone
ISR	incurred samples reanalysis
IU	International Units
kD	kilodalton
KPP	Key Process Parameters
LC	liquid chromatography
LMH	liters of permeate per square meter of membrane area per hour – L/m2/hour)

LMW	Low molecular weight species
LOQ	Limit of quantification
LSM	Least-Squares Means
MAA	Marketing Authorization Application
MALDI-TOF MS	Matrix-assisted laser desorption ionization–time-of-flight mass spectrometry
MCB	Master cell bank
MHC	Major Histocompatibility Complex
MMV	mouse minute virus
MW	Molecular weight
NA	Not applicable
NIBSC	National Institute for Biological Standards and Control
Ni-NTA	Nickel Nitrilotriacetic Acid
NMT	not more than
NOR	Normal operating range
OOS	Out of specification
OOT	Out of trend
PACMP	post-approval change management protocol
PAR	Proven acceptable range
PDL	Population doubling level
PCN	Plasmid copy number
PDE	permitted daily exposure
Ph.Eur	European Pharmacopoeia
pI	isoelectric point
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PLC	Phospholipase C
PPQ	Process Performance Qualification
PRM	primary reference material
PTH	parathyroid hormone
PTH1R1	parathyroid hormone receptor 1
PUPSIT	pre-use post sterilization integrity testing
PVDF	polyvinylidene difluoride
PW	Purified water
P044	Teriparatide active substance (internal code)
q.s.	Quantity sufficient;
QTPP	Quality Target Product Profile
REO	reovirus type 3
RFB	Required Formulation Buffer
RMP	Risk Management Plan
RP-HPLC	reverse phase high pressure liquid chromatography
RPC-ELISA	Residual Process Components-Enzyme-linked immunosorbent assay
RPN	risk priority number
RRM	research reference material
RT	Room temperature

RVLP	retrovirus-like particles
SC	Subcutaneous(ly)
SD	Standard deviation
SE-HPLC	size exclusion- High Performance Liquid Chromatography
SEC-MALS	Size exclusion chromatography with multi-angle static light scattering
SFB	Stock Formulation Buffer
SIP	Steamed in place
SmPC	Summary of Product Characteristics
SST	System suitability
t1/2	Plasma Elimination Half-Life
TAMC	Total aerobic microbial count
TDK	Thymidine kinase
TFF	tangential flow filtration
TI	Tolerance interval
tlast	Time of Last Quantifiable Concentration
tmax	Time to Maximum Serum Concentration
TOR	Time out refrigeration
TRIS	2-amino-2-hydroxymethyl-propane-1,3-diol, tris(hydroxymethyl)aminomethane
TSH	Thyroid-Stimulating Hormone
TYMC	Total yeast and mold count
UF	ultrafiltration
ULOQ	upper limit of quantification
Vz/F	Apparent Volume of Distribution
WCB	Working cell bank
WFI	Water for injection
WRM	working reference material
XmuLV	xenotropic murine leukemia virus
λz	Terminal Elimination Rate Constant

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Zandoriah
Active substance	teriparatide
INN or common name	teriparatide
Applicant	Cinnagen Co Unipessoal Lda. Rua Alfandega 78 Andar 3 9000-059 Funchal PORTUGAL
EMA Product Number	EMEA/H/C/006688
ATC code and Pharmacotherapeutic group	H05AA02
Pharmaceutical form(s) and strength (s)	Solution for injection 20 micrograms/80 microlitres
Packaging	Pre-filled pen
Package size(s)	Each pen contains 2.4 mL of solution enough for 28 doses
Route of administration	Subcutaneous
Device or diagnostic	Not applicable
Orphan designation	No
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 10(4) of Directive 2001/83/EC
Final indication	Teriparatide 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).
New active substance status	Not applied for

1.2. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
27 June 2019	Quality/Non-Clinical/Clinical	EMA/CHMP/SAWP/344141/2019	The Scientific advice pertained to the following quality, non-clinical, and clinical aspects: drug substance storage, comparative analytical package adequacy of non-clinical package. Planned PK/PD clinical trial. Immunogenicity testing. Adequacy of the overall development to support MAA.

1.3. Eligibility to the centralised procedure

The applicant Cinnagen Co Unipessoal Lda. Submitted on 3 February 2025 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zandoriah (teriparatide), through the centralised procedure falling within the Article 3(1), point 1 of Annex, of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 November 2024.

The applicant applied for the following indication: osteoporosis in postmenopausal women and in men at increased risk of fracture, as well as osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

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

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

The chosen reference product is: medicinal product which is or has been authorised in accordance with European Union provisions in force for not less than 8 years in the EEA:

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

1.5. Information on paediatrics

Not applicable.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

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 from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Steps taken for the assessment of the product

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

Rapporteur:	Maria Grazia Evandri
Co-Rapporteur:	Ewa Balkowiec Iskra

The application was received by the EMA on	3 February 2025
The procedure started on	20 February 2025
The CHMP Rapporteur's first Assessment Report was received on	13 May 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	14 May 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	26 May 2025
The Biologics Working Party agreed on the Assessment Overview during their meeting on	12 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	19 June 2025
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: GCP inspections at the clinical and analytical site in Bulgaria were conducted between 21-25 July 2025. The outcome of the inspection carried out was issued on	5 September 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 September 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	21 October 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 October 2025

The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	7 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	13 November 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 January 2026
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 February 2026
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	20 February 2026
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 Zandoriah on	26 February 2026

1.8. CHMP outcome

1.8.1. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.8.1.1. Similarity with authorised orphan medicinal products

Not applicable.

1.8.2. Opinion

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

Teriparatide 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 conditions described in the following sections.

1.8.3. Conclusions on biosimilarity and benefit risk balance

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

1.8.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.8.5. Other conditions and requirements of the marketing authorisation

1.8.5.1. 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.

1.8.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.8.6.1. 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.

1.8.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. Therapeutic Context

Osteoporosis is a systemic disease of the skeleton characterised by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue with consequent increased bone fragility that increases fracture risk.

The diagnosis of osteoporosis is established by means of bone densitometry or by the presence of a fragility fracture. Any bone may be affected; although the skeletal sites most prone to fracture include proximal femur (hip), vertebrae (spine), and distal forearm (wrist). Osteoporotic fractures lead to pain and occasional disability. More importantly, they increase mortality. Osteoporosis is commonly experienced in postmenopausal women due to declining oestrogen levels. However, osteoporosis can also occur in both sexes as a side effect of prolonged treatment with glucocorticoid medications. Glucocorticoid-induced osteoporosis may be responsible for up to 20% of all osteoporosis cases. Fractures, primarily hip fractures, decrease a patient's quality of life by increasing pain, medical costs, morbidity, and mortality.

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

Current treatments for osteoporosis include anti-resorptive drugs like bisphosphonates, denosumab, and raloxifene, which slow bone loss, as well as anabolic agents such as teriparatide and romosozumab, which stimulate new bone formation. Calcium and vitamin D supplementation, along with lifestyle changes like exercise and fall prevention, also play an essential role in managing the disease.

2.2. Aspects of development

Quality

The Zandoriah drug substance (teriparatide) is a polypeptide consisting of amino acids 1-34 of the N-terminal fragment of human parathyroid hormone. The peptide is manufactured in Escherichia coli (E. coli) using recombinant DNA technology and does not contain glycosylation or any other post-translational modification.

The "Pharmaceutical Development" data package supporting the control strategy proposed both for the Zandoriah Drug Substance (DS) and Drug Product (DP) manufacturing processes can be considered overall acceptable.

Non-Clinical

Three in vitro Primary Pharmacology studies have been conducted to demonstrate comparability between Zandoriah and Forsteo:

- a qualified surface plasmon resonance (SPR) method with regards to the comparative binding of Teriparatide to PTH1R (parathyroid hormone 1 receptor);

- two potency assays using two different osteosarcoma cell lines: UMR-106 rat osteosarcoma cell line and Saos-2 human osteosarcoma cell line.

These data were also submitted as part of the comparability assessment in the Biosimilarity Report, Module 3.2.R.3.

Moreover, a custom in silico immunogenicity analysis was performed according to the peptide sequence by artificial neural networks in order to have a propensity to over-predict T cell epitopes.

No PK/PD studies have been planned in animals based on knowledge of safety and efficacy from years of clinical use with reference medicine. A 28-day repeated dose toxicity study in Sprague Dawley rats by subcutaneous route was performed to assess toxicity and immunogenicity of amino acid sequence variant

Clinical

The clinical program for Zandoriah comprises one single pivotal PK/PD bioequivalence study (CM-389) in healthy female subjects which was designed to demonstrate PK/PD bioequivalence of Zandoriah with the reference medicinal product, Forsteo. The Applicant has not conducted any clinical efficacy (or safety) studies on the treatment of osteoporosis in patients.

The clinical development programme for Zandoriah has been aligned to the respective EU guidance, in particular:

- Guideline on similar biological medicinal products (CHMP/437/04 Rev 1)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance – non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1)
- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

2.3. Description of the product

Zandoriah (also referred to as P044) is developed as a biosimilar to the reference medicinal product, Forsteo 20 micrograms/80 microliters solution for injection in pre-filled pen, which contains teriparatide as its active pharmaceutical ingredient. Teriparatide, PTH (1-34) is the international non-proprietary name (INN) for the biologically active 34-amino acid N-terminal fragment of the 84-amino acid native parathyroid hormone, PTH (1-84). Zandoriah has identical primary amino acid sequence as teriparatide. Teriparatide belongs to the pharmacotherapeutic group of calcium homeostasis, parathyroid hormones and analogues, ATC-code H05AA02.

The biologically active ingredient teriparatide 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.

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 expressed on the surface of osteoblast cells at the bone and distal convoluted tubular in the kidney. PTH-1R is a 7-transmembrane, G protein–coupled receptor linked to heterotrimeric G proteins Gs and Gq. The activation of PTH-1R by PTH signals through several intracellular pathways, including adenylyl cyclase/cycle AMP/protein kinase A (PKA) through Gs pathway or to the phospholipase C (PLC)/protein kinase C (PKC) through Gq pathway, although a preference for certain pathways is apparent in each organ and function.

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. In the bone, PTH plays an important role in maintaining Ca2+ balance and remodelling of the bone. PTH pulses and sustained PTH elevations promote calcium release from the bone using various mechanisms. Direct effects of PTH on osteoblasts and osteocytes and indirect actions on osteoclasts promote both bone formation and bone resorption.

The sought therapeutic indications and posology for Zandoriah reflects those approved for the reference product, Forsteo, authorised within EU since 2003:

> Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture (see section 5.1). In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures have been demonstrated.
>
> Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture (see section 5.1). "
>
> The recommended dose for teriparatide is 20 micrograms once daily administered subcutaneously. The maximum total duration of treatment with teriparatide should be 24 months. The 24-month course of teriparatide should not be repeated over a patient's lifetime.

Zandoriah is formulated with the same excipients as Forsteo and presented as solution for in injection in pre-filled pen for subcutaneous injection only, same as its reference medicinal product.

2.4. Inspection issues

2.4.1. GMP inspection(s)

Based on the initial evaluation made by the EMA GMP Office in the validation phase, no inspections to verify GMP compliance of the involved manufacturing sites were deemed necessary within the scope of this MAA procedure.

No specific issues that would trigger a GMP inspection have been identified during the assessment of the information provided in Module 3.

2.4.2. GLP inspection(s)

No inspection required.

2.4.3. GCP inspection(s)

A request for a routine GCP inspection was issued for the clinical study CM-389, 2019-004477-82 – an open label, two-treatment, two-sequence, two-period, crossover study to assess the bioequivalence of proposed Teriparatide biosimilar, Zandoriah, for subcutaneous injection after single dose administration of 20 mcg versus Forsteo 20mcg in 60 healthy female subjects.

The inspection was conducted at the clinical and analytical site in July 2025. A technical issue related to electronic source records was identified, fully resolved, and verified by the inspectors with no impact on GCP compliance or data integrity.

Having reviewed the responses to the inspection findings and related corrective and preventive actions (CAPA), the Inspectors concluded that the study CM-389 has been conducted with an acceptable level of compliance with GCP, with applicable GLP and with internationally accepted ethical standards and that there was no negative impact on the validity and reliability of data, which could be used for the evaluation.

3. Quality aspects

3.1. Introduction

The finished product is presented as solution for injection containing 20 micrograms of teriparatide as active substance in 80 microliters of solution.

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

The product is available in 2.4 mL solution in cartridge (siliconized glass USP type I borosilicate glass) with a plunger (halobutyl rubber), disc seal (polyisoprene/bromobutyl rubber laminate)/aluminium assembled into a disposable pen.

Zandoriah solution for injection is a proposed biosimilar to the EU authorised product Forsteo.

Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied.

3.2. Active substance

3.2.1. General information

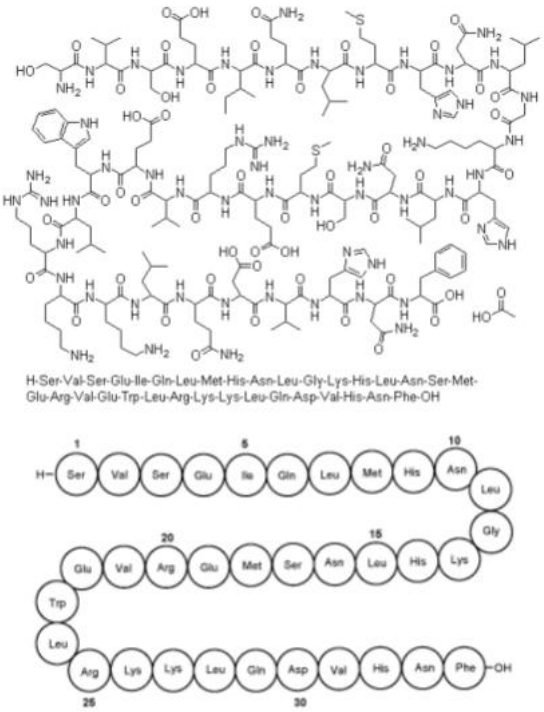
Zandoriah active substance (teriparatide, also referred to as P044) is a single-chain polypeptide consisting of amino acids 1-34 of the N-terminal fragment of human parathyroid hormone, [rhPTH(1-34)], which is believed to confer the biological activity of the 84-amino acid human parathyroid

hormone (PTH) by binding to PTH receptor 1 (PTH1R). Teriparatide has a molecular weight of 4117.8 Daltons and molecular Formula C181H291N55O51S2.

Teriparatide is manufactured in Escherichia coli (*E. coli*) using recombinant DNA technology and does not contain glycosylation or any other post-translational modification.

The structure of teriparatide is given in Figure 1.

Figure 1: Chemical structure of teriparatide



3.2.2. Manufacture, characterisation, and process controls

Description of manufacturing process and process controls

The manufacturers responsible for the manufacturing and quality control activities related to Zandoriah (teriparatide) active substance (AS, also referred to as drug substance (DS)) are summarised in Table 2.

Table 2: Active Substance Manufacturers

Manufacturer, address	Responsibility /function	GMP compliance documentation
CinnaGen Research and Production Company (CinnaGen Co.) Address: Plot 87, 88, 3rd Sq., Simin Dasht Non-Governmental Industrial Area, Fardis County, Alborz Province, Iran	MCB/WCB Preparation, Testing and Storage Drug Substance Manufacturing Testing of unprocessed bulk In-process testing Release and Stability testing Storage of AS	EU GMP certificate n. BG/GMP/2024/254 QP Declaration n. QP-2025-TER-002
QUINTA ANALYTICA s.r.o. *(El spol. S r.o. contract lab*) Prazska 1486/18c, 102 00 Praha 10 – Hostivar, Czech Republic	Quality control testing for Related protein by LC-MS method	EU GMP certificate n. *sukls19984/2025*

A valid proof of GMP compliance for the CinnaGen Co. manufacturing site has been submitted. A post-approval inspection covering all proposed activities was requested for CinnaGen Co. manufacturing site. The inspection was successfully conducted prior to approval (BG/GMP/2025/331).

For all sites involved in the manufacture, control and batch release of the active substance valid evidence of GMP compliance has been provided.

Teriparatide is a fusion protein produced by recombinant DNA technology by E. coli bacteria.

The AS manufacturing process can be divided into two major stages, briefly described below.

The upstream process includes Working Cell Bank (WCB) vial thaw, shake flask expansion, production of the fusion protein into a fermenter based on fed-batch mode, followed by supplementary feed. At the end of cell culture, the batch is harvested, and the supernatant is centrifuged in preparation for the purification process.

The downstream purification includes cell lysis, enzyme cleavage and a series of chromatography steps. Filtered Teriparatide AS is buffer-exchanged and stored at -20°C.

No reprocessing is foreseen within the manufacturing process of Zandoriah AS.

All process steps are described and a list of IPCs, alongside with acceptance ranges, is submitted. A schematic flow diagram of the commercial manufacturing process is also provided alongside with acceptance criteria for all critical process parameters (CPP), key process parameters (KPP), in-process controls (IPC) and in-process quality controls (IPQC).

Information about buffers and solution used in the teriparatide manufacturing process as well as process resin and filter lifetime are provided, all filters are single-use. Bioburden and endotoxin are monitored throughout the process while process intermediates and process solutions are 0.2 µm filtered.

A single batch of AS is defined as resulting from the processing of one vial of WCB, using a fermenter with an established harvest yield producing a commercial batch of teriparatide AS.

No pooling of production fermenter harvest is performed.

Filter integrity test is performed during several steps. Based on a risk assessment, bioburden testing is required at the digestion step only; omission at the other purification stages is acceptable.

Adequate information has been provided regarding the solutions, culture media and containers used to store production intermediates within the process.

The information provided on teriparatide AS manufacture is considered sufficient. The process has been sufficiently described and the in-process controls are adequately set to control the process.

Teriparatide AS is stored in a freezing bag, , it confirms with Ph. Eur. requirements. Results of the risk assessment and extractables and leachable study further confirm the suitability of the container.

Control of materials

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

During the procedure, upon request of the CHMP, additional specification and related information on the in-house test, were provided. A general description on gene construction and genetic stability is given. A detailed component map of the final expression construct plasmid containing the teriparatide transgene sequence is presented, together with a full relevant DNA sequence.

A two-tiered cell banking system is used and sufficient information is provided regarding testing of Master Cell Bank (MCB) and WCB and release of future WCBs. Suitable studies to define population doubling level (PDL) as well as limit of in vitro cell age were performed.

Identity testing (for species level identity confirmation), as well as plasmid copy number (PCN) determination, are respectively performed by means of a validated PCR-based method with TDK (thymidine kinase) gene primers and real time PCR according to SYBR Green technique. Likewise, the genetic stability of recombinant teriparatide gene in E. coli cell banks at DNA level was evaluated by quantitative real-time PCR method.

Cell banks characterisation also included tests to establish the absence of adventitious bacteria, fungi and inducible phages.

Evidence for banked cell stability under defined storage conditions was also provided according to ICH Q5D.

The description and characterisation of the cell banks are considered adequate, they sufficiently encompass all the key aspects, including the description of the research cell bank (RCB), which is the original cell line used to prepare the MCB, end of production cell bank (EoPC), the suitability of the identity test for the BL-21 strain, genetic stability studies, the MCB and WCB storage management approach, the qualification protocol for future cell banks alongside with appropriate acceptance criteria as well as details about cell banks stability verification protocol.

Control of critical steps and intermediates

During the procedure, the CHMP raised a quality major objection (MO) requesting the applicant to further substantiate the overall control strategy of the AS and finished product by providing an exhaustive risk assessment conducted in accordance with ICH Q9, the rational for the selection of the parameters and additional details on process development studies. The applicant resolved the MO by providing an overview of CPP, KPP, IPCs, IPQC and related response applied throughout the AS manufacturing process. This classification is based on their criticality for product quality or their role in

process monitoring. Acceptable information was provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

The analytical methods used to control process steps are described with qualification data for non-compendial methods.

Process validation

The AS manufacturing process has been validated adequately. Consistency in production has been shown on three full scale consecutive commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces the AS of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

The resin life-time small scale evaluation was conducted for Ni-NTA, cation exchange, size-exclusion and G10 interaction steps for a prospective estimation of resin life-time which is confirmed concurrently at full scale, through a verification study.

With the exception of Ni-NTA, no leachables are expected from the size exclusion, cation exchange, or chromatography resins, based on the vendor claim about chemical stability, this approach has been supported by a risk assessment and it is considered acceptable.

The proposed hold-times for buffer and intermediates are adequately supported by data. Shelf-life results for biomass are presented and considered acceptable.

Satisfactory qualification data are provided supporting the transport of the AS from the AS production cold room to the FP warehouse cold room (at 2-8 °C and at -20 °C).

Manufacturing process development

To further address the above-mentioned MO regarding control strategy, the applicant explained that the manufacturing development have been evaluated through the use of risk assessment to identify CPP, KPP, IPC, IPQC and response parameters (process performance indicators), on the basis of impact on CQA. The risk identification was based on the prior knowledge as well as on the experience from formulation development, small scale models and scale-up studies. The scoring was fully adequately explained. The CPPs have been adequately identified.

Small process changes to the process were implemented when the manufacturing equipment was transferred within two sites of the same manufacturer. The version used at the first site was named P1 and the version used at the second site was named P2. P1 and P2 processes are identical (in terms of scale, equipment, raw materials, CPPs, and control strategy). An initial risk assessment was done and recommended actions for decreasing the potential risks were implemented. To determine impact of this change, pre- and post-change comparability exercisewas perfomed, including routine batch analysis, IPCs, extended characterisation studies, process validation data and stability studies. After statistical evaluation of the comparability results, it can be concluded that the AS from P1 and P2 process versions are comparable.

Characterisation

Characterisation studies were performed on three AS batches (P1 process) using state of the art techniques such as MALDI-TOF MS analysis, amino acid composition analysis (with three different hydrolysis conditions) and amino acid sequencing by peptide mapping fingerprinting (analysis of

peptides after digestion using reverse-phase HPLC) for primary sequence, circular dichroism for higher order structure, SDS-PAGE under reducing conditions for molecular weight, RP-HPLC and UV for protein content, an in-vitro cell-based assay (which can monitor the production of cyclic-AMP by cells exposed to teriparatide) for biological activity and icIEF (Imaged capillary isoelectric focusing) together with capillary zone electrophoresis for charge variant analysis. Analysis confirms that the AS is a single peptide chain consisting of the 34 N-terminal amino acids of human parathyroid hormone, with sequence identity to the reference product and no post-transitional modification, as expected for bacterial expression system. The use of AS manufactured with the P1 process for the purpose of the characterisation is acceptable as comparability between P1 and P2 has been demonstrated.

The biological activity of product-related teriparatide proteins, that include modified forms due to truncation (fragmentation), deamidation (aspartate formation), oxidation, aggregation, and charge variants. Process- and product-related impurities were identified and quantified by state-of-the-art analytical methods

Impurities with higher molecular masses, , can be effectively removed during the purification process.

During the procedure, the CHMP raised a MO related to the presence of the potentially immunogenic thioredoxin His-tag impurity: to avoid any potential increase of the immunogenicity risk it is important that the process-related impurity thioredoxin His-tag is effectively removed in the purification step, so that any residual level is comparable or lower to that of the reference product Forsteo.

Based on the analytical data obtained by liquid chromatography/electrospray ionisation mass spectrometry (LC/ESI/MS) on six batches of Zandoriah and three batches of Forsteo, the absence of detectable fusion protein in both products can be concluded. Additionally, clearance studies employing two distinct methodologies (by RP-HPLC and by SE-HPLC) have quantitatively measured the thioredoxin His-tag impurity in all the involved batches to be below the limit of quantification Overall, the data support the conclusion that the process-related impurity profile of Zandoriah is comparable to that of the reference product Forsteo. However, suitable analytical control measures were implemented at the AS level, to ensure the absence or consistent low levels of His-Tag (BLOQ) in the AS, namely: 1. An in-process test has been added to the final chromatography step to monitor the amount of His-tag thioredoxin during the manufacturing process; 2. A suitable validated test (residual fusion protein and Thioredoxin His-tag) has been added to the AS specifications with a defined acceptance criterion (< 1μg/ml equivalent to < 1 ppm) in line with acceptable levels for HCP impurities in biologics. With these measuresthe MO was considered resolved.

A list of process-related impurities such as mineral impurities and low-molecular-mass organic impurities derived from the culture media are effectively removed during the UF/DF step, and calculations are reported to demonstrate that theoretical metal levels in formulated bulk are below the recommended limits for parenteral PDE. Sufficient data to support the elimination of major process-related impurities, which include Host cell DNA, Host cell proteins and a number of critical reagents used in the processhave been reported from three batches produced with the commercial process. HCD (Host Cell DNA) and HCP (Host Cell Proteins) are even registered as AS release tests and so they are adequately controlled.

As nickel is a metal of significant safety concern (class 1C), the Ni+2 leaching pattern was correctly characterised during downstream processing of three different batches of Teriparatide using ICP-OES analysis, demonstrating that downstream processing can significantly reduce the minimum residual nickel released from the Ni-NTA (nickel-nitrilotriacetic acid) column.

Moreover, data from heat-treated samples obtained with a suitable method demonstrate that the level of aggregation is not affected by heat. Taking into account that SEC purification process cannot eradicate the related proteins with similar or close molecular weights to Teriparatide, subsequent

cation exchange chromatography step is claimed to effectively address this issue. In this regard, the levels of relevant impurities as detected by RP-HPLC were provided at different steps of process purification (from SE pooled fraction up to Drug substance) in terms of LC-UV chromatograms and Area%. The data provided are overall considered comprehensive since they include relevant information (in terms of relevant peaks in the chromatograms and quantity %) for all the relevant product-related impurities including deamidated and truncated forms.

Comprehensive studies were performed on an impurity species that was observed by LC-MS in Zandoriah samples but not present in the batches of Forsteo reference material. This impurity is consistent with a single amino acid sequence variant. A toxicity study was carried out in order to show that this particular species does not exhibit any safety concerns at the dose present in Zandoriah samples. comprehensive data support the fact that in the current normal operating range, the amount of imuprity species in teriparatide samples remains within the low levels In this regard, the quantification of the component has been correctly addressed by means of a suitable method, with the objective of ensuring the maintenance of consistently low levels in all the batches.

As general consideration, teriparatide is a small fully human molecule without post-translational modifications with a generally negligible immunogenic potential, as evidenced for the reference product over the 20 years that it has been available on the market.

Ultimately, sufficient data on bioburden and bacterial endotoxins were provided to show adequate control of Microbial Contaminants during the Teriparatide production process.

3.2.3. Specification

Specifications

The specification for Zandoriah (teripratide) active substance includes tests for: appearance (Ph. Eur.), visible particulate matter (Ph. Eur.), identification (Peptide mapping (Ph. Eur.) and assay (RP-HPLC)), potency (assay of Teriparatide (RP-HPLC), protein Concentration (RP-HPLC), biological activity (in-vitro cell based assay)), purity-product related variants (related proteins (RP-HPLC), impurity with molecular masses greater than that of teriparatide (RP-HPLC),
molecular weight (SDS-PAGE), related protein-(LC-MS), host-cell-derived proteins (ELISA), host-cell and vector-derived DNA (real-time PCR), residual of thioredoxin-His-tag (in house)); bacterial endotoxin (gel clot (Ph. Eur.), bioburden (Ph. Eur.), pH (Ph. Eur.).

The proposed tests, methods and specification values are in line with ICH Q6B guideline and with the Ph. Eur. monograph on Teriparatide (01/2017:2829). The specifications are considered adequate.

Analytical procedures

Sufficiently detailed description of analytical procedures has been presented.

Standard compendial methods are used for appearance (Ph. Eur. 2.2.1, Ph. Eur. 2.2.2), bacterial endotoxin (Ph. Eur. 2.6.14), bioburden (Ph. Eur. 2.6.12 and Ph. Eur. 2.6.13) and pH (Ph. Eur. 2.2.3). The following methods are performed in accordance with the Ph. Eur. monograph for teriparatide (2829): peptide mapping, assay (content) by RP-HPLC and product-related variants by RP-HPLC. Sufficient validation data has been presented to support the suitability of the compendial methods. In-house methods are described for biological activity, molecular weight (SDS-PAGE), host cell protein (HCP) and host cell DNA (HCD). An in-house method is also described for the SE-HPLC method to determine impurity with molecular masses greater than teriparatide although this method is based on the pharmacopoeia method described in Ph. Eur. 2829.

In general, the method descriptions are sufficient and a clear description of the sample preparation procedure has been provided.

Regarding the biological activity, the CHMP raised a quality MO requesting the applicant to provide adequate validation data for the biological activity assay.The MO was resolved with the provision of clarification provided by the applicant and the method is adequately described and validated.

A description and validation of the LC-MS analytical method introduced for monitoring the minoacid sequence variant,have been provided and found adequate. However, the Applicant is recommended to update the relevant CTD sections with specific reference to a clear description of the stress protocol adopted for generation of samples used in method validation, as well as all relevant details describing how the analytical range defined during validation adequately supports and encompasses the proposed specification range (**REC1**). Moreover, the Applicant is recommended to further optimise the LC-MS method and to submit any resulting improvement, including updated validation parameters, once available, through an appropriate regulatory procedure (**REC2**).

The proposed specification limits are in line with the Ph. Eur. limits. The approach for setting the specification limits is based on a statistical analysis which involves the determination of the mean ± 3SD, except for the Biological activity where the approach is mean ± 2SD, which is endorsed. The use of different limits for biological activity between release and shelf life can be considered adequately justified. The proposed specification limit for the aminoacid sequence variant is within the limit set by Ph. Eur. monograph for Teriparatide (2829) for any other related protein (≤ 0.5%), is supported by consistent historical batch data, quantitative patient exposure assessment, and non-clinical toxicology studies demonstrating a substantial safety margin. The proposed limit for endotoxin is below the limit specified in the Ph. Eur. Monograph of 50 IU/mg and is therefore acceptable. The proposed specification for bioburden is considered acceptable as it is in line with Ph.Eur. 2.6.34.

Batch analysis

Batch release data has been provided for thirteen AS batches. The batches were used for characterization, stability, process validation and one batch were used in clinical studies. The data provided are consistent and in line with the specifications.

Reference standards

Three reference standards are registered for Teriparatide. The potency is assigned according to the WHO NIBSC International Standard. The use of this reference standard for potency assignment is considered appropriate. The EDQM Teriparatide CRS is used to calibrate the working reference standard, which is used for physicochemical testing. It is stated that the working reference standard is qualified according to the EDQM CRS, a protocol for qualification of the working reference standard has been provided, which includes a series of additional relevant characterization tests in addition to the release tests. The shelf life of the working standard is 12 months and the protocol for stability testing is provided. The EDQM teriparatide system suitability CRS is also used and is considered acceptable. Batch analysis data for all standards mentioned in Section 3.2.S.5 have been provided. Complete pdf leaflets for EDQM standards have also been presented.

Stability

The proposed shelf life for teriparatide active substance is 12 months when stored in the proposed container below -20°C.

Real time, real condition stability data on six commercial scale batches of the AS manufactured using the commercial manufacturing process stored in the intended container for up to 24 months below -

20°C and for up to 6 months under accelerated conditions at 5ºC according to the ICH guidelines were provided.. The selected statistical approach for the evaluation of stability data is a covariance model analysis involving one or more continuous and categorical variables, such as time and batch. In line with ICH Q1E, the results of these models have been provided.

All stability results at the long-term and accelerated storage conditions meet the specifications. No trends are observed during the 24 months stability study, hence the proposed 12 months shelf life in the proposed container, when stored below -20°C, is fully justified.

Photostability testing following the ICH guideline Q1B was performed on three commercial scale batches. No trends were observed, hence no special storage conditions are indicated.

Results on stress conditions (i.e. acidic and basic condition, oxidative, freeze-thaw, thermal stress at 25 for up to 7 days) were also provide on three commercial batches. The stability indicating nature of the methods for related proteins, assay and biological activity has been demonstrated.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product (FP, also referred to as drug product (DP)), is Zandoriah, 20 micrograms/80 microliters solution for injection in pre-filled pen. It is presented as a sterile clear, colourless essentially particle free solution supplied in a cartridge contained in a pre-filled disposable pen.

Each pre-filled pen contains 28 doses of 20 micrograms (per 80 microlitres) to be used in 28 days.

An overfill is considered based on the 2.4 mL label claimed, to supply exact doses for patient use in 28 days, this is adequately justified.

There are no overages included in the manufacture of Zandoriah Solution for Injection.

All the excipients are compendial and widely used in pharmaceutical preparations. All the excipients used are proposed to be controlled using Ph.Eur. requirements. Since Zandoriah FP is designed as a multiple-dose pen device, metacresol is included as a preservative. The use of Metacresol Ph. Eur. compliant as a preservative can be considered acceptable and its appropriateness is established for use as a preservative in other approved products including the reference medicinal product Forsteo. Preservative efficacy test results have been provided.

No excipients of animal/human origin nor novel excipient are used in the Zandoriah formulation.

The primary container closure system of the FP consists of a Siliconized type 1 glass cartridge with a halobutyl rubber plunger and disc seal. The primary container closure is assembled into a disposable Shaily pen device, a multiple-use, fixed dose, non-refillable pen-injector delivery system consisting of three major components: body-subassembly, cartridge holder, and cap as its functional secondary packaging material. Pen components are fully assembled at CinnaGen Co. with non-user replaceable pre-filled cartridges. Needles are not supplied with the product, and insulin pen injection needles can be used (30-32 gauge with a length range between 5-8 mm). The Shaily device components and Zandoriah medicinal product form a single integral product, according to Article 117 of the Medicinal Device Regulation (EU) 2017/745 (MDR). Upon request of the CHMP (MO), the Applicant provided a Notified body (NB) opinion confirming the conformity of the integral device part with the relevant general safety and performance requirements set out in Annex I of the MDR. This MO was considered resolved.

Pharmaceutical development

The Zandoriah FP formulation has been developed to qualitatively and quantitatively match the formulation of the reference medicinal product Forsteo.

Summary results of the relevant formulation studies have been provided and are considered adequate. Based on the information obtained from the reference product, no incompatibility between the excipients is noted and all the excipients result safe for human use and subcutaneous administration.

The quality target product profile (QTPP) and was defined as biosimilar to Foresteo. In response to the MO on control strategy, the CQAs were identified to match the reference product.

The manufacturing process consists of the following main stages: formulation buffer preparation, AS thawing, formulation of the AS, filtration of formulated AS (1st and 2nd filtration), filling and stoppering.

The control strategy of the FP was further substantiated in line with that of the AS when addressing MO2. The manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify CPP, KPP, IPC, IPQC and response parameters (process performance indicators), on the basis of impact on CQA. A risk analysis was performed using the failure mode effect analysis (FMEA). The risk identification was based on the prior knowledge as well as small scale models and scale-up studies. Process parameter ranges were challenged at their edges, demonstrating the robustness of the process. Overall, the approach followed to substantiate the proposed control strategy, the selection of process parameters, their categorisation as CPP/KPP/IPQC and the justification of the acceptance limits can be considered adequate.

In addition, details of the risk assessment and consequent control strategy relative to the administration device has been provided to support that an adequate control is in place to guarantee proper functionality and accuracy of the administered dose.

The main change implemented during the pharmaceutical development of Zandoriah is the change of pre-filled pen administration device from a variable-dose pen device, to the Shaily fixed-dose pen device. The CHMP raised a multidisciplinary MO requesting confirmation of what pen was the one used in the clinical trials and to provide adequate equivalence dose-accuracy data between the two pens. The applicant confirmed that clinical data have been generated by using the variable-dose pen device only, hence, to address the multidisciplinary MO, a satisfactory dose-accuracy comparability study was provided demonstrating that the dose delivered by the two devices can be rated as fully equivalent has been provided.

Adequate information concerning the development of the integral medical device, the rationale for device selection, functional performance and the development of the device's control strategy have been described and adequately justified in line with the Guideline EMA/CHMP/QWP/BWP/259165/2019.

Concerning "baking silicone and sterilisation" activities on glass cartridges, suitable measures are proposed to avoid silicone oil burning when cartridges are stored in the sterile tunnel, ensuring a robust depyrogenation cycle.

The safety and suitability of the proposed container closure system can be overall considered adequately demonstrated through stability studies, extractable/leachable testing, and compliance with pharmacopeia requirements. A toxicological evaluation has been conducted for the leachable species identified in the Zandoriah final product.

A full-scale qualification of the two compounds was performed and PDE values were calculated. No toxicological risk was identified.

Stainless steel insulin needles with a length range between 5-8 mm and ranging between 30-32 gauge have been used during development and in-use stability studies.

3.3.2. Manufacture of the product and process controls

Name, address and responsibilities of the manufacturers and the facilities involved in the manufacturing, testing and batch release of Zandoriah FP are summarised in Table 3.

Table 3: Manufacturing and control testing sites of Zandoriah FP

Manufacturer, address	Responsibility / function	
CinnaGen Research and Production Company (CinnaGen Co.) Address: Plot 87, 88, 3rd Sq., Simin Dasht Non-Governmental Industrial Area, Fardis County, Alborz Province, Iran	Drug Product Manufacturing	
UAB Profarma V.A.Graiciuno 6, LT02241 Vilnius, Lithuania	EU Batch Release and Physical Importation	
Kymos S.L. Ronda De Can Fatjo 7b, Parc Tecnologic Del Valles, Cerdanyola Del Valles, 08290, Spain	EU Batch control: Biological activity test	

For all sites involved in the manufacture, control and batch release of the finished product valid evidence of GMP compliance has been provided.

Zandoriah FP manufacturing process can be considered overall standard for an aseptically prepared sterile solution for injection in pre-filled pen.

In summary, the process consists in the preparation and sterile filtration of the two formulation buffers, thawing of the frozen teriparatide AS, formulation and sterile filtration) of the AS and filling into glass cartridges (, capping, visual inspection, device assembly, labelling and packaging. The make and models of the filters used are given.

A detailed description of the manufacturing process, along with process parameters (CPP, KPP, IPQC) and relevant acceptance limits, has been provided and it is satisfactory.

A single batch size is proposed. The proposed batch size is adequately supported by the FP PPQ exercise, based on three consecutive batches at commercial scale. No blending of multiple batches nor use of sub-batches is proposed. The batch numbering system is in place.

Concerning the different filter integrity tests listed as IPQCs throughout the Zandoriah FP manufacturing process, information concerning the planned integrity tests (bubble point/diffusion test) and the relative acceptance criteria have been provided as prescribed by EMA/CHMP/CVMP/QWP/850374/2015 guideline. Both pre-use and a post-use filter integrity tests are expected for the last chance sterile filtration and a pre-use post-sterilization integrity testing is performed as pre-use integrity test for such sterile filtration step of the FP.

The description of the Zandoriah FP manufacturing process can be considered overall adequate.

Pooling of different AS batches is not permitted for the manufacturing of Zandoriah FP, while pooling of multiple AS containers belonging to the same AS batch is allowed.

No reprocessing is foreseen within the manufacturing process of Zandoriah FP. Moreover, there is no intermediate storage step in the FP manufacturing process.

Hold-times are proposed. Adequate CPPs are in place.

100% of the filling units undergo visual inspection in accordance with Ph. EU 2.9.20 method.

An adequate description of the device assembly procedures, including process parameters, performed by adopting a semi-mechanical process, is given in the dossier.

The manufacturing process has been validated, including media-fill and filter validation. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

The transport validation data package includes simulation and real-world data and is considered acceptable.

Results of Low Endotoxin Recovery (LER) test protocol has been provided showing that LER effect was not observed in Zandoriah drug product.

3.3.3. Product specification

The release and end of shelf-life specification for Zandoriah (teriparatide) finished product includes tests for: general characteristics uniformity of dosage form (content uniformity (Ph. Eur.), extractable volume (Ph. Eur.), leak test by vacuum decay); physico-chemical characteristics (appearance (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.) visible particulate matter (Ph. Eur.), subvisible particulate matter (Ph. Eur.)); device characteristics (appearance by visual Inspection, dose accuracy and gliding force, all in house); identification (assay of Teriparatide (RP-HPLC), assay of metacresol (RP-HPLC), biological activity (in-vitro cell based assay)); purity-product related variants by RP-HPLC and dimer and related substance of higher molecular mass (SE-HPLC); safety (bacterial endotoxin (gel clot (Ph. Eur.) and edotoxin (Ph. Eur.)).

Specification for the applied product is set in accordance with the principles defined in ICH Q6B, TERIPARATIDE Ph. Eur. monograph (2829) in EP, and/or regulatory guidelines. The approach for setting the specification limits is mostly identical to the one proposed for the AS. Briefly, it is based on a statistical analysis. The rationale provided for the specifications is considered appropriate and sufficiently substantiated. During the procedure, upon request of the CHMP, the limits for related impurities have been tightened.

Overall, the quality attributes of the FP are adequately controlled.

Upon request of the CHMP, the applicant confirmed that commercial release testing is performed on packed products. This is considered acceptable as testing the final packaged product provides further assurance of the quality of the medicinal product.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Data on samples of the excipients and cartridges of the FP using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

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

Reference materials

The reference standard used for FP is the same as the reference standard used for the AS.

The container closure system used for Zandoriah preparation is a 3 mL type I Borosilicate glass cartridge with Plunger stopper for cartridge and combiseal (Polyisoprene/Aluminum laminate with a Bromo-butyl rubber cap) assembled into a disposable cartridge to meet USP and Ph. Eur. requirements.

No human or animal origin materials are used in producing the packaging materials for the DP.

Proof of compliance with Ph. Eur. Monographs and relevant guidelines is provided. Specifications and analytical methods were submitted as well as the relevant certificates of compliance.

The materials of construction have been described, and the components proposed for routine storage are considered appropriate for the intended use. Analytical methods were submitted.

Information concerning adequate protection from microbial contamination is provided.

Drawings, photographs of cartridges and device components are provided, along with a description of instruction for use and the key operation steps for a correct use of the integral medicinal product. A brief description of the secondary packaging has been also provided. The description and specifications of the container closure system are acceptable.

3.3.4. Stability of the product

Based on available stability data, the proposed shelf-life of 24 months at 5 ± 3°C with the following storage conditions: "Store in a refrigerator (2°C-8°C) at all times. The pen should be returned to the refrigerator immediately after use. Do not freeze. Store in the original package in order to protect from light", as stated in the SmPC, is acceptable.

Real time/real condition (5°C) stability data of six full scale batches of finished product for 24 months and for up to 6 months under accelerated conditions at 25ºC / 60% RH according to the ICH guidelines were provided. The batches of the FP are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. All batches used in stability studies are stored in the

proposed commercial container. Additional supporting data have been provided with AS manufactured with the old process version (P1, prior to site transfer) and packed in the variable-dose pen device, used in clinical trials.

The FP shelf-life specifications, are the same of the release specifications, except for biological activity and purity product related variants.

The shelf life is evaluated using a covariance model analysis involving one or more continuous and categorical variables, such as time and batch. A graphical representation for each batch with the single data points as well as the results of covariance model analysis have been provided.

All the long term and accelerated stability remain in acceptability criteria values.

Results of in-use stability studies conducted on the product assembled with both the variable-dose pen device and the Shaily fixed-dose pen devices are available. Stability trends for key quality attributes remained within the predefined acceptance criteria across all tested time points, thus indicating that the transition to the fixed-dose pen does not impact the product's stability, with all parameters showing comparable performance to the variable-dose pen device.

The shelf life and its in-use stability of Zandoriah is the same as the one of the reference product.

In addition, samples of the finished product were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Minor differences in related substances were observed in photostability studies. To minimise the potential risk to the quality of the product, protection from light storage condition has been proposed for Zandoriah and duly reflected in the Product Information.

Results from stress condition studies on three batches of the finished product have shown that the analytical stability indicating methods are related proteins, assay of teriparatide, and biological activity. Equivalent results to those obtained for the AS were obtained for the DP. Additionally, teriparatide is degraded when the FP is exposed to thermal conditions (40 ± 2°C) for 7 days and related substances increase.

3.3.5. Biosimilarity

During the procedure a MO was raised by the CHMP as the biosimilarity assessment was not considered appropriate. To address the MO, the applicant further substantiated the comparability exercises conducted to demonstrate analytical similarity between Zandoriah product and the reference product Forsteo.

The Applicant refers to three different approaches (Tiers) adopted to assess biosimilarity of Zandoriah to Forsteo: Tier 1, to be applied to CQA having an high impact on bioactivity, safety and immunogenicity, that is an equivalency analysis by TOST; Tier 2, to be applied to those CQA having a moderate impact on bioactivity, safety and immunogenicity, that is a statistical evaluation using a predetermined quality range; Tier 3, to be applied to low risk CQA, using only graphical representation of data.

Overall, the various statistical approaches used to assess biosimilarity have been sufficiently explained and justified. The established similarity ranges for quantitative CQAs have been adequately summarised in the relative table. The number of batches used for biosimilarity evaluation is overall adequate.

The Applicant provided a summary table (Table 4) including all the testing labs involved in the comparability exercise, detailing all the batches and methods run at each site and reference to method qualification descriptions. The verification of the status of qualification of analytical methods is

satisfactory. It is also specified that to ensure the reliability and comparability of data across different testing sites and campaigns, the Applicant employed bridging samples from previous campaigns. These samples were tested at each site/campaign to confirm method performance and data consistency. This approach is taken to align with ICH guideline and to ensure that data pooling does not introduce variability that could impact the assessment of product quality, safety, or efficacy. This is deemed acceptable. The Applicant provided detailed information on how the TOST was implemented, explaining both the choice of equivalence bounds and the sample size. Furthermore, the Applicant evaluated and discussed the role of the age effect.

As already mentioned under characteirsation of the active substance, a MO was raised in relation to the impurity comparison between Zandoriah and Forsteo. A variant consistent with a single aminoacid variant has been identified. Zandoriah batches have been analysed to assess the levels of this amino acid sequence variant, present in all Zandoriah batches, but not present in the reference product Forsteo. To address this MO, a release test has been implemented for the variant with a specification limit) lower the Ph. Eur. limit for any other related protein stated in Teriparatide monograph (≤0.5%). The limit has been adequately justified on the basis of historical batch data patient exposure assessment, in silico immunogenicity analysis and 28-day repeated dose non-clinical toxicology study - all of them reassuring about potential safety risks. Additionally, Zandoriah contains a very small peptide (34 amino acids of human PTH) manufactured on E. Coli by recombinant DNA technology, which does not contain glycosylation or any other post-translational modification. Moreover, a single aminoacidic substitution would unlikely represent a risk to generate a new immunogenic epitope in such small peptide and that, considering the expected daily dose (20 µg/day), the absolute amount of the variant is extremely small, thus further reducing the plausibility of a clinically meaningful immunogenic impact. Thus, the totality of these factors points toward the conclusion that such trace amount of the mutated variant has extremely low intrinsic immunogenic potential.

As already discussed under analytical methods for the active substance, the rationale provided and the data presented largely support the suitability of the LC-MS assay proposed for monitoring the variant at low levels. Additional updates are recommended to relevant CTD sections to improve the description of the stress protocol used for generation of samples used in method validation (**REC1**). Moreover, the applicant is recommended to continue the optimisation of the LC-MS method and to submit any improved method or optimised parameters resulting in a more robust analytical performance via an appropriate variation (**REC2**).

The biosimilarity assessment can be considered overall adequate to allow a conclusion on the physicochemical and biological similarity between the products and the related MOs are considered as adequately addressed.

Table 4: Comparative analysis of Forsteo and Zandoriah

Attribute		Measurement	Tier	Explanation	Summary of findings
General properties	**protein concentration**	Protein concentration	2	-	Slight difference
	Identity	Peak profile	3	Tier 3 was assigned because nature of the assays is qualitative	Identical
Primary Structure	**Amino Acid Analysis (AAA)**	Molar absorptivity/ Extinction coefficient	2	As it is not expected to have lot-to-lot variation, less batches were analysed	Highly similar
	Peptide Mapping	Peak profile	3	Tier 3 was assigned because nature of the assays is qualitative	Highly similar
	Amino Acid Sequencing	Sequence identity	3	Tier 3 was assigned because nature of the assays is qualitative	Identical
Higher Order Structure	**Circular Dichroism(CD)**	Protein structure	2	Numerical values are checked using tier 2	Highly similar
	Fluorescence	Protein structure	3	As it is not expected to have lot-to-lot variation, less batches were analysed	Highly similar
	Nuclear Magnetic Resonance (NMR)	Protein structure	3	As it is not expected to have lot-to-lot variation, less batches were analysed	Highly similar
Product related variants and impurities	**Charge variant-Ion Exchange (IEX)**	Main peak	2	Numerical values are checked using tier 2	Highly similar
		Peak profile	3	Tier 3 was assigned because nature of the assays is qualitative	Highly similar
	Capillary Gel Electrophoresis (CGE)	variants	2	Numerical values are checked using tier 2	Highly similar
		Peak profile	3	Tier 3 was assigned because nature of the assays is qualitative	Highly similar
	Capillary Isoelectric Focusing (cIEF)	pI value	2	Numerical values are checked using tier 2	Highly similar
		Peak profile	3	Tier 3 was assigned because nature of the assays is qualitative	Highly similar
	Size exclusion (SE)— HPLC SEC/MS	variants	2	Numerical values are checked using tier 2	Highly similar
		Peak profile	3	Tier 3 was assigned because nature of the assays is qualitative	Highly similar
	Reverse Phase -HPLC/MS LC/MS/MS	variants	2	Numerical values are checked using tier 2	Highly similar
		Peak profile	3	Tier 3 was assigned because nature of the assays is qualitative	Highly similar
	RP-HPLC UV	variants	2	Numerical values are checked using tier 2	Highly similar
		Peak profile	3	Tier 3 was assigned because nature of the assays is qualitative	Highly similar
	SDS-PAGE	Profile of Electropherogram	3	Tier 3 was assigned because nature of the assays is qualitative	Highly similar
Functional Assay	**Bioassay by UMR-106 cell line**	Main In Vitro Bioactivity	1	-	Highly similar
	Bioassay using Saos-2 cell line	In-vitro Bioactivity	2	-	Highly similar
	Binding to PTH1R	Receptor biding kinetic by SPR	2	-	Highly similar
	Western Blot	immunoreactivities	3	As it is not expected to have lot-to-lot variation, less batches were analysed this method is qualitative and because of that we assigned to tier 3	Highly similar
Stability studies	**Accelerated stability study**	Similar degradation pathway	3	3 batches is sufficient for degradation pathway	Highly similar
	Stress stability study	Similar degradation pathway	3	1 batch is sufficient for degradation pathway	Highly similar

Other studies	**Assay of Metacresol**	Preservative concentration	2	-	Highly similar
	Appearance	Colour and clarity	3	Visual similarity	Highly similar

3.3.6. Post approval change management protocols

Not applicable.

3.3.7. Adventitious agents

In the manufacturing process of Zandoriah, none of the materials are directly derived from animal source and the cell used are of *E. coli* bacteria origin without risk of animal and human virus contamination.

TSE assessment and certificate of analysis of the starting materials of biological origin and a risk assessment have been presented.

3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

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

During the procedure several MOs were raised and have been adequately addressed. A multidisciplinary MO was raised in relation to the use of the injector pen used in the clinical trial which is different from the one intended for marketing; this MO was resolved by demonstrating delivery dose accuracy for both devices.

A MO was raised related to the control strategy of the AS and FP and it has been addressed by providing a risk assessment and related control strategy in line with ICH Q9.

Another MO was raised in relation to a specified impurity whish is present in the FP. The MO has been resolved by including a suitable analytical control to ensure consistently low levels (BLOQ) of this impurity in the AS.

An additional MO was resolved by providing adequate validation data for the biological activity assay.

Upon request of the CHMP (MO), a Notified body (NB) opinion supporting the conformity of the integral device part of the product with the relevant general safety and performance requirements set out in Annex I of the MDR has been provided is uring the procedure.

To address a biosimilarity MO, the applicant further substantiated the comparability exercises conducted to demonstrate analytical similarity between Zandoriah product and the reference product Forsteo. Another biosimilarity MO was raised in relation to a variant due to a single aminoacid mutation which is present at consistent low level in the biosimilar product but not present in the Forsteo reference material. This MO was resolved by including by duly monitoring the variant to ensure that it is consistently retained at low level in AS batches, by introducing an LC-MS release test in the AS specification.

The applicant is recommended to improve the description of the stress protocol used for generation of samples used in method validation (REC1) and to continue the optimisation of the LC-MS method and to submit any improved method or optimised parameters resulting in a more robust analytical performance via an appropriate variation (REC2).

The demonstration of biosimilarity between Zandoriah and the reference medicinal product Forsteo can be considered acceptable to allow a conclusion on the physicochemical and biological similarity between the two products.

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.

3.4.1. 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. Data has been presented to give reassurance on viral/TSE safety.

3.5. Recommendations for future quality development

The Applicant has been recommended to:

1. The Applicant is recommended to update CTD sections 3.2.S.4.3 and, as applicable, 3.2.S.7.1 to ensure consistency across the dossier, with specific reference to a harmonised and traceable description of the stress protocol used for generation of samples used in method validation LC-MS for the single aminoacid sequence variant. The update is also expected to include confirmation of the reproducibility of the applied thermal stress protocol, as well as all relevant details describing how the analytical range defined during validation (based on mixtures of 0–100% thermally stressed and non-stressed samples) adequately supports and encompasses the proposed specification range for the mutated variant in routine testing.

2. The Applicant is recommended to continue the optimisation of the LC-MS method to monitor the single aminoacid sequence variant, as committed, and to submit any improved method or optimised parameters resulting in a more robust analytical performance via an appropriate variation for analytical method/validation.

4. Non-clinical aspects

4.1. Introduction

Three in vitro Primary Pharmacology studies have been conducted to demonstrate comparability between Zandoriah and Forsteo:

- A qualified surface plasmon resonance (SPR) method with regards to the comparative binding of Teriparatide to PTH1R (parathyroid hormone 1 receptor)
- Two potency assays using two different osteosarcoma cell lines:
    - UMR-106 rat osteosarcoma cell line
    - Saos-2 human osteosarcoma cell line

These data were also submitted as part of the comparability assessment in the Biosimilarity Report.

Moreover, a custom in silico immunogenicity analysis was performed according to the peptide sequence by artificial neural networks in order to have a propensity to over-predict T cell epitopes.

The in vitro comparability program was performed in agreement with the EMA Scientific Advice (EMEA/H/SA/4125/1/2019/III).

A 28-day repeated dose toxicity study in Sprague Dawley rats by subcutaneous route was performed to assess toxicity and immunogenicity of synthesized aa sequence variant (Please refer to Section 4.4. of the assessment report for further details).

4.2. Analytical methods

Not applicable

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Two potency assays were carried out to compare **Zandoriah and the reference medicinal product in two different osteosarcoma cell lines: UMR-106 rat osteosarcoma cell line; Saos-2 human osteosarcoma cell line.**

In the rat Osteosarcoma cell-based (UMR-106) bioassay used for routine assessing the biological activity of Teriparatide, Zandoriah showed closer similarity to the teriparatide reference standard than did Forsteo. However*, deficiencies in the results were identified, therefore data from such assay do not seem to support biosimilarity between Zandoriah and Forsteo.*

In the Human osteosarcoma cell line (Saos-2) based bioassay, the 90% confidence interval of the mean difference was found to be between the equivalence bounds set. The results led therefore to the Applicant's conclusion that the *Zandoriah and the reference medicinal product, Forsteo are equivalent.*

According to the results of PTH1R binding assay *using surface plasmon resonance, slightly higher binding of Zandoriah batches was seen, which may lead to higher potency. However, of the three results batches above the Forsteo range, these are only slightly outside and therefore this data can be considered generally supportive. Overall, data from PTHR1 binding assay can be supported.*

4.3.1.2. Secondary pharmacodynamics

As declared by the Applicant, in line with the relevant biosimilar guidances specifying that biosimilar development can have a more selective and targeted approach to animal testing than the development path for new molecular entities, no secondary pharmacodynamics studies were conducted for the biosimilar candidate. Primary pharmacodynamics studies provide extensive information demonstrating functional similarity of the Zandoriah and Forsteo, thus, no additional nonclinical studies were considered necessary as it has been also stated by CHMP thorough scientific advice procedure. The Applicant's declaration is endorsed.

4.3.1.3. Safety pharmacology

A custom in silico immunogenicity analysis was performed according to the peptide sequence by artificial neural networks in order to have a propensity to over-predict T cell epitopes. Sequence is analysed by artificial neural networks for their affinity to MHC class II alleles. 9-residue peptides with potentially direct interaction with the MHC class II molecules are recognized as binding cores. Residues

next to the binding cores with potential to influence the binding indirectly are also examined as masking residues. Peptides comprising both the binding cores and masking residues are marked as strong binders when their predicted affinity to the MHC class II molecules is lower than 50 nM. The strong binders have greater chance to introduce strong T cell immunogenicity. The peptide did not show significant predicted binding to the MHC alleles.

4.3.1.4. Pharmacodynamic drug interactions

No studies have been undertaken for pharmacodynamic interactions. No requirements for pharmacodynamic drug interactions studies have been detailed in relevant guidelines including the draft CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMEA/CHMP/BMWP/42832/2005). In view of the comparable primary pharmacodynamics for Zandoriah and Forsteo, information in Section 4.5 (Interaction with other medicinal products and other forms of interaction) of the Summary of Product Characteristics of Forsteo are applicable.

4.3.2. Pharmacokinetics

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

4.3.2.1. Pharmacokinetic drug interactions

No pharmacokinetic drug interactions studies have been carried out. No drug interaction study was performed for reference medicine, which is acceptable for a recombinant hormone and in line with Forsteo EPAR. There was no induction of hepatic microsomal enzymes in male and female Cynomolgus monkeys given daily subcutaneous doses of Teriparatide for 3 months.

4.3.2.2. Other pharmacokinetic studies

Not applicable.

4.4. Toxicology

4.4.1. Single-dose toxicity

No comparative single-dose toxicity study was performed in line with the CHMP Guideline, EMEA/CHMP/BMWP/42832/2005 on studies required for similar biological medicinal products.

4.4.2. Repeat-dose toxicity

No comparative repeated-dose toxicity study was performed.

A 28-day repeated dose toxicity study in Sprague Dawley rats by subcutaneous route was performed to assess toxicity and immunogenicity of synthesized aa sequence variant. No toxicological effects were elicited under the test conditions. Therefore, the MTD was considered to be 300 µg/kg bw, which exceeds the human equivalent dose by several orders of magnitude. No immunogenicity was detected in different collected samples from rats.

4.4.3. Genotoxicity

In line with EU guidance on similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005) which advice that other routine toxicological studies such as mutagenicity and carcinogenicity are not required for similar biological medicinal products, comparative genotoxicity studies have not been performed for Zandoriah biosimilar product. As stated in the EPAR, Forsteo was not genotoxic.

4.4.4. Carcinogenicity

In line with EU guidance on similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005) which advice that other routine toxicological studies such as mutagenicity and carcinogenicity are not required for similar biological medicinal products, comparative carcinogenicity studies have not been performed for Zandoriah biosimilar product.

As stated in the EPAR, Forsteo was not carcinogenic in the primate. The major safety concern (pre-clinical) was raised due to the findings from evaluation of the carcinogenicity potential in the 2-year rat bioassay. A pronounced treatment- and dose-related occurrence in malignant metastatic osteosarcoma in both males and females' rats was observed. No cases of osteosarcoma have been reported in Forsteo clinical studies. A second rat oncogenicity study as well as the review of clinical data leads to the conclusion that Forsteo will be safe in this respect in clinical use.

4.4.5. Developmental and reproductive toxicity

According to EU guidance on similar biological medicinal products (EMEA/CHMP/BMWP/42832/2005), reproduction toxicology studies are not required for non-clinical testing of biosimilars.

4.4.6. Toxicokinetics and exposure margins

Not applicable.

4.4.7. Local tolerance

Not applicable.

4.4.8. Other toxicity studies

Not applicable.

4.4.9. Ecotoxicity/environmental risk assessment

As declared by the Applicant, "Given that teriparatide is a biosimilar medicinal product containing 34 amino acids and sharing an identical sequence with endogenous 84-amino-acid-parathyroid hormone (PTH), it would be categorized as a medicinal product consisting of naturally occurring substance. Consequently, the absence of a risk assessment and PBT/vP assessment can be inferred based on its biosimilarity, and the product does not necessitate a Phase II assessment". Zandoriah, being developed as a biosimilar to Forsteo, and having teriparatide as the active substance, is not expected to pose a risk to the environment and dedicated studies for an environmental risk assessment are not required for this medicinal product.

The active substance is a natural substance, 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.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Primary Pharmacodynamics

Surface plasmon resonance measurements were performed to measure the binding kinetics of Zandoriah to recombinant human PTH1 receptor. Similar measurements were also performed for the reference product Forsteo. The calculated KD values for Zandoriah were within the range of those measured for Forsteo. According to the Applicant one-tailed t-test ($t(17)=-1.26$ $p=0.1125$) showed no significant difference between the Forsteo batches and the Zandoriah batches. Calculation to support this claim has been provided by the Applicant.

The Applicant has also performed cell-based potency assays in a rat (UMR-106) and a human (Saos-2) cell lines in which cAMP levels were measured as a surrogate for the binding of teriparatide to the PTH1 receptor expressed in both cell lines.

In a direct comparison against National Institute for Biological Standardization and Control) reference standard in UMR-106 cell-based bioassay, 10% higher relative activity was observed in bioactivity of Zandoriah compared to Forsteo batches, the latter showing lower-than-nominal potency (mean 94.51%), while Zandoriah was closer to 100% (mean 102.31%). When the results are normalized for protein content, the unadjusted "higher" activity observed in Zandoriah is because protein content is close to centre-point of the label claim, while Forsteo batches trend towards the low end (near 90%) of the specification limit. Importantly, there were no differences in retention time using RP-HPLC which confirms structural identity and rule out impurities or variants as causes.

With regards to the human osteosarcoma cell line Saos-2 based bioassay, the Applicant claims that 90% confidence interval of the mean difference falls between the equivalence bounds set.

In vivo assessment of comparative activity has not been undertaken by the applicant. This is acceptable and in line with the EMAs "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1)".

Safety Pharmacology

The Applicant provided data of an in-silico immunogenicity analysis to check the peptide sequence for their affinity to MHC class II alleles. According to these data, the peptide did not show significant predicted binding to the MHC alleles. This data however does not allow for a final conclusion on the immunogenic potential of teriparatide. As indeed pointed out by the Applicant in the report, the immunogenicity analysis by artificial neural networks has a propensity to over-predict T cell epitopes. Experimental verification, such as an in vivo PK study, would need to be carried out for further characterization. Although data coming from an in-silico study are not considered entirely reliable due to the limitations explained by the Applicant, reassurance of lack of immunogenicity may be given by lack of significant MHC alleles binding, with consequent lack of "false positive" which could trigger a T cell response.

Toxicity
In a 28-day repeated dose toxicity study in Sprague Dawley rats by subcutaneous route with synthesized aa sequence variant administered, no immunogenicity was detected in different collected samples from rats. However, it is acknowledged that immunogenicity studies in the non-clinical setting are not predictive of immunogenicity in the clinic, as per ICH S6.

Product information
The proposed information in Section 5.3 of the SmPC is in line with that of the reference product.

ERA
Teriparatide, the active substance of Zandoriah, being developed as a biosimilar to Forsteo, is not expected to pose a risk to the environment as it is categorized as a medicinal product consisting of naturally occurring substance. Dedicated studies for an ERA are therefore not warranted for this kind of products.

Overall, the Applicant's justification for not submitting an Environmental Risk Assessment as per CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), is endorsed.

Overall, the non-clinical package to support the MAA, including the overview and written summaries can be considered acceptable for this type of the MAA.

4.5.2. Conclusions

Generally, the provided data from the Saos-2 potency assay and the surface plasmon resonance (SPR) method PTH1R binding assay support similarity between Zandoriah and the reference medicinal product.

Several deficiencies regarding the UMR-106 potency assay have been identified, which should not be considered reflecting differences in biologic function but rather result from reference medicinal product batch variability, likely due to acceptable manufacturing tolerances for protein content.

A justification for the absence of ERA studies can be considered acceptable.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant. A routine GCP inspection has been requested by EMA as reported in section 3.4.3.

Based on the review of clinical data and the above-mentioned report, CHMP did not identify the need for a further GCP inspection of the clinical trials included in this dossier (see section 3.4.3).

5.1.2. Tabular overview of clinical trials

Table 5: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
PK/PD study					
CM-389	OL, randomised, two-treatment, two-sequence, two-period, crossover study to compare the pharmacokinetics, relative bioavailability, tolerability and safety after a single dose administration of both Test and Reference formulations of teriparatide	20 µg of each formulation of Teriparatide (Test and Reference) administered as a single dose	Healthy female volunteers under fasting conditions.	Equivalence of Zandoriah (P044) and the reference medicinal product, Forsteo Primary PK endpoints: - Cmax - AUC0-inf Secondary PK endpoints - AUC0-t - Tmax - T1/2 -AUCextr% - Terminal elimination rate constant (λz) - Vz/F - CL/F - tlast	60 planned, 66 enrolled and 56 analysed (48 for PK)

OL =open label; SC = subcutaneous

5.2. Clinical pharmacology

5.2.1. Methods

The analytical methods applied during the clinical development included a PK method to measure human plasma levels of the active ingredient teriparatide and a routine serum calcium level test for the PD endpoint.

Pharmacokinetic determination

ELISA-based method was validated in compliance with the European Medicine Agency (EMA) Guideline for Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2).

Validation results obtained in this study showed acceptable results of linearity, parallelism, selectivity, specificity, sensitivity, accuracy, precision, stability, dilution linearity and carry over.

Teriparatide quantification assay in CM-389 clinical study

In the clinical study CM-389, Human PTH (1-34) concentrations were obtained by performing sample analysis with the validated bioanalytical method (validation report no VR2024 teriparatide).

The PK method assay performance in study may be found below.

Table 6: Bioanalytical PK method performance in study CM-389				
Assay passing rate	**Standard curve Performance excluding fall runs**	**QC performance excluding fall runs**	**Method reproducibility**	**Study sample analysis/ stability**
The study consisted of 39 analytical runs, 36 of which were marked as accepted and 3 runs were marked as rejected in respect to the run acceptance criteria	The correlation coefficients of the calibration curves for all accepted runs presented r>0.99 Cumulative bias range: -7.2 to 9%	Cumulative bias range: -11.4 to -1.4% Cumulative precision: ≤ 12.87%	Incurred sample re-analysis was performed in 168/2016 of assayed study samples, and 96.4% of the samples met the pre-specified criteria.	All study samples were analyzed within the established stability period.

The validated method using commercial kit demonstrated acceptable performance for the quantification of Human PTH (1-34) in human K2EDTA plasma when used in clinical study CM-389.

The resulting concentrations of PTH (1-34) in the unknown samples were accepted and reported when the respective analytical run fulfilled its run acceptance criteria in terms of calibration standards, quality controls and selectivity.

Pharmacodynamic determinations

A routine calcium test was used for the evaluation of PD. Serum calcium was determined using the Arsenazo III methodology.

The immunogenicity has not been evaluated in the Study CM-389; therefore, no bioanalytical methods have been submitted.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The clinical program of Zandoriah includes 1 pivotal PK/PD bioequivalence study in healthy female subjects which was designed to demonstrate PK/PD equivalence of Zandoriah and the reference medicinal product, Forsteo, in terms of the primary endpoints (Cmax and AUC0-inf).

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

Not applicable.

5.2.2.2.2. Physiology based pharmacokinetic model

Not applicable.

5.2.2.3. Absorption

According to Forsteo EPAR and SmPC, following subcutaneous injection, absorption of teriparatide was rapid with peak concentrations after 30 minutes and half-life of approximately 1 hour.

5.2.2.4. Bioequivalence

Study CM-389 (EudraCT number 2019-004477-82) was an open label, randomised, two-treatment, two-sequence, two-period, crossover study to assess the bioequivalence after single dose administration of 20 mcg subcutaneous injection of the proposed Teriparatide biosimilar, Zandoriah, versus Forsteo 20mcg in 60 healthy female subjects.

The study was conducted in only one investigational site located in Bulgaria; the date of First Subjects Enrolled was 23 Feb 2020 and that of Last Subject Completed 03 Jul 2020.

In this bioavailability study, Zandoriah (Test Product) was compared to Forsteo 20 micrograms/ 80 microliters solution for injection in pre-filled pen (Reference Product) product of Eli Lilly Nederland B.V. The manufacturer of P044 is Cinnagen, Iran.

Both products, Test and Reference, have same concentration. One pre-filled pen of both products has a volume of 2.4 mL and contains 600 micrograms of teriparatide (corresponding to 250 micrograms per mL). According to the instruction for use of the study for Pen, each subject exactly received 20 µg (equal to 80 µL) of Test product or reference medicinal product.

As the study is an open-label study, the application Pen for Zandoriah and reference medicinal product was different. For the test product (Zandoriah), the instruction for use was used in this study for administration of Zandoriah. The instruction for use (IFU) was provided in the study center and study teams were trained to administer the right dose for each subject. Regarding the reference product, as the administered dose was based on the treatment dose of this product, the instructions for use as mentioned in the SmPC was applied.

The **primary objective** of this study is to assess the bioequivalence following single dose administration of 20 mcg Zandoriah (Test Product) versus 20 mcg Forsteo (Reference Product) in healthy female volunteers under fasting conditions. The primary PK endpoints are Camx and AUCinf.

The **secondary objectives** include additional PK parameters (AUC0-t, Tmax, t1/2, AUCextr%, λz, Vz/F, CL/F, Tlast), change in calcium levels as PD endpoint and evaluation of safety and tolerability. Time of last quantifiable concentration (tlast).

Subject were randomized in 1:1 ratio to one of 2 study sequences (A and B) and received a unique two-digit randomization number. Half of the subjects were randomized to receive Zandoriah first and Forsteo second (Sequence A), and the other half were randomized to receive the drugs in reverse sequence (Sequence B).

On Day 1, each subject was dosed with the assigned treatment (as per randomization to Sequence A or B) under fasted conditions. Food consumption was restrained for 4h after dosing. All volunteers received 20 µg of each formulation of Teriparatide (Test and Reference) by subcutaneous injection in the abdominal wall, with a minimum 3-day washout period between injections. All injections were performed by qualified medical staff of the study center.

According to the inclusion criteria, female volunteers of Caucasian origin, aged 18-45 (both inclusive) with Body Mass index (BMI) between (≥)18.5 and (≤) 30.0 kg/m2 were enrolled; postmenopausal women (defined as age above 45 years and 12 consecutive months without menstrual period) or subjects with history or presence of hypercalcaemia, metabolic bone disease, skeletal malignancies or bone metastases, were not enrolled in the study.

PK sampling time-points were chosen based on the available literature data for teriparatide. In order to determine a reliable estimate of peak exposure, PK sampling scheme was chosen in a way to adequately observe the Cmax normally seen within 0.5 to 2 hours (median 1 hour) and the mean Cmax is generally near 30 minutes.

The terminal half-life of teriparatide is generally in the range of 1 hour. The chosen washout period of 3 days is therefore considered adequate to allow elimination of the drug and to avoid any carryover effects.

Blood samples for Teriparatide measurements were collected at the following time points during each treatment period: Pre-dose (within 30 minutes prior to dosing), 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 45 min, 1h, 1h 15 min, 1h 30 min, 2h, 2h 30 min, 3h, 4h, 6h, 8h and 12 hours post-dose.

A total of one hundred twenty-seven (127) subjects were screened in one study site in Bulgaria and sixty-six (66) subjects were enrolled in the study.

All 66 subjects were randomized, and 56 subjects completed the study.

The Pharmacokinetic (PK) analysis population had 48 subjects and included all subjects who completed the PK sampling for both treatment periods, who did not have any deviations that could affect the PK profile, and who had sufficient concentration data points to accurately estimate the PK profiles for both treatments. According to the European medicines agency (EMA) guidelines (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), subjects with non-zero baseline concentrations > 5% of Cmax, have been excluded from bioequivalence calculation.

The PD Population consisted of 56 subjects, and they were all subjects who completed the PD sampling for both treatment periods, who did not have any major deviations and who had sufficient concentration data points to accurately estimate the PD profiles for both treatments.

The Safety population included 66 subjects, and they were all subjects who received the study drug, i.e. test and/or reference product.

The calculation of PK parameters was done with WinNonlin (WNL) Version 8.3. All statistical analyses were conducted with SAS® Version 9.4 using procedures appropriate for each analysis.

Descriptive statistics for calculated PK parameters include: n, arithmetic mean, SD, CV%, geometric mean, median, minimum and maximum values. For tmax, only median, minimum and maximum values were presented.

The PK parameters for teriparatide were derived by non-compartmental analysis.

Analysis of Variance (ANOVA) was performed using SAS/General Linear Model (GLM) procedure on the log-transformed PK parameters Cmax and AUC0-inf. The ANOVA model included sequence, treatment, period and subject nested within sequence as fixed effects.

Ratios of Least-Squares Means (LSM) were calculated using the exponentiation of the LSM from the analyses on the ln transformed AUC0-inf and Cmax. Consistent with the Schuirmann's two one-sided test for bioequivalence, 90% confidence intervals for the ratios were derived by exponentiation of the confidence intervals obtained for the differences between formulation LSM resulting from the analyses on the ln-transformed AUC0-inf and Cmax. The confidence intervals are expressed as a percentage.

To establish bioequivalence, the calculated confidence intervals for ln-transformed AUC0-inf and Cmax, expressed as a percentage, relative to the reference formulation should fall within the interval of bioequivalence (80%, 125%).

The PK parameters for Teriparatide observed after administration of 20 µg Teriparatide of Test (Zandoriah) and Reference (Forsteo) formulation are presented in table below.

Table 7: Summary of PK parameters by treatment (PK population)

Parameter (Unit)	Statistic	Test (N = 48)	Reference (N = 48)
$AUC_{0\text{-}inf}$ (h.pg/mL)	n	48	48
	Arithmetic Mean	194.73	179.10
	SD	90.38	95.13
	CV%	46.41	53.11
	Median	173.21	159.62
	Minimum	65.33	56.12
	Maximum	487.71	565.43
	Geometric Mean	176.27	161.14
AUC_{extr} (%)	n	48	48
	Arithmetic Mean	5.16	4.87
	SD	6.98	5.88
	CV%	135.28	120.83
	Median	2.54	3.13
	Minimum	0.64	0.69
	Maximum	39.21	37.69
	Geometric Mean	3.01	3.33
$AUC_{0\text{-}t}$ (h.pg/mL)	n	48	48
	Arithmetic Mean	183.41	167.12
	SD	81.11	73.82
	CV%	44.22	44.17
	Median	170.40	154.68
	Minimum	58.96	53.37
	Maximum	431.85	440.38
	Geometric Mean	166.64	152.95
CL/F (L/h)	n	48	48
	Arithmetic Mean	125.38	136.69
	SD	58.45	62.74
	CV%	46.62	45.90
	Median	115.46	125.35
	Minimum	41.01	35.37
	Maximum	306.12	356.38
	Geometric Mean	113.46	124.12
C_{max} (pg/mL)	n	48	48
	Arithmetic Mean	195.52	198.89
	SD	78.37	88.11
	CV%	40.09	44.30
	Median	204.73	186.67
	Minimum	77.83	84.17
	Maximum	473.37	442.62
	Geometric Mean	181.89	182.46
$t_{1/2}$ (h)	n	48	48
	Arithmetic Mean	0.95	0.86
	SD	1.80	0.86
	CV%	189.30	99.61
	Median	0.55	0.57
	Minimum	0.30	0.30
	Maximum	12.83	4.45

Parameter (Unit)	Statistic	Test (N = 48)	Reference (N = 48)
	Geometric Mean	0.64	0.67
λ_z (h^{-1})	n	48	48
	Arithmetic Mean	1.25	1.21
	SD	0.56	0.55
	CV%	44.70	45.54
	Median	1.26	1.22
	Minimum	0.05	0.16
	Maximum	2.33	2.31
	Geometric Mean	1.07	1.04
t_{last} (h)	n	48	48
	Median	3.00	3.00
	Minimum	1.98	2.00
	Maximum	12.00	12.22
t_{max} (h)	n	48	48
	Median	0.17	0.17
	Minimum	0.08	0.08
	Maximum	0.50	0.50
Vz/F (L)	n	48	48
	Arithmetic Mean	140.25	147.18
	SD	172.73	105.93
	CV%	123.16	71.97
	Median	99.27	109.12
	Minimum	38.08	38.96
	Maximum	1204.91	552.82
	Geometric Mean	105.54	119.59

The point estimate of Test/Reference GMR (%) and their 90% CIs of the primary PK parameters were 109.39% (101.50% - 117.90%) for AUC0-inf and 99.69% (92.45 % - 107.49%) for Cmax and were within EMA bioequivalence limits (80.00 - 125.00%). The point estimate of Test/Reference GMR (%) and its 90% CI for for AUC0-t as secondary endpoint was 108.96% (100.86 % - 117.70%), see Table 8.

Intra-subject CV (%) was 22.81 for AUC0-t, 22.11 for AUC0-inf and 22.27 for Cmax. The inter-subject CVs for AUC0-t, AUC0-inf and Cmax are respectively 39.65%, 41.62% and 34.87%.

Post-hoc power based on Cmax, AUC0-inf and AUC0-t was 99.88%, 90.29% and 90.35% respectively.

Table 8: Statistical analysis of PK parameters (PK population)

Statistical Analysis of Pharmacokinetic Parameters (Pharmacokinetic Population)

ANOVA

Comparison	Parameter (Unit)	N	LSMeans Reference	LSMeans Test	% Ratio (Test/Reference)	90% Confidence Interval of Ratio	Intra-Subject CV%	Inter-Subject CV%
Test vs. Reference	AUC_{0-t} (h.pg/mL)	96	152.95	166.64	108.96	100.86 - 117.70	22.81	39.65
	AUC_{0-inf} (h.pg/mL)	96	161.14	176.27	109.39	101.50 - 117.90	22.11	41.62
	C_{max} (pg/mL)	96	182.46	181.89	99.69	92.45 - 107.49	22.27	34.87

N: number of observations used in the analysis.

Additional statistical analysis of PK endpoints was conducted based on the time of recruitment and washout period.

The volunteers were recruited in three groups, greatly separated in time due to the COVID19 pandemic. First group consists of volunteers recruited in February 2020 and completed the study in March 2020. The second group consists of volunteers recruited in March 2020 and completed the study in May 2020 – those are the subjects with the longest washout period. The third group consists of volunteers recruited in May/June 2020 and completed the study also in May/June 2020. Based on the washout period, the subjects were divided into two groups based on the washout period (no noteworthy deviation from the duration vs. extensively excessed due to the COVID19 pandemic).

Based on time of recruitment, the point estimate of Test/Reference GMR (%) and their 90% CIs of the primary pharmacokinetic parameters were 105.94% (97.58 % - 115.00%) for AUC0-t, 107.05% (98.84 % - 115.95%) for AUC0-inf and 98.80% (91.28 % - 106.94%) for Cmax and were within EMA bioequivalence limits (80.00 - 125.00%).

Based on wash-out period, the point estimate of Test/Reference GMR (%) and their 90% CIs of the primary pharmacokinetic parameters were 104.55% (95.35% -114.63%) for AUC0-t, 106.80% (97.58% -116.19%) for AUC0-inf and 98.11% (89.41% -107.65%) for Cmax and were within EMA bioequivalence limits (80.00 - 125.00%).

5.2.2.5. Distribution

Not applicable.

5.2.2.6. Metabolism

Not applicable.

5.2.2.7. Elimination

Not applicable.

5.2.2.8. Dose proportionality and time dependency

Not applicable.

5.2.2.9. Pharmacokinetics in the target population

No studies were conducted in the target population.

5.2.2.10. Special populations

Not applicable.

5.2.2.11. Pharmacokinetic interaction studies

Not applicable.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Endogenous 84-amino-acid parathyroid hormone (PTH) is the primary regulator of calcium and phosphate metabolism in bone and kidney. Teriparatide, PTH (1-34) is the international non-

proprietary name (INN) for the biologically active 34-amino acid N-terminal fragment of the 84-amino acid native parathyroid hormone, PTH (1-84).

Target organs of PTH include bone and kidney. In the bone, PTH plays an important role in maintaining Ca2+ balance and remodeling of the bone. PTH pulses and sustained PTH elevations promote calcium release from the bone using various mechanisms. Direct effects of PTH on osteoblasts and osteocytes and indirect actions on osteoclasts promote both bone formation and bone resorption.

Function of the PTH in the kidney includes decreasing of phosphate reabsorption (primarily in the proximal portion) and facilitating calcium reabsorption (distal portion by transient receptor potential vanilloid 5 (TRPV5) channel). Calcium entry into the renal tubule epithelial cell through calcium channels, TRPV5 or TRPV6, is enhanced in the presence of PTH. Another important effect of PTH in the kidney is the stimulation of the synthesis of the 1a-hydroxylase (by the gene CYP27B1) in proximal tubule cells (by attaching to PTH-1R) and bone cells. This enzyme is responsible for the synthesis of 1,25-dihydroxyvitamin D3 [1,25 2D3], which, in turn, promotes the intestinal absorption of dietary calcium and the release of calcium from bone.

5.2.3.2. Primary and secondary pharmacology

Physiological actions of PTH include stimulation of bone formation by direct effects on bone-forming cells (osteoblasts) indirectly increasing the intestinal absorption of calcium and increasing the tubular re-absorption of calcium and excretion of phosphate by the kidney. As a result, serum calcium levels were obtained during dosing periods in order to evaluate the pharmacodynamic effect observed after single dose administration of the test and reference product.

According to Forsteo EPAR and SmPC, serum total calcium concentration increased transiently reaching a maximum concentration between 4 and 6 hours, returning to baseline within 16 to 24 hours after injection.

The PD markers were: the maximum serum concentration (Cmax); the area under the serum concentration versus time curve from time 0 to last determined concentration (AUC0-t); time to maximum serum concentration (tmax).

Blood samples for calcium levels measurement were collected at pre-dose (within 30 minutes prior to dosing), 2h, 4h, 5h, 6h, 8h, 12h, 16h and 24 hours post-dose (Day 2).

After administration of 20 µg single dose of teriparatide (Zandoriah), arithmetic mean (CV(%)) for Cmax for calcium was 2.27 (3.99%) mmol/L and geometric mean was 2.27 mmol/L. This Cmax was achieved in most subjects within 5.00 hours after the teriparatide administration, with 8 subjects reaching a tmax of 24.00 hours. Arithmetic mean (CV(%)) of AUC0-t was 52.59 (3.57) h.mmol/L and GM was 52.55 mmol/L.

After administration of 20 µg single dose of the reference Forsteo, arithmetic mean (CV(%)) for Cmax for calcium was 2.27 (3.71) mmol/L and GM was 2.27 mmol/L. This Cmax was achieved in most subjects within 4.00 hours after the Teriparatide administration, with 8 subject reaching a tmax of 24.00 hours. Arithmetic mean (CV(%)) of AUC0-t was 52.50 (3.53) h.mmol/L and GM was 52.47 mmol/L.

The difference of least squares means (LSM) of pharmacodynamic parameters observed in Test versus Reference formulation and their 95% CIs didn’t show differences in the calcium levels between treatment groups.

Analysis of Variance for Cmax and AUC0-t for calcium parameters are summarized in table Statistical analysis of Pharmacodynamic parameters below. The point estimate of Test/Reference and their 95% CIs of the PD parameters were 0.08 (-0.27; 0.44) for AUC0-t and 0.01 (-0.01; 0.03) for Cmax.

Additional Analysis of Variance for AUC0-t and Cmax for calcium was performed and the results were re-calculated according to the following ANOVA model: time group, sequence, subjects nested within sequence and time group, period nested within time group, treatment and treatment*time group. The volunteers were recruited in three groups, greatly separated in time due to the COVID19 epidemic. This may be an additional source of variation which must be controlled. So, the parameter "time group" accounts for this circumstance. All required p-values were greater than 0.05, so the time group is not a factor of influence on the results.

The point estimate of Test-Reference and their 95% CIs of the PD parameters were 0.09 (-0.30; 0.47) for AUC0-t and 0.01 (-0.01; 0.03) for Cmax.

Analysis of Covariance for calcium change from baseline are evaluated. The estimated differences of Least Squares Means, and their 95% CIs were 0.001 mmol (-0.02; 0.02 mmol). P-value for treatment difference was 0.924 determining that there was no significant difference among treatment means. Additional ANCOVA for calcium change from baseline was performed and the results were re-calculated according to the following model: baseline, time group, sequence, subjects nested within sequence and time group, period nested within time group, treatment and treatment*time group. The volunteers were recruited in three groups, greatly separated in time due to the COVID19 epidemic. This may be an additional source of variation which must be controlled. So, the parameter "time group" accounts for this circumstance.

All required p-values were greater than 0.05, so the time group was not a factor of influence on the results.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Not applicable.

5.2.3.4. Genetic differences in PD response

Not applicable.

5.2.3.5. Immunological events

No immunogenicity evaluation has been conducted in the bioequivalence study. The Applicant justification includes considerations on the small size of the molecule (low molecular weight, 34 Amino Acid), lack of glycosylation or posttranslational modification which would account for the low immunogenicity potential of teriparatide.

The lower incidence of immunogenicity during post marketing experience for Forsteo (2.8 % of patients who receiving Forsteo) or clinical study of Teriparatide (1.6% of patients who receiving Forsteo as reference product) confirms low immunogenicity for Teriparatide after 52 weeks of the evaluation.

The immunogenicity endpoint was not evaluated in Phase III study conducted for the Iranian licensing of this product and was not included in post-marketing studies in Iran.

The Applicant plans to evaluate immunogenicity as a post-marketing study in EU. The Applicant submitted the protocol of the study which is in line with the other EMA approved teriparatide biosimilar, Livogiva.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Not applicable.

5.2.5. Dose selection and therapeutic window

The dose used in Zandoriah bioequivalence study is the same approved for Forsteo.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

The clinical program for Zandoriah comprises one single pivotal PK/PD bioequivalence study (CM-389) in healthy female subjects which was designed to demonstrate PK/PD bioequivalence of Zandoriah with the reference medicinal product, Forsteo.

Bioanalytical methods

The analytical methods included a PK method to measure human plasma levels of the active ingredient parathyroid hormone (1-34) and a routine serum calcium level test for the PD endpoint.

A commercial ELISA-based method was validated at Comac Medical for determination of PTH (1-34) in human K2EDTA plasma for samples collected in the study CM-389. The full validation of the method for determination of teriparatide was in accordance with the relevant EMA guideline (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2.).

The validation results showed that the ELISA assay was sufficiently accurate, precise (bias ≤ 20% and CV≤ 20%) and selective (no cross-reactivity with iPTH at 20, 50 and 100 pg/mL) to reliably allow the quantification of teriparatide in human plasma samples in the examined range from 2.5 to 231.0 pg/mL. The lower limit of quantitation was less than 5% of Cmax for all subjects. The detection range was adequately defined for the plasma concentration of teriparatide in clinical samples. Human samples (4032) with K2EDTA as an anticoagulant were received, with 2016 samples held as a backup. 2016 samples were analyzed for teriparatide using the ELISA method.

Assessments of the stability of the analyte in frozen human plasma were conducted and long-term stability up to 172 at -80°C and up to 146 days at -20°C was demonstrated.

Following to the assessor’s request, the Applicant described the design of the experiment performed to evaluate prozone/hook effect. Results obtained by diluting QC samples with a concentration approximately 10 times higher than the upper limit of quantification (ULOQ) of the assay were discussed and meet acceptable criteria. These data demonstrated that concentrations within 2200 ng/mL can be accurately measured by the assay after dilution. The maximum concentration used to evaluate the hook effect was considered adequate in light of the pharmacokinetic study data, which did not detect samples with results greater than or equal to 2200 pg/mL. According to the Applicant's response, in compliance with EMA guideline, the linearity of dilution and the prozone effect were assessed correctly for the use of bioanalytical method in the clinical study.

Bioanalytical PK method performance in study CM-389 including precision, accuracy and incurred samples reanalysis (ISR), have been evaluated and calculated, and met acceptance criteria. The ISR has been performed on 169 samples out of 2016, representing 8.4% of samples in line with the GL EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2.

In order to properly measure samples above the ULOQ, re-analyses of these samples were performed after dilution. Reanalyses of samples above ULOQ were conducted correctly, ensuring the reliability of the dilution process, accuracy in sample traceability and preservation of data integrity.

Since in the initial dossier, the Applicant has not included information on the PD method, therefore detailed information on assay used to determine serum ionised calcium was requested. The technical data sheet of the commercial method used to determine serum ionised calcium was provided. The characteristics of the assay and its analytical performance supported its use in clinical studies. The performance of the method when applied in the PD study was not provided, but reliability was ensured by the laboratory's routine diagnostic procedures.

Study CM-389

Study CM-389 was an open label, randomised, two-treatment, two-sequence, two-period, crossover study to assess the bioequivalence after single dose administration of 20 mcg subcutaneous injection of the proposed teriparatide biosimilar, Zandoriah, versus Forsteo 20mcg in healthy female subjects.

The study was conducted in only one investigational site located in Bulgaria; the date of First Subjects Enrolled was 23 Feb 2020 and that of Last Subject Completed 03 Jul 2020.

The primary PK endpoints were Cmax and AUCinf.

The secondary objectives are the comparison of additional PK parameters between the test product and the reference product (AUC0-t, Tmax, t1/2, AUCextr%, λz, Vz/F, CL/F, tlast); the evaluation of change in calcium levels after single dose administration of the test and reference product and the general safety and tolerability of the two formulations.

Subjects were randomised 1:1 to one of the study sequences (Zandoriah first and Forsteo second as sequence A and the reverse sequence B). All volunteers received 20 µg of each formulation of teriparatide (Test and Reference) by subcutaneous injection in the abdominal wall, with a minimum 3-day washout period between injections. All injections were performed by qualified medical staff of the study center.

The PK population included all subjects who completed the PK sampling for both treatment periods, who had no deviations that could affect the PK profile, and who had sufficient concentration data points to accurately estimate the PK profiles for both treatments. The PK Population was used for the descriptive summaries and statistical analyses of the PK concentrations and parameters.

The PK parameters were analysed using ANOVA model including effects for sequence, period, treatment and subject within sequence. The data were transformed prior to analysis using a logarithmic transformation. A confidence interval for the difference between formulations on the log-transformed scale was obtained from the ANOVA model. This confidence interval was then back transformed to obtain the desired confidence interval for the ratio on the original scale.

Overall, the analysis of the PK parameters and the statistical methods are considered appropriate and in line with the standard approach stated in the EMA guideline for bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). ANOVA model on log-transformed PK parameters Cmax, AUC0-inf, and AUC0-t was applied; bioequivalence was tested using 90% confidence intervals of the test/reference ratios of the PK parameters considering an acceptance limit of 80-125% for both primary endpoints.

The overall study design is in line with the EMA guidelines CPMP/EWP/QWP/1401/98 Rev. 1/Corr, EMEA/CHMP/BMWP/42832/2005 Rev1 and obtained EMA scientific advice, and is considered adequate.

The open-label design can be considered acceptable from a PK/PD perspective, although the double-blind design would be more appropriate for the assessment of safety profile. The cross-over design and the wash-out of minimum 3 days is considered adequate due to the short half-life of teriparatide (approximately 1 hour). The wash-out ranges from a minimum of three days for subject enrolled in substitution of withdrawn participants to about 70 days for subjects dosed in March 2020 due to the COVID pandemic. The administration site was the abdomen that is in line with that foreseen for Forsteo that could be injected in the thigh or abdomen.

As per "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues ((EMEA/CHMP/BMWP/42832/2005 Rev1)", in a single dose PK study the primary parameters to be evaluated are AUC0-inf and Cmax in case of subcutaneous administration. The secondary parameters Tmax, volume of distribution and half-life should be also estimated. The PK parameters evaluated in Study CM-389 are in line with the mentioned guideline, moreover additional parameters were included as secondary such as AUC0-t, AUCextr%, terminal elimination rate constant (λz), CL/F and tlast.

The study enrolled all female, aged 18-45 (both inclusive) with Body Mass index (BMI) between (≥)18.5 and (≤) 30.0 kg/m2. The mean (standard deviation [SD]) age was 33.20 (7.03) years, with the youngest subject aged 18 years and the oldest subject aged 45 years. The inclusion and exclusion criteria are considered acceptable. The enrolment of only female subjects is considered acceptable since the systemic exposure of teriparatide (AUC) has 20-30% higher in men than in women, therefore choosing only females provides a more homogeneous population in which detect potential differences between the originator and the biosimilar. As requested by the SA, the upper limit of age for women is 45 years old and no post-menopausal women are included in the study.

Groups were sufficiently balanced with regard to demographic and other baseline characteristics.

In study CM-389, Zandoriah was compared to Forsteo 20 micrograms/ 80 microliters solution for injection in pre-filled pen product of Eli Lilly Nederland B.V. The manufacturer of Zandoriah is Cinnagen, Iran and the batch number is E069ER; the batch number of Forsteo is D019338G.

Both products, Test and Reference, have the same concentration. One pre-filled pen of both products has a volume of 2.4 mL and contains 600 micrograms of teriparatide (corresponding to 250 micrograms per mL).

During development, the administration device - variable dose pen (delivery system allowing manual self-injection with user adjustable volume increments) was changed to Shaily pen (a fixed-dose delivery system). However, it was unclear which device was used in clinical study CM-389. In the CSR, the Applicant refers to Instruction for Use (IFU) provided for Zandoriah and Forsteo, however they were not attached to the CSR, hampering clear understanding of which device was used in the study. The Applicant was asked to clearly state which device was used in the clinical study, to provide a comparability study demonstrating that dose accuracy of the commercial drug product is comparable to that of the product used in the clinical study (see quality part) and details of the measures in place during the clinical study to ensure that the correct dose was administered to each subject. The Applicant has clarified that the variable-dose pen was used as administration device of the clinical trial material. This was further confirmed by the GCP inspection (July 2025) report, i.e., that only one batch E069ER was used and that the variable-dose was the delivery device used. Based on quality data provided, the equivalence of the expelled volume per dose and the dose accuracy between the different administration devices tested is considered sufficiently demonstrated. Regarding the measures in place during the clinical study to ensure that the correct dose was administered to each subject, as confirmed by the GCP inspection report, a specific training on how to use the Vystra pen to inject the IMP was required and it was documented in the source documentation of the subjects with a form reporting a check list to be completed for each injection.

Blood samples for teriparatide measurements were collected at the following time points during each treatment period: pre-dose (within 30 minutes prior to dosing), 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 45 min, 1h, 1h 15 min, 1h 30 min, 2h, 2h 30 min, 3h, 4h, 6h, 8h and 12 hours post-dose. Additional sampling timepoints were added following the SA, since the initially planned 15 minutes sampling time as the first one was considered too late. The sampling timepoints used through the study and close to Tmax (5 minutes as the first sampling time) are considered adequate to detect the Cmax.

As reported in the Forsteo EPAR, following a subcutaneous injection, absorption of teriparatide was rapid with peak concentrations after 30 minutes and half-life was approximately 1 hour. As reported in the table on Summary of PK parameter by treatment reported in the results section, the observed Zandoriah Tmax ranges from 0.17 h (10 minutes) to 0.50 h (30 minutes) confirming that the Tmax is in the expected range.

The number of subjects to be enrolled in Study CM-389 was determined according to the following assumptions: significance level 5% (consumer risk), probability for Type II error 20% (risk of manufacturer), bioequivalence range 80.0% - 125.0%, geometric mean ratio 90% - 110%, coefficient of within-subject variation (CV) for both AUC and Cmax <25% (Farías, J. et al, 2016).

A total of 66 females were assigned at random to one of two sequences A (Test-Reference Product) or B (Reference-Test Product) in order to reach, in case of dropouts, the final number of 56 evaluable subjects necessary for statistical analysis. There were 10 drop-out subjects before the Period 2. As per protocol, subjects withdrawn from the study after randomization could be replaced and 6 out of 10 drop-out subjects were replaced. Among the replaced subjects, 2 (389-1-003, 389 -1-051) were randomised to sequence AB, 4 subjects (389-1-046, 389-1-047, 389-1-052, 389-1-054) were randomised to sequence BA. The reasons of discontinuation were withdrawn consent in 4 cases, positive opiates at the screening of Period 2 (1 case) and history of drug abuse in one case (389-1-052), although the drug abuse was one of the exclusion criteria. These subjects were not included in the PK and PD analysis but were included in the safety analysis.

All six subjects replacing the withdrawn (120, 121, 122, 123, 125, 127) were included in the safety and PD analysis (finally including 56 subjects, 85%). Five out of these six subjects showed pre-dose concentration above 5% of their Cmax and therefore were excluded from the PK analysis as per EMA guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). Subject 389-1-127 was included in the PK analysis, since its pre-dose concentration is lower than 5% Cmax.

Of the 56 healthy volunteers who completed the study CM-389, 15 subjects showed PTH 1-34 pre-dose concentrations and 8 of them (14%) were excluded from PK analysis due to pre-dose concentrations >5% of Cmax in period 1 (i.e. before the first treatment in the study). The final PK analysis includes 48 subjects. The Applicant was asked to provide explanations for the detectable levels of PTH 1-34 in pre-dose samples, before any treatment was given, discuss the potential bias of the analytical method when applied to unknown samples (matrix effect, interference, high intact PTH (i-PTH) level, etc.) and whether and how excluded data may affect the validity of the study result.

The Applicant discussed the possible reasons for pre-dose concentrations in particular in 8 subjects with pre-dose >5% Cmax and therefore excluded from the PK analysis.

The pre-dose concentration > 5% Cmax has been observed in 2 subjects only prior the Period 1, whereas 6 subjects had pre-dose concentration prior both periods. Among these 6 subjects, only one showed pre-dose concentration prior the Period 2 higher than prior the Period 1. This subject had a wash-out period of three days that was the minimum requested by protocol considering the short half-life of teriparatide (about 1 hour). Other 4 participants had three days wash-out period, whereas 3

subjects had longer (8 days and about 2 months) wash-out periods. As a result, carry-over effect has been excluded as possible reason for high pre-dose level in 8 subjects.

The Applicant also excluded that sampling days can be the reason of pre-dose, since in the same day the analysed samples had BLQ or less than 5% Cmax concentrations. Concomitant drug or disease are also excluded.

The Applicant states that the internal metabolism of i-PTH and the formation of its fragments could be the cause of detectable concentrations of PTH 1-34 in pre-dose samples observed in some subjects before treatment.

Three published review articles and reports of other teriparatide biosimilars have been provided to support this hypothesis: the articles (Slatopolsky et al, 1980; Evenepoel et al, 2016; Chen et al, 2018) describe the presence of different PTH fragments in the body's circulation, including the N-terminal fragment.

According to Slatopolsky et al (Parathyroid hormone metabolism and its potential as a uremic toxin. American Journal of Physiology-Renal Physiology. 1980), circulating i-PTH consists of a mixture of intact hormone and fragments from the carboxy- and amino-terminal portion of the PTH molecule. Fragments of the hormone rapidly appear in the circulation following the injection of purified intact PTH (1-84) to animals. The site of cleavage has been localized to amino acid position 33-34 and 36-37 of the PTH molecule. Since the structural requirement for the biological activity of PTH resides within the first 34 amino acids of the amino-terminal portion of the molecule, cleavage of the intact hormone at these positions could potentially give rise to hormonal fragments that have full biological activity. The principal organs involved in the cleavage of intact PTH are the liver and the kidney.

The article of Evenepoel P, Bover J, Torres PU. (Parathyroid hormone metabolism and signalling in health and chronic kidney disease. Kidney International, 2016) reported that "Synthesis and secretion of PTH are tightly regulated by extracellular calcium (Ca2). Hypercalcemia not only reduces overall PTH secretion but also favors release of PTH fragments, whereas hypocalcemia stimulates overall PTH secretion and favors (1-84) PTH release. After secretion, (1-84) PTH and its fragments are further metabolized in the kidney and liver. The half-life of C-terminal PTH fragments is much longer than the half-life of (1-84) PTH, being 2 to 4 minutes. Thus, circulating PTH is a heterogeneous mixture of full-length hormone and fragments, with (7-84) PTH accounting for as much as 50% of overall PTH".

The possible presence of PTH fragment is also reported in the article of Chen H, et al (Parathyroid hormone fragments: new targets for the diagnosis and treatment of chronic kidney disease-mineral and bone disorder. BioMed research international. 2018) in which it is reported that "after secretion, PTh is further metabolised into different fragments in the liver; in the circulation, PTH is composed of full-length (1-84) PTH, amino-terminal PTH, carboxyl-terminal PTH, and middle-PTH; (1-84) PTH accounts for 18% of the circulating PTH; long C-PTH, including (7-84) PTH, (10-84) PTH, and (15-84) PTH, represents only about 5%. Like other C-PTH fragments, (7-84) PTH can be both degraded from (1-84) PTH in the liver and secreted by the parathyroid glands".

The possibility of bias in bioanalytical method to explain the presence of pre-dose levels of teriparatide, was also discussed by the Applicant. Validation results demonstrated that the ELISA-based method used in CMD-389 study was sufficiently specific (no cross-reactivity with i-PTH at 20, 50 and 100 pg/mL) and selective (17 individual sources of human plasma including one lipemic and one hemolyzed sample were analyzed in method validation) to allow reliable quantification of teriparatide in human plasma.

It is not possible to establish with absolute certainty the reason of pre-dose concentrations, however, according to the method validation results and information provided, the cross-reactivity with endogenous PTH 1-34 fragments remains the main hypothesis.

In addition to the presence of PTH fragments as possible explanation of pre-dose concentrations, the Applicant provided information on other teriparatide medicinal products, such as Livogiva and Movymia/Terrosa in which 4 and 1 subjects, respectively, had pre-dose >5% Cmax; a possible reason has not been discussed in that cases and subjects were excluded from the analysis.

As requested, a discussion on whether and how excluded data may affect the validity of the study result has been provided by the Applicant.

A total of 66 females were enrolled to achieve the required 56 evaluable subjects for statistical analysis. The PK analysis population comprised 48 subjects, as 8 (14%) were excluded due to pre-dose concentrations exceeding 5% of Cmax, per EMA guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr).

The study met the primary endpoints (Cmax and AUC0-inf) and the key secondary endpoint (AUC0-t). All 90% confidence intervals (CIs) for the test/reference geometric mean ratios (GMR) were within the predefined bioequivalence limits of 80-125%: 99.69% (92.45-107.49%) for Cmax, 109.39% (101.50-117.90%) for AUC0-inf, and 108.96% (100.86-117.70%) for AUC0-t, respectively.

To investigate if excluded data might affect the validity of the study results, a PK analysis was conducted, including all 56 subjects regardless of whether their pre-dose levels exceeded 5% of Cmax.

The point estimate of test/reference GMR and their 90% CIs of the PK parameters are the following: 102.87% (94.43-112.06%) for Cmax, 107.96% (100.20-116.32%) for AUC0-inf, and 109.22% (101.21-117.85%) for AUC0-t, respectively.

Results of the new PK analysis are consistent with the primary analysis, and the 90% CIs for Cmax, AUC0-inf, and AUC0-last are contained within the acceptance interval (80-125%).

All the above discussion allows to conclude that the exclusion of data from the 8 subjects with pre-dose concentration above the 5% of Cmax does not affect the final results of the study.

PK results

After administration of 20 µg single dose of Zandoriah, arithmetic mean (CV%) for Cmax was 195.52 (40.09%) pg/mL and geometric mean (GM) was 181.89 pg/mL. For Forsteo, the arithmetic mean (CV%) for Cmax was 198.89 (44.30%) pg/mL and geometric mean (GM) was 182.46 pg/mL.

For both products, the Tmax was achieved in most subjects within 0.17 hour, with 1 subject reaching a tmax of 0.50 hours.

In Zandoriah, the concentrations declined with an apparent t1/2 (arithmetic mean [SD]) equal to 0.95 (1.80) hours; in Forsteo, t1/2 is equal to 0.86 (0.86) hours.

Arithmetic mean (CV(%)) of total exposure (AUC0-inf) in subjects after a single dose administration of 20 µg Zandoriah was 194.73 (46.41) h.pg/mL and the geometric mean (GM) was 176.27 h.pg/mL. Arithmetic mean (CV(%)) of systemic exposure to the last determined concentration (AUC0-t) was 183.41 (44.22) h.pg/mL and the GM was 166.64, which are slightly lower than the total exposure AUC0-inf.

In Forsteo, the arithmetic mean (CV(%)) of total exposure (AUC0-inf) was 179.10 (53.11) h.pg/mL and the GM was 161.14 h.pg/mL. Arithmetic mean (CV(%)) of systemic exposure to the last determined concentration (AUC0-t) was 167.12 (44.17) h.pg/mL and the GM was 152.95, which are slightly lower than the total exposure AUC0-inf.

In Zandoriah, the mean (SD) apparent clearance (CL/F) of teriparatide was 125.38 (58.45) L/h with apparent volume of distribution (Vz/F) of 140.25 (172.73) L. In Forsteo, the mean (SD) apparent

clearance (CL/F) of Teriparatide was 136.69 (62.74) L/h with apparent volume of distribution (Vz/F) of 147.18 (105.93) L.

The point estimate of Test/Reference GMR (%) and their 90% CIs of the PK parameters were 99.69% (92.45 % - 107.49%) for Cmax, 109.39% (101.50% - 117.90%) for AUC0-inf, and 108.96% (100.86 % - 117.70%) for AUC0-t.

The 90% CIs of the geometric LS mean ratios for the primary analysis for 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 Teriparatide test product and Forsteo.

Intra-subject CV (%) was 22.27 for Cmax, 22.11 for AUC0-inf, and 22.81 for AUC0-t. The inter-subject CVs for Cmax, AUC0-inf, and AUC0-t were 34.87%, 41.62%, and 39.65% respectively.

Results of the point estimate of Test/Reference GMR (%) and their 90% CIs re-calculated to check for interaction between PK parameters and time group were 98.80% (91.28 % - 106.94%) for Cmax, 107.05% (98.84% - 115.95%) for AUC0-inf, and 105.94% (97.58% - 115.00%) for AUC0-t.

Additional statistical analysis of PK endpoints was conducted based on the time of recruitment and washout period. The sensitivity analysis confirmed the primary findings as the time group was not a factor of influence on the study results.

All p-values for PK analysis were greater than 0.05 level.

The study met its primary (Cmax and AUC0-inf) and key secondary (AUC0-t) endpoints. All of the 90.00% CIs of the test/reference ratios for primary/key secondary PK parameters fall into the pre-defined bioequivalence limits of 80.00-125.00%. Therefore, according to the EMA guideline for bioequivalence, the test product Zandoriah is considered bioequivalent to the reference product Forsteo. Following the assessor's request, the Applicant provided both the SAS scripts and the outputs of the PK/PD ANOVA models. The analyses included the primary model (assessing effects for sequence, period, treatment, and subject within sequence) and an additional model to account for the three-period separation in study conduct due to the COVID-19 pandemic (covering time group, sequence, subjects nested within sequence and time group, period nested within time group, treatment, and treatment-by-time group interaction). The data from the statistical analyses, conducted using a logarithmic transformation, were subsequently backtransformed to provide estimates and confidence intervals for the geometric mean (GM) and GM ratio on the original scale. The SAS outputs fit with the Tables of PK/PD included in the clinical study report.

PD results

Physiological actions of PTH include stimulation of bone formation by direct effects on bone-forming cells (osteoblasts) indirectly increasing the intestinal absorption of calcium and increasing the tubular re-absorption of calcium and excretion of phosphate by the kidney. As a result, serum calcium levels were obtained during dosing periods in order to evaluate the pharmacodynamic effect observed after single dose administration of the test and reference product.

According to Forsteo EPAR and SmPC, serum total calcium concentration increased transiently reaching a maximum concentration between 4 and 6 hours, returning to baseline within 16 to 24 hours after injection.

The PD markers were Cmax, AUC0-t and Tmax. Blood samples for calcium levels measurement were collected at pre-dose (within 30 minutes prior to dosing), 2h, 4h, 5h, 6h, 8h, 12h, 16h and 24 hours post-dose (Day 2).

After administration of Zandoriah, arithmetic mean (CV%) for Cmax for calcium was 2.27 (3.99%) mmol/L and geometric mean was 2.27 mmol/L. For Forsteo, the Cmax arithmetic mean for calcium was 2.27 (3.71) mmol/L and GM was 2.27 mmol/L.

The Tmax was achieved in most subjects within 5.00 hours after Zandoriah, with 8 subjects reaching a Tmax of 24.00 hours. Arithmetic mean (CV(%)) of systemic exposure to the last determined concentration (AUC0-t) was 52.59 (3.57) h.mmol/L and GM was 52.55 mmol/L.

In Forsteo, the Tmax was achieved in most subjects within 4.00 hours, with 8 subjects reaching a tmax of 24.00 hours. Arithmetic mean (CV(%)) of systemic exposure to the last determined concentration (AUC0-t) was 52.50 (3.53) h.mmol/L and GM was 52.47 mmol/L.

ANCOVA model including baseline value, period, sequence, subject within sequence, and treatment as covariates was performed on PD parameters. The point estimate of Test/Reference and their 95% CIs were 0.01 (-0.01; 0.03) for Cmax and 0.08 (-0.27; 0.44) for AUC0-t. The estimated differences of Least Squares Means for calcium change from baseline and their 95% CIs were 0.001 mmol (-0.02 mmol; 0.02 mmol). Statistical analysis did not show significant differences in calcium levels between treatment groups.

All p-values for PD analysis were greater than 0.05 level.

However, it is noted that the calcium concentration demonstrated a t_{max} at 24 hours post-dose in 8 subjects. The Applicant clarified that the observed variability in time to maximum concentration for ionized calcium should not be considered related to any product-related differences, but was caused by phenomenon of calcium homeostasis, as described in literature.

5.2.6.2. Conclusions

In general, the PK/PD study is in line with the requirement of the relevant guidelines. Results show bioequivalence between Zandoriah and Forsteo.

5.3. Clinical efficacy

5.3.1. Dose response study

No dose-response study has been performed and the proposed dose of 20 mcg/daily subcutaneously is the same as of the reference product, Forsteo.

5.3.2. Main study

Only one pivotal PK/PD equivalence study (CB-389) was conducted for Zandoriah in healthy volunteers. No dedicated efficacy study has been performed. Information on the efficacy of teriparatide is based on the documentation of the reference medicinal product Forsteo.

5.3.3. Clinical studies in special populations

Not applicable.

5.3.4. Supportive study

A phase III, randomized, two-armed, double-blind, parallel, active-controlled clinical trial to compare efficacy and safety of biosimilar recombinant human parathyroid hormone [1-34] (Zandoriah) with the

reference product (Forsteo) conducted in postmenopausal osteoporotic women in Iran is provided as supplementary efficacy study.

The primary measured objective of the study was to compare both bone formation (P1NP, BSAP, OC) and resorption biomarkers (CTX and NTX) of patients in both treatment arms over the study period. Also, P1CP concentrations were evaluated in both treatment arms during the study.

As the secondary endpoints:

- Data regarding bone mass densitometry (BMD) at baseline and the 6th month after treatment were gathered in a certain center by DEXA scan. Afterwards, the percentage changes in T-scores relating to the lumbar spine, femoral neck and total hip were considered as the target points of therapy.

- To evaluate the incidence of new fractures in the lumbar spine, dorsal spine and hip and comparing them in the groups, radiography was conducted at the beginning and the end of the study.

Also safety profile of two products was compared during the study.

A total of 104 eligible women patients were enrolled in the study. 52 patients were assigned to group a (Forsteo arm), and 52 patients were assigned to group b (Test Teriparatide product arm). 94 patients completed the trial (45 in group a, and 49 in group b).

Main criteria for inclusion:

Patients were postmenopausal women aged between 45 and 75 who had the following conditions:

1. Being menopause

2. Willingness to participate and signing informed consent form

3. T-score≤-3 at femoral neck or total hip or lumbar spine, without low trauma fractures

4. T-score≤-2.5 at femoral neck or total hip or lumbar spine, with low trauma fractures

5. Age ≥55 years old and T-score≤-2.5 at femoral neck or total hip or lumbar spine, without low trauma fractures

6. Age ≥55 years old and T-score≤-2 at femoral neck or total hip or lumbar spine, with low trauma fractures.

Treatments Administered:

20 µg of rhPTH (1-34) (either Forsteo or Test Teriparatide product) was subcutaneously injected to the patients by special pens (250µg/ml) for duration of 6 months.

5.3.4.1. Results

Demographic and Other Baseline Characteristics

The mean age was 59.8 (7.1) and 65.9 (9.0) for groups Test Teriparatide product and Forsteo respectively. Comparing the baseline characteristic of patients showed no significant differences in treatment groups. Comparing the baseline bone markers of the study including P1NP, OC, BSAP, CTX, NTX, P1CP and Bone Mineral Density (BMD) scores of patients showed no significant differences in treatment groups.

Efficacy results

Evaluation of serum concentration of P1NP, OC, BSAP, CTX, NTX, P1CP and Bone Mineral Density (BMD) scores of patients from baseline to the 1, 3, and 6-month between treatment groups showed for:

-P1NP no significant difference in mean percentage change (P-value=0.46 at the 1st month, P-value=0.28 at 3rd month, P-value=0.27 at 6th month).

-OC no significant difference in mean percentage change (P-value=0.55 at the 1st month, P-value=0.81 at 3rd month, P-value=0.54 at 6th month).

-BSAP no significant difference in mean percentage change (P-value=0.55 at the 1st month, P-value=0.68 at 3rd month, P-value=0.58 at 6th month).

-CTX concentration no significant difference in mean percentage change (P-value=0.65 at the 1st month, P-value=0.54 at 3rd month, P-value=0.69 at 6th month).

-NTX concentration no significant difference in mean percentage change (P-value=0.62 at 1st month, P-value=0.65 at 3rd month, P-value=0.91 at 6th month).

-P1CP concentration no significant difference in mean percentage change (P-value=0.25 at the 1st month, P-value=0.28 at 3rd month, P-value=0.23 at 6th month).

Femoral, lumbar and total hip BMD showed in the Forsteo arm compared to the Test Teriparatide product arm:

-mean femoral neck BMD increased 1.74±1.99% compared to 2.34±1.99% i(P-value=0.83)

-mean lumbar spine BMD increased 8.31±1.78% compared to 8.68±1.32% (P-value=0.87)

-mean total hip BMD increased 0.95±1.87% compared to 6.27±2.45% (P-value=0.09).

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

Not applicable.

5.3.6. Overall discussion and conclusions on clinical efficacy

5.3.6.1. Discussion

No dedicated comparative efficacy study was conducted; this is acceptable since comparability has been proven on the grounds of quality, non-clinical and PK data.

For completeness of MAA the Applicant submitted data obtained for Forsteo, the reference product.

Further, supplementary summary data coming from a Phase III, randomized, double-blind, active-controlled trial to compare efficacy of Zandoriah and Forsteo in postmenopausal osteoporotic women are provided. No significant difference between Zandoriah and Forsteo in the mean percentage change of any bone markers (P1NP, OC, BSAP, CTX, NTX, P1CP) and Bone Mineral Density scores at 1, 3, or 6 months were found. Similarly, no significant differences were observed between the groups in the percentage change in BMD (T-score) over six months at any of the measured sites: femoral neck, total hip, and lumbar spine.

No data on treatment-emergent ADA were provided.

5.3.6.2. Conclusions on the clinical efficacy

No dedicated comparative efficacy was conducted for Zandoriah. To support the MAA the Applicant submitted efficacy data obtained with Forsteo, the reference product, in the approved indications.

Further, results of a comparative study conducted in Iran with Zandoriah and Forsteo are provided as supplementary information. Overall, results support the use of teriparatide in the approved indications and no significant differences between teriparatide and Forsteo were found over a 6-month period regarding the bone markers and bone density score.

5.4. Clinical safety

5.4.1. Safety data collection

The present MAA is primarily based on one pivotal PK/PD study; thus, no dedicated clinical study has been conducted to assess efficacy and safety of teriparatide. The pivotal PK/PD study evaluated as secondary endpoints the safety and tolerability of teriparatide and the reference medicinal product, Forsteo after one single dose of 20 mcg the products. Safety data in the pivotal PK/PD study were collected by performing physical examination, routine laboratory parameters testing, ECG, vital signs measuring, monitoring and recording of the incidence and severity of clinical AEs and SAEs by general questioning in a non-suggestive manner throughout the study. Adverse events of interest for Zandoriah were identified based on the knowledge of the reference product.

Supportive safety results obtained in two post-marketing Phase 4 studies conducted in Iran are provided.

5.4.2. Patient exposure

An open label, randomised, two-treatment, two-sequence, two-period, crossover study to assess the bioequivalence of proposed Teriparatide biosimilar, Zandoriah, for subcutaneous injection after single dose administration of 20 mcg versus Forsteo 20 mcg in 60 healthy female subjects (CM-389) was conducted with first subject enrolled on 23 Feb 2020 and last subject completed on 03 Jul 2020. A minimum 3-day washout period was planned between injections.

The Safety population included 66 subjects, that received at least one dose in Period 1; 10 subjects were not received the second dose (drop-out). Overall, 60 subjects received the test product, and 62 subjects received the reference product. All of the subjects who participated in this study were healthy adult female volunteers of Caucasian origin and aged 18-45 years. Overall, the mean (SD) age was 33.20 (7.03) years, with the youngest subject aged 18 years and the oldest subject aged 45 years. The mean height was 1.58 meters (m) and the mean weight was 60.29 kilograms (kg). The mean BMI was 24.21 kg/m2. The mean age, height, weight, and BMI were similar across sequence groups. There wasn’t reported any medical history, prior medication, nor prior and concomitant procedure.

Further, in the two Phase IV studies study participants were 284 patients with a follow up between 6 and 12 months.

Table 9: Patient exposure (cut off)

	Patients enrolled	*Patients exposed**	*Patients exposed to the proposed dose range*	*Patients with long term** safety data*
Open studies	122	60	60	N/A
Post marketing	284	284	284	193 pts: 12 months 91 pts: 6 months

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

5.4.3. Adverse events

The Safety population included all subjects who received the study drug, i.e. test and/or reference product. In the PK/PD study:

- No serious AEs, and no AEs leading to death were reported in this study.
- All TEAEs were with mild severity, and fifteen were considered as related to the Study Drug.
- Overall, there were three clinically significant changes in hematology parameters, in two subjects, between Screening and End of study visit and there were no clinically significant change in any of the blood chemistry or urinalysis.
- No clinically significant physical examination, vital signs or ECG findings were detected during the present study.

Table 10: Summary of adverse events (full analysis set)

Table 2.7.4 3 Summary of Adverse Events (Safety Population)

Characteristics	Statistic	Overall Study (N = 66)
Total AEs	n (%) E	18 (27.27) 20
TEAEs	n (%) E	18 (27.27) 20
Serious TEAEs	n (%) E	0 (0.00) 0
Severe TEAEs	n (%) E	0 (0.00) 0
Related TEAEs	n (%) E	14 (21.21) 15
TEAEs Leading to Withdrawal	n (%) E	1 (1.52) 1
TEAEs Leading to Death	n (%) E	0 (0.00) 0

E: adverse event; TEAE: treatment emergent adverse event.

E: Number of events; N: The number of subjects in the safety population; n: Number of subjects with characteristic; %: Calculated using the number of subjects in the safety population as the denominator (n/N*100).

5.4.3.1. Adverse drug reactions

As the Applicant claims biosimilarity the ADRs proposed for inclusion by the Applicant in the SmPC are those reported for the reference product, Forsteo.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

ADRs of special interest

The adverse events of interest included special warning and most common adverse events for Teriparatide according to the SmPC of Forsteo. Special warning for Teriparatide includes: serum calcium level, orthostatic hypotension, and Urolithiasis.

Serious ADRs

No cases of Serious Adverse Events were observed during the conduct of the PK/PD study.

Deaths causally related to the medicinal product

No cases of Death were observed during the conduct of the PK/PD study.

5.4.5. Discontinuation due to adverse events

One TEAE led to subject withdrawal.

5.4.6. Safety in special populations

Not applicable

5.4.7. Immunological events

The Applicant states that, considering the low potential of Zandoriah for inducing immunogenicity because of its small size (low molecular weight, 34 Amino Acid), lack of glycosylation or posttranslational modification, together with the low rate of cross-reacting ADA with Forsteo (2.8%), an evaluation of immunogenicity in the PK/PD study was not considered. See Section 5.4.11. for further considerations on immunogenicity potential.

5.4.8. Safety related to drug-drug interactions and other interactions

Not applicable.

5.4.9. Vital signs and laboratory findings

Clinical Laboratory Evaluations

Overall, there were three clinically significant change hematology parameters between Screening and End of study visit (one for Hematocrit and two for Hemoglobin) related to two subjects while all three events were non-serious. One of them had CS change in Hemoglobin values at end of study visit with adverse event (AE) reported as Anemia and Ongoing (This subject received Reference product at her first period and Zandoriah at her second visit). The other subject had CS change in both Hemoglobin and Hematocrit values at end of study visit and also AE reported as Anemia and Ongoing. (This subject received Zandoriah product at her first period and reference product at her second visit).

There was no clinically significant change in any of the blood chemistry or urinalysis.

Vital Signs and Physical Findings

There were overall abnormal non-significant values reported for SBP, DBP and heart rate, but no clinically significant change was noted in any of the parameters.

ECG

There were overall abnormal non-significant values reported for SBP, DBP and heart rate, but no clinically significant change was noted in any of the parameters. The majority of the results were normal, and some cases of abnormal data were reported, but no clinically significant data was noted in any of the parameters.

5.4.10. Post marketing experience

Zandoriah is authorised and marketed in Iran and two post-marketing Phase IV studies were conducted.

Study CG-Zandoriah-401 was a Phase IV observational cohort study designed to evaluate safety and effectiveness of Zandoriah in patients diagnosed with osteoporosis in Iran. The study duration was 12 months and took place between September 2015 (date of first enrolment) and March 2019 (date of last completed). A total of 193 patients were included and analysed (92% female), the mean age was 65(±SD 10.70). The median exposure time is 9 months with a total follow-up od 1436 person-month. Patients received 20 µg Zandoriah daily, subcutaneously in the thigh or abdomen region. Calcium and vitamin D supplements were advised in patients with a low dietary intake of these nutrients.

Overall, 21 patients experienced at least one adverse event classified by SOC as follows: Cardiac disorder 3.63%, Endocrine disorder 3.63%, Gastrointestinal disorder 3.63%, General disorder and administration site condition 3.63%, Musculoskeletal and connective tissue disorder 1.55%, Nervous system disorder 2.59%, Respiratory, thoracic and mediastinal disorders 1.04%, Skin and subcutaneous tissue disorder 1.04%, Vascular disorder 0.52%. In addition, 7 out of 193 patients (3.63%) experienced abnormal serum calcium during the study.

There were no Deaths, no Serious adverse events and no drug discontinuation regarding safety concerns.

Study CG-P044-402 was a Phase IV observational cohort study which had been designed to evaluate safety and effectiveness of Zandoriah in orthopedic indications in Iranian patients. Orthopedic indications such as fracture (osteoporotic and/or non-union fractures), infected elbow prosthesis, osteogenesis imperfect, osseous defects, pyogenic spondylitis were included.

The study duration was 6 months and took place between June 2016 (date of first enrolment) and March 2019 (date of last completed). A total of 91 patients were included and analysed (87.9% female, mean age 66.4 years (SD±15.1)). The median exposure time are 3 with a total follow-up time in the study of 323 person-month. Patients received 20 µg Zandoriah daily, subcutaneously administered once daily by subcutaneous injection in the thigh or abdomen. Calcium and vitamin D supplements were advised in patients with a low dietary intake of these nutrients.

Among 91 patients, 12 patients experienced at least one adverse event classified by SOC as follows: Endocrine disorder 9.89%, Nervous system disorder 1.10%, General disorder and administration site condition 1.10%, Skin and subcutaneous tissue disorder 1.10%, Vascular disorder 2.20%.

There were no deaths, no serious adverse events and no drug discontinuation regarding safety concerns.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

The Applicant submitted a MAA for Teriparatide claiming biosimilarity with the reference medicinal product, Forsteo. For the safety evaluation data from the only pivotal PK/PD study, an open-label, randomised, two-treatment, two-sequence, two-period, crossover trial, are presented. In this study safety and tolerability of Zandoriah were investigated as secondary endpoints and a comparative analysis with Forsteo was carried out, following a single dose of teriparatide (20 micrograms subcutaneous injection). The safety population included 66 subjects that received at least the test or the reference medicinal product; 56 received both administrations. Participants were healthy adult females of Caucasian origin with mean age of 33.2 years (range 18-45). The limited size of the safety population and the open label conduction of the study are considered not ideal and may have biased adverse event collection.

Overall, in this study no Serious AEs, and no AEs leading to Death were reported. In total, twenty AEs were reported in 18 subjects (27.27%). All adverse events were TEAE, of which 15 occurring in 14 subjects were considered related to the study drug. All TEAEs were graded as mild, and one event led to subject withdrawal. The Applicant was requested to provide the description (including severity and outcome) of the TEAE that conducted to the patient's withdrawal together with an evaluation of relationship to study medication. The Applicant provided data on drop-out subjects (N=10) in which the reasons for discontinuation were withdrawn consent in 6 cases, history of drug abuse in 3 cases (although the drug abuse was one of the exclusion criteria) and 1 case of positive COVID test. These subjects were not included in the PK and PD analysis, but were included in the safety analysis.

The AEs reported in the subjects for which the causality has been classified as "certain" are "redness at the application site" and "erythema around the application site"; "headache" was reported as possible related to the medication. These events did not lead to discontinuation from the study.

Only one subject (Subject No. 064), discontinued from the study due the COVID infection and this event is unlikely correlated with study medication. Most AEs occurred in less than 5% of subjects and were evenly distributed among study groups. The type of AEs reported with Zandoriah was in line with those listed in the Forsteo SmPC and comprised mainly Injection site reaction/erythema and Headache. Among SOC and PT, a higher incidence of Nervous System Disorders (15% vs 3.2%, respectively) and Headache TEAE (13.3% vs 4.8%, respectively) was found in Teriparatide-exposed subjects when compared to those exposed to Forsteo. The Applicant corrected the typing error in the updated version of the table [Nervous System Disorders (13.3% vs 4.8%, respectively) and Headache TEAE (13.3% vs 4.8%, respectively)]. The difference in headache rate among treatment arms is recognised by the Applicant and attributed to the small sample size. As headache ADR is already reported in SmPC table 4.8 with common frequency, and the information is adequately provided to HCP.

Laboratory parameters did not show relevant findings, and no safety signals were identified by biochemistry, urine, and serology assessments. Hematology laboratory results showed three non serious AEs: one case of clinically significant data for Hematocrit and two for Hemoglobin. Vital signs, physical findings and ECG remained stable over time.

Since no immunogenicity study has been performed, the Applicant was requested to justify the lack of immunogenicity evaluation by performing an overall assessment of the immunogenic potential of Zandoriah in terms of structural and functional comparability with Forsteo, also in light of concerns raised in the quality assessment regarding the presence of impurities The Applicant initially provided a

general discussion focusing on the low inherent immunogenicity of the molecule and the evidence of high structural and functional comparability demonstrated at the quality and non-clinical levels between teriparatide and the reference product, Forsteo. The aspects on which the discussion is focused are the low molecular weight, the lack of chemical modifications that might impact antigenicity, the equivalent biological activity.

Regarding the presence of thioredoxin His-tag impurity a control strategy has been put in place to achieve comparability to Forsteo.

With respect to the detected aminoacid sequence variant that is consistently present in Zandoriah and absent in Forsteo, the Applicant was asked to include a new DS specification for its monitoring, with the objective of ensuring a consistently low level. The Applicant justified the specification limit also from a toxicological and immunological point of view (see Quality and non-clinical part for further details).

Teriparatide is a small fully human molecule (34 amino acids of human PTH) with a generally negligible immunogenic potential, as evidenced for Forsteo in which only 2.8% of women developing antibodies over 12 months. Zandoriah is manufactured by recombinant DNA technology, without post-translational modifications. The presence of a single aminoacid variant although observed only in Zandoriah, has been sufficiently characterized and the current available data indicate that it is retained at controlled and systematically low levels. This variant would unlikely represent a risk to generate a new immunogenic epitope in such small peptide; moreover, with the expected daily dose (20 µg/day), the absolute amount of the variant is extremely small (~0.04 µg/day, i.e. ~0.67 ng/kg/day for a 60-kg patient), thus further supporting that a clinically meaningful immunogenic impact is unlikely. Non-clinical data, although not perfectly suitable to conclude on immunogenic potential, did not show predictive sign of a potential antibody formation. Therefore, the totality of these factors points toward the conclusion that the variant has extremely low intrinsic immunogenic potential.

Data from studies conducted for the Iranian licensing and from post-marketing experience has been also provided during the procedure. The immunogenicity was not included among the endpoints of the phase III clinical study of 6 months duration conducted in Iran. As reported in Forsteo SmPC, generally, antibodies were first detected following 12 months of treatment. Therefore, the 6-months length of the Iranian phase III clinical trial, although useful to give some information on ADA presence, could be no sufficient anyway to detect antibody formation.

Data from two phase IV observational cohort studies conducted in Iran (one in osteoporosis and one in orthopaedic indication) which have been designed to evaluate safety and effectiveness of teriparatide are also provided, but no immunogenicity evaluation was included.

The Applicant states that based on the comparable efficacy and safety profile with Forsteo in phase III trial, as well as the absence of clinical signal indicative of immune response in post-marketing studies, it can be indirectly concluded that the ADA formation does not represent a concern.

Additional safety data are available from two post marketing observational studies for safety surveillance conducted in Iran, where the product is already marketed. The studies were conducted either for 12 months (CG-P044-401: Sept 2015 – March 2019) or for 6 months (CG-P044-402: Jun 2016 to March 2019) and enrolled, respectively, 193 and 91 patients with osteoporosis and orthopaedic indications. Study population were 88-92% females. Patients received teriparatide 20 mcg /daily subcutaneously (CG-P044-401) or intravenously (CG-P044-402). Median follow up was 3 (CG-P044-401) and 9 months (CG-P044-402). AEs, which were physician-recorded, occurred in 11-13% of

patients with causality judged to be "possibly" related in 93% and 79% of cases. Hypercalcemia was the most common side effect (3.6-9.9%), followed by Nausea (3.11%), Pain (3.11%), Headache, Dizziness, Rash, Muscle spasms (1% each). AEs observed in >1% of the patients pertained to the following SOCs: Gastrointestinal disorders, General disorders and administration site conditions, Musculoskeletal and connective tissue disorders, Nervous system disorders, Respiratory, thoracic and mediastinal disorders, Skin and subcutaneous tissue disorders and Vascular disorders.

In general, post-marketing safety data are in line with the known safety profile of teriparatide (Forsteo SmPC); however, a higher incidence of Hypercalcemia in the post-marketing setting than that reported in the Table of section 4.8 of the SmPC is noted (3.6-9.9% in the post-marketing studies vs "uncommon"). The Applicant discussed the discrepancy of the incidence hypercalcemia observed between the post-marketing studies (common) and the incidence reported for Forsteo (uncommon) and provided a possible explanation such as the incomplete laboratory evaluation and calcium supplement use. This is considered reasonable. The clinical relevance of hypercalcemia is considered negligible as it was not associated with treatment discontinuation. No deaths, no serious adverse events and no drug discontinuation regarding safety concerns in the post marketing studies occurred.

5.4.11.1.2. Adverse drug reactions in the SmPC

Not applicable.

5.4.11.2. Conclusions on clinical safety

According to the current CHMP Guideline on similar biological medicinal products, CHMP/437/04 Rev 1, the clinical development of a biosimilar could solely consist of a comparative PK trial given that the relevant mandatory conditions are fulfilled. This requires that comparability is established on the analytical and in vitro pharmacological level in a stepwise approach. Based on the limited amount of safety data available and the design of the PK/PD study (open-label, cross-over, single dose), a confirmatory assessment of similarity on safety level cannot be deducted from the clinical development programme provided by the Applicant. Thus, similar clinical safety must be inferred from stringent evaluation of analytical comparability, in vitro pharmacology, and results from the comparative clinical PK trial. Immunogenicity was not evaluated during the study. The presence of aminoacid variant is retained at controlled and systematically low levels in Zandoriah and its impact on immunogenicity is considered to be negligible. Thus, the inclusion of immunogenicity potential as "missing information" in the RMP, is not needed.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The Applicant submitted a RMP version 0.2 with data lock point 01 January 2025. The Applicant proposed the following summary of safety concerns in the RMP:

Table 11: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	none
Important potential risks	none

Summary of safety concerns	
Missing information	none

6.1.2. Discussion on proposed safety specification

No safety concerns have been identified by the Applicant.

As required in the guideline Similar biological medicinal products containing biotechnology derived protein as active substance EMEA/CHMP/BMWP/42832/2005 Rev1, immunogenicity should specifically be addressed by the applicant in the submission dossier. Although no immunogenicity study has been carried out with Zandoriah, the inclusion of the missing information "potential for immunogenicity" in the RMP appears not considered justified from a pharmacovigilance point of view in accordance with the GVP.

Medication errors will be closely monitored in PSURs as well as accidental overdose and other safety topics/PSUR safety concerns as recommended in the latest PSUSA procedure (EMEA/H/C/PSUSA/00002903/202409). To comply with the PSUR requirements, the applicant was asked to provide a video accessed via a QR code to instruct the patients on the safe use of the pre-filled pen (see section 8.2). The submitted video was assessed and found acceptable.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

Routine pharmacovigilance proposed by the applicant is reporting and signal detection.

The applicant did not propose any additional pharmacovigilance activities.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

Routine pharmacovigilance proposed by the applicant is reporting and signal detection. At this stage, it is appropriate as there are no RMP safety concerns.

6.2.2.2. Additional pharmacovigilance activities

The applicant does not propose additional pharmacovigilance activities. This is endorsed as the RMP of the reference product has no additional pharmacovigilance activities and considering the absence of RMP safety concerns at this stage.

6.3. Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are proposed by the applicant in the RMP.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

The applicant did not propose any additional risk minimisation measures.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The applicant did not propose any routine risk minimisation measures. Since there are no RMP safety concerns, this is considered acceptable.

6.4.2.2. Additional risk minimisation measures

The applicant did not propose additional risk minimisation measures. Since there are no RMP safety concerns, this is considered acceptable.

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

6.6. PRAC Outcome

PRAC endorsed the PRAC Rapporteur's assessment of the RMP and its conclusions, without further additions.

6.7. Overall conclusion on the Risk Management Plan

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

The Applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

7.1. Pharmacovigilance system

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

7.2. 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.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The same indication approved for Forsteo (reference product) is applied to Zandoriah.

8.2. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Teriparatide SUN and Alunbrig. The bridging report submitted by the Applicant has been found acceptable.

The Applicant submitted a bridging test to demonstrate that the leaflet and IFU of Zandoriah and Forsteo are sufficiently similar in both content and layout. The Applicant declared that no deviation from the reference medicinal product's package leaflet content exists in the Zandoriah package leaflet and belonging to the same therapeutic class as Forsteo, Zandoriah will be used in the same population. Moreover, according to CMDh/100/2007, Rev. 3, the key messages for safe use identified for the reference medicinal product are similar, and the package leaflets (PLs) are designed, laid out, and written in an identical manner to the reference medicinal product.

The Applicant declared that the IFU has been designed in accordance with the recommended procedures provided by the pen device manufacturer (Shaily Company).

The grounds for bridging are based on reference to test with same class of medicinal products, reference to test with same safety issues, reference to test with common design, layout and style of writing.

A multiple bridging is proposed; the parent leaflet considered for key safety messages is that of Teriparatide SUN authorised in 2022, the parent leaflet identified for layout/design is that of Alunbrig (film-coated tablets) authorised in 2018. Both parent leaflets were positively tested for readability. A full User Testing has been submitted for teriparatide SUN in the IMA with one question focused on the IFU.

Regarding the key safety messages in PL and IFU, they are essentially the same between Teriparatide SUN and Zandoriah and no new safety issues are identified. Therefore, the 'parent' and 'daughter' leaflets are sufficiently similar for bridging in terms of safety messages. It is of note that teriparatide SUN PL and IFU are aligned with that of Forsteo.

The design and layout of Zandoriah are the same as Alunbrig PL in which the layout foresees the use of two columns. While the use of the two columns has no impact on the readability of the package leaflet, this cannot be concluded for the user pen manual that is not present in Alunbrig PI. Zandoriah mock-up submitted in the contest of user test bridging includes a portrait format using two columns, whereas it seems not present in Forsteo as well as Teriparatide SUN pen user manuals. The Applicant was asked to discuss the impact of the presence of the two columns in the User pen manual of Zandoriah on the readability considering that the use of the columns may affect the correct reading in a sequential manner of the steps to be followed for the correct administration of the medicinal product. In response to this request, the Applicant provided a mock-up of the PI in module 1.3.2 in which the IFU are written in one column. The updated mock-up was considered acceptable.

8.3. Quick Response (QR) code

A QR code in the package leaflet for the purpose of instructing via a video on how to safely use the prefilled pen has been submitted by the applicant and has been found acceptable.

8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zandoriah (teriparatide) is included in the additional monitoring list since 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 will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Biosimilarity assessment

9.1. Comparability exercise and indications claimed

Zandoriah (teriparatide) is developed as a biosimilar candidate to the reference medicinal product, Forsteo. The claimed therapeutic indications and posology for Zandoriah are those for Forsteo , which is authorised in the EU since 2003 for treatment of osteoporosis in postmenopausal women and in adult men at increased risk of fracture, and treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in adult women and men at increased risk for fracture.

The recommended dose for teriparatide is 20 micrograms once daily administered subcutaneously. The maximum total duration of treatment with teriparatide should be 24 months.

Zandoriah 20 micrograms/80 microlitres is a solution for injection in pre-filled pen. Each pre-filled pen of 2.4 mL contains 600 micrograms of teriparatide (corresponding to 250 micrograms per mL) sufficient to deliver 28 doses of 20 µg/ 80µl/ dose. The presentation is available in a pack of one disposable pen.

The aim of the comparability exercise was to assess the analytical similarity between Zandoriah and Forsteo. The comparability exercise has been based on a set of structural and functional characterization studies covering CQAs that have high impact on biological activity, safety, or immunogenicity.

The clinical program comprises of one single pivotal PK/PD study (CM-389) in healthy female subjects which was designed to demonstrate bioequivalence of Zandoriah with the reference medicinal product, Forsteo, in terms of the primary PK endpoints (Cmax and AUC0-inf). CM-389 study has been conducted according to the relevant guideline.

The Applicant has not conducted any clinical efficacy or safety studies in the sought indications. According to the EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1), a stepwise approach is normally recommended throughout the development programme starting with a comprehensive physicochemical and biological characterisation. A comparative clinical trial may not be necessary; however, this requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. This aspect is further stressed in the draft "Reflection paper on a tailored clinical approach in biosimilar development" (currently in public consultation phase) stating that in general, analytical tools are considered sensitive enough to detect differences between a biosimilar and its reference medicinal product, and comparative efficacy studies may not add essential scientific knowledge in the decision for biosimilar approval. Although for teriparatide, the well-known mechanism of action and receptor mediating effects further support clinical comparability, if the biological aspects are not well-characterised or if the impact of observed differences on clinical outcomes is unclear, it would be challenging to fully rely on comparative analytical data for the demonstration of similar efficacy and safety.

The development of Zandoriah was subject of a Scientific Advice (SA) from the European Medicines Agency (EMA/CHMP/SAWP/344141/2019, June 2019) covering quality, non-clinical and clinical aspects.

Overall, advice on quality, non-clinical and clinical parts has been taken into consideration by the Applicant.

9.2. Results supporting biosimilarity

Quality

Overall, the comparability exercises conducted to demonstrate analytical similarity between Zandoriah and the reference product Forsteo can be considered overall adequate and the biosimilarity can be considered adequately demonstrated. Due to the presence in Zandoriah of a small amount of an aminoacid variant, the Applicant has duly updated the DS specification and has introduced an additional LC-MS test to monitor that the variant is retained at consistently low levels in Zandoriah batches

Non-clinical

Non-clinical PTHR1 binding assay data were submitted, which support biosimilarity between Zandoriah and Forsteo.

Clinical

The **PK/PD** study CM-389 has been conducted according to the relevant guideline. The point estimate of Test/Reference GMR (%) and their 90% CIs of the PK parameters were 99.69% (92.45 % - 107.49%) for Cmax, 109.39% (101.50% - 117.90%) for AUC0-inf (both primary endpoints), and 108.96% (100.86 % - 117.70%) for AUC0-t (key secondary endpoint). Thus, PK/PD study CM-389 met its primary and key secondary endpoints. All of the 90.00% CIs of the test/reference ratios for primary/key secondary PK parameters fall into the pre-defined bioequivalence limits of 80.00-125.00%. Therefore, according to the EMA guideline for bioequivalence, the test product Zandoriah is suggestive of being bioequivalent to the reference product Forsteo.

The serum calcium level was considered for the PD similarity. The PD markers were Cmax, AUC0-t and Tmax. The concentration-time plot did not reveal significant differences between the test and reference product. Analysis of Variance showed that the point estimate of Test/Reference and their 95% CIs of the PD parameters were 0.08 (-0.27; 0.44) for AUC0-t and 0.01 (-0.01; 0.03) for Cmax. All p-values were greater than 0.05. Therefore, the effect on serum calcium level of Zandoriah and Forsteo are similar after single dose administration in healthy volunteers.

No dedicated comparative clinical study was conducted to evaluate the efficacy and safety of Zandoriah. **Efficacy** is derived from data pertaining to the reference product. Data on teriparatide **safety** from the PK/PD study and two post-marketing studies conducted in Iran seem to align with the reference product's safety profile, except for a higher incidence of Nervous system disorders and Headache TEAEs in the PK/PD study and of Hypercalcemia events in the post-marketing studies.

9.3. Uncertainties and limitations about biosimilarity

No immunogenicity evaluation has been conducted by the Applicant due to the low immunogenicity potential of teriparatide. The immunogenicity has not been evaluated even in the pivotal CM-389 study; however, a phase I study is not the best scenario in which explore the potential immunogenicity, due to the crossover design and the single dose administration of the medicinal products.

The uncertainties related to the presence of impurities are duly mitigated by the quality control strategy in place to monitor that such impurities remain at consistent low levels.

Based on the limited amount of safety data available and the design of the PK/PD study (open-label, cross-over, single dose), a confirmatory assessment of similarity on safety level cannot be deducted from the clinical development programme provided by the Applicant.

9.4. Discussion on biosimilarity

Quality

The demonstration of biosimilarity between Zandoriah and the reference medicinal product Forsteo can be considered adequately demonstrated.

The potential risk related to the presence in Zandoriah of a single aminoacidvariant that is absent in the reference product Forsteo has been adequately mitigated by the introduction of a release specification method that will take under due control the presence of such mutated variant at very low levels in all Zandoriah batches, thus allowing to consider as negligible the potential for immunogenicity of this mutated variant.

Clinical

As per stepwise approach foreseen by the GL on biosimilar products, the clinical comparability is strictly dependent on the demonstration of quality as well as non-clinical comparability exercise.

Formally, the acceptance criteria to conclude on bioequivalence were met in study CM-389 for Cmax and AUC0-inf, as well as for AUC0-t.

The Applicant has clarified that the variable-dose pen was used as administration device of the clinical trial material. This was further confirmed by the GCP inspection (July 2025) report, i.e., that only one batch was used and that the variable-dose pen was the delivery device used. Based on quality data provided, the equivalence of the expelled volume per dose and the dose accuracy between the different administration devices tested may be considered sufficiently demonstrated.

No immunogenicity clinical data are available.

The uncertainties related to the presence of impurities are mitigated by the quality control strategies in place. The presence of variant in Zandoriah is retained at controlled and systematically low levels; this variant consists of a single amminoacid substitution unlikely representing a risk to generate a new immunogenic epitope in such a small peptide; the absolute amount of the variant with the expected daily dose is very low; no predictive sign of a potential antibody formation is observed from non clinical data; teriparatide shows a low immunogenicity potential per sè. All these factors point toward the conclusion that such trace amount of the mutated variant has extremely low intrinsic immunogenic potential.

9.5. Extrapolation of safety and efficacy

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