30 March 2022
EMA/105831/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sondelbay

teriparatide

Procedure No. EMEA/H/C/005827/0000

Note

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

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Administrative information

Name of the medicinal product:	Sondelbay
Applicant:	Accord Healthcare S.L.U. World Trade Center Moll de Barcelona S/N Edifici Est, 6a Planta 08039 Barcelona SPAIN
Active substance:	Teriparatide
International Non-proprietary Name/Common Name:	teriparatide
Pharmaco-therapeutic group (ATC Code):	Calcium homeostasis, parathyroid hormones and analogues (H05AA02)
Therapeutic indication(s):	Sondelbay is indicated in adults. Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture (see section 5.1). In postmenopausal women, a significant reduction in the incidence of vertebral and non-vertebral fractures but not hip fractures have been demonstrated. Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture (see section 5.1).
Pharmaceutical form(s):	Solution for injection
Strength(s):	20 µg/80 µl
Route(s) of administration:	Subcutaneous use
Packaging:	Cartridge (glass) in a pre-filled pen
Package size(s):	1 pre-filled pen and 3 pre-filled pens

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List of abbreviations

α	Alpha
°C	Degrees Celsius
µg	Microgram
µL	Microlitre
AE	Adverse event
ALP	Alkaline phosphatase
AM	Arithmetic mean
ANOVA	Analysis of variance
AUC	Area under the plasma concentration versus time curve
$AUC_{\%extrap}$	Percent of area under the plasma concentration versus time curve to infinity extrapolated
AUC_{0-inf}	Area under the plasma concentration versus time curve to infinity
$AUC_{0-tlast}$	Area under the plasma concentration versus time curve to the last measurable concentration
BE	Bioequivalence
BLQ	Below limit of quantitation
BMD	Bone mineral density
BMI	Body Mass Index
BP	Blood pressure
bpm	Beats per minute
C0	Teriparatide predose concentration
Ca	Calcium
cAMP	Cyclic adenosine monophosphate
CBD	Chitin binding domain
CD	Circular dichroism
CEX	Cation exchange chromatography
CI	Confidence interval
CL/F	The apparent total plasma clearance after extravascular administration
CLID	Client ID number
cm	Centimetre
C_{max}	Maximum measured plasma concentration
CO	Carbon monoxide
CoA	Certificate of analysis
CPP	Critical process parameter
CQA	Critical quality attribute
CRF	Case report form
CRO	Clinical research organisation
CRU	Clinical research unit
CS	Clinically significant
CV%	Coefficient of variation
dIRS	Developmental Internal Reference Standard
dL	Decilitre
DNA	Deoxyribonucleic acid
DoE	Design of experiments
DTT	Dithiothreitol
E. coli	Escherichia coli

EC	European Commission
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EPCB	End of production cell bank
EU	European Union
FMEA	Failure Modes Effect Analysis
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GCV%	Geometric CV%
GLSMR	Geometric Least Squares Means Ratio
GM	Geometric mean
GMR	Geometric mean ratio
HBV	Hepatitis B virus
HCL	Hydrochloric acid
HCP	Host cell protein
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMW	High molecular weight
hPTH	Human parathyroid hormone
hr	Hour
HR	Heart rate
IB	Investigator´s brochure
IB	Inclusion bodies
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INN	International non-proprietary name
IMP	Investigational medicinal product
IPCs	In-process controls
IPL	Intas Pharmaceuticals Limited
ISO	International organisation for standards
K3EDTA	Tripotassium ethylenediaminetetraacetic acid
KD	equilibrium dissociation constant
k_{el}	Apparent terminal elimination rate constant
kg	Kilogram
kg/m2	Kilogram per metre square
KPP	key process parameter
L	Litre
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
ln	Natural log
LSM	Least-squares means
MedDRAsq	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency

MIA Manufacturing and Importation Authorisation
mIU Million International Units
mL Millilitre
MMC Mixed mode chromatography
mmHg Millimetre of mercury
mmol Millimole
msec Millisecond
N Sample size; number of observations
NCS Not clinically significant
NKPP Non-key process parameter
No. Number
OD Optical density
PAR Proven acceptable range
PD Pharmacodynamic(s)
PDE Permitted daily exposure
PETG Polyethylene Terephthalate Glycol
Ph. Eur. European Pharmacopoeia
PI Principal Investigator
PK Pharmacokinetic(s)
PR Interval between the P and R waves on the ECG
PRS Primary reference standard
PTH Parathyroid hormone
PTH (1-84) Full-length parathyroid hormone
PTH1R Parathyroid hormone-receptor-1
PV Process validation
QA Quality Assurance
QC Quality Control
QRS Value of the interval between the Q and S waves on the electrocardiogram tracing
QT Value of the interval between the Q and T waves on the ECG
QTc Corrected value of the interval between the Q and T waves on the ECG tracing using Bazett´s [QTcB] and Fridericia´s [QTcF] corrections
R^2 Coefficient of determination
REC Research Ethics Committee
rhPTH (1-34) Recombinant human parathyroid hormone 1-34
RP-HPLC Reverse phase high performance liquid chromatography
RPN Risk priority number
RP-UPLC Reverse phase ultra-performance liquid chromatography
SAE Serious adverse event
SAP Statistical Analysis Plan
sc Subcutaneous
SD Standard deviation
SDS-PAGE Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEC Size exclusion chromatography
SE-HPLC Size exclusion high performance liquid chromatography
SEM Standard error of the mean
SID Screening identification number

SIV	Site initiation visit
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SPR	Surface plasmon resonance
SST	System suitability testing
STRAW	Stages of Reproductive Aging Workshop
$t_{1/2}$	Apparent terminal elimination half-life
TEAEs	Treatment-emergent AEs
t_{last}	Last measurable concentration
t_{max}	Time of the maximum measured plasma concentration
TP	Time point
TSE	Transmissible spongiform encephalopathy
U	Units
ULN	Upper limit of normal
ULOQ	Upper limit of quantitation
USA	United States of America
Vd	Volume of distribution
Vz/F	The apparent volume of distribution after extravascular administration
WCB	Working cell bank
WHO	World Health Organisation
WRS	Working reference standard

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 5 March 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Sondelbay, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Sondelbay is indicated in adults.

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

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

1.2. Legal basis, 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 products

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

The chosen reference product is:

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

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

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

- Product name, strength, pharmaceutical form: Forsteo 20 micrograms/80 microliters solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 10-06-2003
- Marketing authorisation granted by:
  - Union

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

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

- Product name, strength, pharmaceutical form: Forsteo 20 micrograms/80 microliters solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 10-06-2003
- Marketing authorisation granted by:
  - Union
  - (Union) Marketing authorisation number(s): EU/1/03/247/001-002
- Bioavailability study number(s): Study 0258-20

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
25 September 2014	EMEA/H/SA/2880/1/2014/III	Prof. Markku Pasanen, Dr Mario Miguel Rosa

The applicant received Scientific Advice on one occasion as mentioned in the table above for the development of Teriparatide (INTG8) for treatment of osteoporosis in men and women, and for treatment of men and women with an increased risk of fractures due to long-term treatment with glucocorticoids. The Scientific Advice pertained to the following Pre-Clinical and Clinical aspects:

- Acceptability of the proposed physico-chemical tests for INTG8 and Forsteo to establish complete similarity
- Acceptability of the differences between the pen device used in the INTG8 and Forsteo
- Acceptability of the proposed tests as part of release and stability specification

- Sufficiency of the physico-chemical characterisation and comparative *in vitro* pharmacodynamic studies with Forsteo
- Sufficiency of a comparative repeat-dose toxicity study at three dosage levels, viz. 1x, 2.5x and 5x of human equivalent dose
- Acceptability of the proposed pharmacokinetic equivalence study
- Acceptability of the proposed comparative physicochemical, toxicological and pharmacokinetic clinical study
- Sufficiency of the comparative pharmacokinetic study for INTG8 described above is sufficient to establish clinical biosimilarity
- Acceptability of the proposed Phase III study design.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Peter Kiely Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	5 March 2021
The procedure started on	25 March 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 June 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 July 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 December 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	16 December 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 December 2021

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 January 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sondelbay on	27 January 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Osteoporosis is a systemic disorder characterised by low bone mass, microarchitectural disruption, and skeletal fragility, resulting in decreased bone strength and an increased risk of fractures of the hip, spine and wrist. Decreased bone strength is related to many factors other than bone mineral density (BMD), including rates of bone formation and resorption (turnover), bone geometry (size and shape of bone), and microarchitecture.

The World Health Organization (WHO) has defined diagnostic thresholds for low bone mass and osteoporosis based upon BMD measurements compared with a young-adult reference population (T-score).

Due to its prevalence worldwide, osteoporosis is considered a serious public health concern. Currently it is estimated that over 200 million people worldwide suffer from this disease. Approximately 30 % of all postmenopausal women have osteoporosis in the United States and in Europe. At least 40 % of these women and 15-30 % of men will sustain one or more fragility fractures in their remaining lifetime. Ageing of populations worldwide will lead to a likely increase in the incidence of osteoporosis in postmenopausal women.

2.2. About the product

INTG8 (Sondelbay) (teriparatide 20 µg/80 µL solution for injection) has been developed as a biological medicinal product claimed to be biosimilar to the EU reference product Forsteo which contains recombinant human teriparatide (rhPTH (1-34) as active substance (20 µg/80 µL solution for injection).

The claimed therapeutic indication is: 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 applicant is claiming all of the approved indications of the reference product.

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

INTG8 (biosimilar teriparatide, 20 µg/80 µL solution for injection) is supplied in a pre-filled multi-dose pen injector. The reference product Forsteo (20 µg/80 µL solution for injection) is also supplied in a pre-filled disposable pen containing 28 doses however the devices are not identical.

2.3. Type of application and aspects on development

The clinical development presented in this application consists of one single dose three period three way

crossover PK study (Study 0258-20) in healthy volunteers comparing teriparatide (INTG8) with, EU sourced Forsteo and US sourced Forteo for bioequivalence and subsequently, biosimilarity.

As this is an EU centralised application the focus of this assessment will be on the comparison of the EU approved teriparatide (Forsteo) with INGT8 (teriparatide).

This clinical study evaluated PK, PD, safety and immunogenicity of INTG8 compared to Forsteo. CHMP scientific advice was sought regarding the clinical development program.

Scientific Advice was given to the applicant as part of scientific advice procedure for teriparatide (INTG8) and as part of a scientific advice EMEA/H/SA/2880/1/2014/III. The advice given in the clinical part of the EMA-SA was generally taken into consideration and the development programme aligned accordingly however there were some deviations and omissions.

The only clinical data included in this submission to support biosimilarity are from a comparative PK study. In line with the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/05 Rev.1) it was agreed that a phase III efficacy study is not regarded as necessary if the molecule can be reliably shown to be highly similar to Forsteo and comparable PD as well as PK data is provided in support of biosimilarity. Specific advice was given regarding proposed PK study design with particular reference to study design, sample size and subject population for a two-treatment cross-over study comparing INTG8 with the EU reference product Forsteo however the applicant subsequently conducted a three treatment, three period crossover study comparing INTG8, Forsteo and Forteo. The study population was originally to comprise of 90 healthy post-menopausal women all of whom were to be of Indian ethnicity and recruited at a single facility in India. In Study 0258-20 both males and postmenopausal female healthy volunteers were recruited.

Following direction from the CHMP to define a strategy to demonstrate potential immunogenicity of INTG8, as part of the scientific advice the applicant proposed to conduct an open label, single arm study on 100 postmenopausal women treated with daily subcutaneous doses of 20 micrograms of INTG8 for a period of 12 months. This approach was supported by CHMP with comments on the proposed power calculation and uncertainty regarding the impact of antibodies on PK/PD, efficacy and safety on the PTH1 and PTH2 receptors with multiple binding sites. The applicant has clarified that this study has not yet been carried out, but that the intention is to carry out this study in the post approval setting to more comprehensively look at the immunogenicity potential of INTG8. While the post marketing immunogenicity study will not be a condition of approval, there is no objection to the applicant carrying out this study post approval, and then submitting the data for assessment.

A paediatric waiver in accordance with Article 13 of Regulation (EC) No 1901/2006 as amended, was granted for Forsteo in 2011. This applies to all subsets of the paediatric population from birth to less than 18 years of age on the grounds that the specific medicinal product is likely to be unsafe. The SmPC of the reference product Forsteo contains the warning that Forsteo should not be used in paediatric patients (less than 18 years), or young adults with open epiphyses. The SmPC for teriparatide contains the same warning. This is acceptable.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a solution for injection containing 20 micrograms of teriparatide per dose as active substance.

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

The product is available as 2.4 mL solution in a cartridge (siliconised Type I glass) with a plunger (bromobutyl rubber), disc seal (bromobutyl lined aluminium seals), assembled into a disposable pen. One pre-filled pen of 2.4 mL contains 600 micrograms of teriparatide (corresponding to 250 micrograms per mL). Sondelbay is available in pack sizes of 1 pre-filled pen or 3 pre-filled pens.

2.4.2. Active Substance

General Information

The active substance (INN: teriparatide, company code: INTG8) is a recombinant, active N-terminal 34 amino acid fragment of the endogenous human parathyroid hormone (PTH). It is expressed in *Escherichia coli* (*E. coli*). The molecular formula is $C_{181}H_{291}N_{55}O_{51}S_2$. The amino acid sequence is presented in the dossier and corresponds to 4118 Da. INTG8 has been developed as a biosimilar to the reference product, the EU-approved Forsteo and the US-approved Forteo (Eli Lilly).

Physiological actions of endogenous 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. Binding of PTH to PTH-specific cell-surface receptor (PTHR1) mediates the biological action of PTH. Upon receptor binding, activation of phospholipases & adenylate cyclase occurs, increasing intra-cellular levels of cAMP and calcium. The anabolic effect of PTH on bone formation is attributed to osteoblastogenesis, attenuation of osteoblast apoptosis & activation of pre-existing osteoblasts.

Manufacture, process controls and characterisation

The active substance is manufactured and tested at Intas Pharmaceuticals Limited, Gujarat, India (IPL). Appropriate evidence of GMP has been provided.

Description of manufacturing process and process controls

In general, the process is typical of protein expression in an *E. Coli* bacterial cell system and is adequately described. The INTG8 active substance manufacturing process is divided into upstream and downstream manufacturing. The batch scale is defined for the production fermenter during upstream manufacturing. INTG8 is expressed as a fusion protein of teriparatide linked to a chitin binding domain (CBD) fusion tag. The purpose of this tag is to increase the size of the transcript to stabilise its expression in *E. Coli*. The teriparatide fusion protein is expressed in insoluble inclusion bodies.

The upstream process begins with thawing of a vial of the working cell bank (WCB) and seed cultivation. Cells are added to a fermenter and fermentation runs for a defined time. Cells are lysed which releases the inclusion bodies (IBs). The IBs are resuspended, centrifuged and washed. The pellet undergoes further homogenisation and washing. The final step of the upstream process is storage of inclusion bodies. An inclusion body hold time is registered and supported by hold time data.

The downstream process starts with thawing of the IBs and solubilisation. The reduced solubilised IBs undergo refolding. The refolded material undergoes ultrafiltration/diafiltration, followed by chromatography purification. The fusion protein is cleaved to remove the CBD tag. Further chromatography purification is carried out. The solution is then diafiltered, diluted and filtered. In the final step of the manufacturing process, the active substance is transferred to storage.

The manufacturing process is controlled by measuring the relevant inputs and outputs for each manufacturing step. The inputs are controlled as operating parameters, these are parameters that can be directly controlled and are therefore analogous to process parameters. The list of which operating parameters are critical process parameters (CPPs) is registered in S.2.4. The term 'process attribute' is used in place of 'in process controls', which is acceptable terminology as they still serve to ensure the process is controlled and reproducible. Process attributes are recorded as either action limits or reported as acceptance criteria. This approach is in line with regulatory guidance for in-process controls (IPCs) and is therefore acceptable. In general, the process attribute action limits and acceptance criteria are considered acceptable.

Control of materials

The applicant provided a list of raw materials used in the active substance manufacture including where in the process they are used as well as supplier, in-house specifications and a representative Certificate of Analysis (CoA). All components (resins, filters and containers) used in the manufacture of the active substance are listed along with identification of where in the process they are used. Details of all chromatography columns as well as wash and elution conditions, and sanitation are provided.

There are no materials of human or animal origin used in manufacture of INGT8 active substance, except one material, which is low risk as its origin is not a transmissible spongiform encephalopathy (TSE) risk species and its processing conditions are harsh.

The applicant has adequately described the microbial species and strain used as a host cell. The genetic manipulation and establishment of the expression vector and transfection of cells have likewise been adequately described.

A two-tier cell banking system is being used. Overall, the MCB is considered to be appropriately characterised in line with ICH Q5D and ICH Q5B. Similar testing has been carried out on the WCB and is also considered acceptable.

An end of production cell bank (EPCB) was prepared and all of the acceptance criteria were met as per the specification. Results for identity, purity, nucleotide sequencing, copy number, viability and plasmid retention are provided in the dossier. The generation number is controlled by proxy through the OD limits.

MCB stability was tested over a 10-year period to ensure stability. Viable cell count, plasmid retention and purity were evaluated. WCB stability has been monitored over a 6-year period for viability, plasmid retention and purity (all data complies with specifications). The applicant's proposal to re-test MCB every 5 years and WCBs every 6 months is considered acceptable to ensure the stability of the cell bank.

The applicant has outlined testing to be performed following the generation of future working cell banks which includes tests for purity by growth on selective media, restriction analysis of plasmid DNA, nucleotide sequencing, gene copy number, bacteriophage testing, viability and plasmid retention. The protocol for establishing new WCBs is considered acceptable.

Control of critical steps and intermediates

All operating parameters are designated into following categories, Critical Process Parameters (CPPs), Key Process Parameters (KPPs) and Non-Key Process Parameters (NKPPs). A CPP is a Process Parameter whose variability has an impact on a critical quality attribute (CQA) and the variability is significant enough to result in a product failing to meet the product specifications. A KPP is a process parameter that, if varied within the characterisation range, results in significant variation in process consistency, but less significant variation in a CQA. If the expected range (in case of process performance parameter) or proven acceptable range (in case of operational parameter) is exceeded, it may affect the performance of the process (e.g., yield, quantity) but not product quality. NKPP are defined as an input process parameter whose variability within a characterised range does not impact the process performance. These parameters that have been demonstrated to be easily controlled or have a wide acceptable range (compared to its operating range) are called NKPPs. A Performance Parameter/ Process Attribute is a process output variable or outcome that cannot be directly controlled, but is an indicator that the process has performed as expected. As such they are analogous to IPCs. They can have acceptance criteria which may lead to batch rejection or can have action limits which may result in investigations.

The applicant has provided specifications for control of the inclusion body intermediate post-harvest. Testing is performed for microbial and protein purity. This is acceptable, considering that extensive testing is performed downstream both in-process and at release.

Process validation and/or evaluation

Process validation (PV) campaigns were performed, in each case process validation reports have been provided. The acceptance criteria for process validation studies are the same as the ranges registered for the commercial manufacturing process.

For the initial campaign (PV1), consecutive batches were manufactured at commercial scale which all successfully passed the acceptance criteria for operations parameters and performance parameters. Following completion of the formal process validation, a new manufacturing suite was qualified. This necessitated repeating the process validation using additional lots (PV2). The majority of operational parameters and process attributes were within their respective acceptance ranges.

Following some additional changes, the process was again revalidated with further lots (PV3). These batches all passed validation apart from some minor deviations.

Overall the data adequately demonstrate that consistent process performance and acceptable product quality are achieved during routine commercial scale manufacturing. All process validation lots met the active substance release acceptance criteria.

Process validation data was provided to demonstrate clearance of process related impurities. Clearance data for host cell protein (HCP) and DNA show that that the process is capable of adequately removing these impurities and further assurance is provided by the active substance release tests for these impurities. Residual enterokinase has been measured using an ELISA. Additional data is also available from small scale multivariate studies demonstrating that the CEX2 step can clear enterokinase when run at the edges of the

proposed ranges. The data package is sufficient to confirm that enterokinase will be consistently cleared during routine manufacture and therefore it is acceptable not to test for this impurity at release.

The levels of residual CDB tag and uncleaved residuals were measured using an SE-HPLC method. The method validation data show that each peak can be clearly differentiated. Both impurities are captured as part of the high molecular weight (HMW) species measured by SE-HPLC. The levels of CBD and uncleaved fusion protein are controlled by an in-process test with acceptance criteria.

Data on the levels of endotoxin and bioburden across the manufacturing steps has been provided. Both of these are also tested at active substance release. In-process testing for bioburden generally shows the active substance process to have low bioburden.

Hold times have been justified.

Data has been provided to support the current resin and membrane reuse conditions. A protocol for validation of the full lifetime of the resins and filters has been provided and is acceptable.

The active substance and finished product are currently manufactured at the same site, therefore shipping validation data for the active substance is not required.

A risk assessment for extractables and leachables was provided and is acceptable.

Manufacturing process development

The commercial process was validated in the PV1 campaign and then revalidated in the PV2 campaign following the move to a new site. The process was validated a third time after further changes (PV3).

A comparability study was presented where different processes are compared. While no formal comparability acceptance criteria are proposed, the batch release data provided does not indicate any obvious differences between the processes. The extended characterisation testing was also supportive of comparability. Comparability data for inclusion bodies and impurity data was also provided, which were supportive of comparability. Furthermore, in-process samples from twelve at-scale batches were analysed by RP-UPLC, which again supported comparability. Overall, the data package submitted sufficiently demonstrates comparability between the manufacturing processes.

As part of the process development, a Failure Modes and Effects Analysis (FMEA) evaluation was used to quantify risk to process parameters by assigning scores to severity, occurrence and detection. The individual scores are multiplied to generate a risk priority number (RPN). This is considered a standard approach to risk assessment and is in principle acceptable. The FMEA scores were used to identify those high-risk parameters to study further in small scale process characterisation studies. The small-scale models were demonstrated to be sufficiently reflective of the full-scale commercial manufacturing process. The small-scale studies were conducted using design of experiments (DoE) univariate and multivariate studies. The outputs tested in each of these studies were deemed to be appropriate for determining the impact of process parameter variation on CQAs. Where the studied range was not found to have an impact on the relevant outputs, the characterised range was denoted as the PAR. Where there were significant effects or multivariate interactions, the PARs were set on the basis of the prediction profiler and contour plots in which narrower ranges are predicted not to impact on the outputs. The final PARs are all supported by relevant experimental data. Overall, the applicant has generated a significant body of data to justify the registered ranges and their criticality. The process development studies and the resulting control strategy are therefore considered acceptable.

Characterisation

The characterisation was carried out using a representative active substance batch and one batch each of the EU reference product (Forsteo) and of the US comparator (Forteo). Primary structure was analysed using several approaches. N-terminal sequencing was carried out using Edman degradation and the N-terminal 15 amino acids correspond to the sequence defined in the Ph. Eur.

Higher order structure was analysed by circular dichroism, FTIR, intrinsic fluorescence, 1D-NMR, and 2D NMR. The secondary and tertiary structure profiles of INTG8 were as expected for teriparatide.

Product related variants were determined using RP-UPLC. Characterisation data is provided for oxidised impurities, including the well-known teriparatide impurities. Data is also provided for other related proteins and total related proteins. Additional impurities analysed by RP-UPLC are provided in the batch data section which includes succinimide and deamidated forms. Charge and size variants were analysed; no aggregates were found.

Functional analysis was carried out using the UMR-106 cell-based potency assay, the Saos-2 cell based assay, and binding to rhPTH1R by SPR.

In general, the data presented confirms the expected primary, secondary and tertiary structure of the active substance. Functional characteristics, product variants, pharmaceutical properties and process related impurities have also been suitably evaluated. The testing panel for characterisation is considered to be acceptable. Details of method qualification have been provided and the methods are considered to be suitable for their intended use.

Impurities

Product related impurities have been adequately characterised and are found at quite low levels. Relevant impurities are appropriately controlled in the active substance release tests.

The process related impurities include HCP, DNA, enterokinase, CBD, DTT, ethylenediaminetetraacetic acid (EDTA), urea and endotoxin. HCP, DNA and endotoxin are all tested on batch release and are therefore sufficiently controlled. Residual enterokinase was determined using a sandwich ELISA. Levels of residual enterokinase in additional batches tested is provided elsewhere in the dossier. Teriparatide, CDB and the fusion protein have differing molecular masses which can be identified by SE-HPLC. Residual CBD therefore appears in the HMW fraction, which has been confirmed during method validation. For DTT, EDTA and urea, the maximum amounts per dose are below the permitted daily exposure (PDE) limits and it is therefore agreed that they pose no safety concern.

For all methods used, sufficient details of method qualification have been provided and it is considered that the methods are suitable for their intended use.

Specification

The active substance specifications include tests for identity, purity, potency and safety related tests.

Identity is tested by two orthogonal methods; peptide mapping and RP-UPLC, which is endorsed. Assay is tested by RP-UPLC and potency is tested using the UMR-106 cell based assay which is acceptable. Purity is controlled by RP-UPLC and SE-HPLC. The RP-UPLC assay has several associated specifications, including total oxidation, total succinimide, total deamidation, total C-terminal truncation, total N-terminal truncation,

isomer of teriparatide, any other related protein and total impurities. The list of RP-UPLC specifications is considered comprehensive and therefore acceptable. Furthermore, data was provided to demonstrate that RP-UPLC can detect all relevant charge variants. Impurity tests are also registered for host cell DNA, HCP, endotoxin and bioburden. The specification tests are in general in accordance with ICH Q6B and with Ph. Eur. Monograph 2829 Teriparatide.

The proposed specifications for appearance and pH are considered standard and are acceptable. Sufficient justification has been provided for the acceptance criteria for identity by peptide mapping and RP-UPLC. The proposed acceptance criteria for protein concentration are acceptable.

For potency, the proposed acceptance criteria are acceptable.

For RP-HPLC, the proposed limits for oxidised impurities any other related protein and total impurity are in accordance with the Ph. Eur. Teriparatide monograph and are therefore acceptable. Additional specifications are registered for succinimide, deamidation, C-terminal truncation, N-terminal truncation, and isomer. The specifications for these are acceptable.

The proposed specification for HCP is not considered to pose any clinical risk.

The proposed specification for DNA is in line with WHO guidance on maximum levels of DNA in therapeutic proteins.

The proposed specification for endotoxin is in conformance with the Ph. Eur. monograph on Teriparatide (2829) and is within the Ph. Eur. limit of 5 EU/kg.

The proposed bioburden acceptance criteria are acceptable. The finished product is also tested for bioburden during production, and sterility at release.

Analytical procedures

The analytical method descriptions were presented as detailed standard operating procedures (SOPs). The method descriptions are considered acceptable with appropriate system suitability testing (SST) and acceptance criteria registered.

The methods have been sufficiently validated in accordance with ICH Q2 guideline on analytical method validation.

Potency is determined using a cell-based potency assay based on the PTH receptor-expressing rat osteosarcoma cell line UMR 106. When teriparatide binds to the PTH receptor, cAMP is released which is subsequently measured. Biological activity of the test sample is determined relative to the reference standard.

Batch analyses

Batch data are provided for multiple batches which include the batches manufactured for the three process validation campaigns, batches used in biosimilarity studies and stability studies. The provided batch data show that all release tests were within the proposed acceptance criteria, and show that the process is capable of manufacturing batches of consistent quality.

Reference materials

The history of all reference standard material throughout development of INTG8 is presented in the dossier and considered acceptable. The information provided is considered acceptable, traceability between primary

and working reference standard as well as between current and future working standards (through the primary standard) is ensured.

Container closure

The commercial active substance container closure system has been described. Appropriate specifications and details of relevant safety testing are provided. Overall, the choice of the container closure is justified and supported by stability data for the active substance. Summaries of the extractables studies including details on the analytical methods employed and evaluation of data against the safety thresholds is clearly presented in the dossier. It can be agreed based on the data presented from these studies that there is no toxicological concern for patients.

Stability

The proposed shelf life for the active substance is based on the long-term stability results. To support the shelf-life claim, the stability program is designed to follow ICH guidelines for stability of active substance (ICH Q1A and ICH Q5C) and a photostability study designed in accordance with conditions as per ICH Q1B. Testing protocols and full stability data is clearly presented in the dossier for long-term, accelerated, photostability studies.

The container closure used in the stability studies is representative of the proposed commercial container.

Data from representative active substance batches manufactured at commercial scale is presented to support the long-term storage conditions. Results for all batches remained within specification over the course of the long-term stability studies with no discernible trends observed, the data show that the active substance is very stable and the data do not give rise to any concern that the active substance would go out of specification. Results from batches at the accelerated condition are also presented. The results for all batches remained within specification and were highly similar to the real time storage condition results.

Photostability testing was carried out in accordance with ICH Q1B. The results of the photostability study show that the active substance is photosensitive on exposure to either UV or white light.

The post-approval stability protocol has been provided and is aligned with ICH Q1A and thus considered acceptable.

In conclusion, the proposed shelf life is endorsed.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is a sterile, clear and colourless liquid formulation (with preservative in acetate buffered, pH 4.0, solution for injection) in a 3 mL glass (Type I) cartridge with a fill volume of 2.7 mL assembled into a disposable pen injector for multiple use. Each pen contains 28 doses and is intended to be administered via subcutaneous injection. Each dose contains 20 micrograms / 80 µl. The finished product composition contains teriparatide as active ingredient and other ingredients are glacial acetic acid, sodium acetate (anhydrous), mannitol, metacresol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

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

There is no overage and the cartridge is filled with 2.7 mL to ensure an extractable volume of 2.4 mL.

Sondelbay will be supplied in pack sizes of 1 pre-filled pen or 3 pre-filled pens. The multiple-use pre-filled pen is supplied in a tray and further packaged in a carton along with the patient information leaflet and instructions for use. The device can be used with 31G – 32G injection needles. The prefilled pen is provided without needles, which must be procured separately, but are referenced in the SmPC. Compatibility studies have been performed with 31G and 32G needles (BD Micro-Fine) and dose accuracy studies have been successfully performed with all needle options as listed in the SmPC.

Pharmaceutical development

The applicant has presented a logical and comprehensive approach to product development. The formulation is based on that of the reference product Forsteo, and so excipient compatibility studies are not required. All excipients are widely used in parenteral formulations and comply with their respective European Pharmacopoeia monographs.

The clinical batches of finished product were manufactured at IPL using active substance also manufactured at IPL. The process used to manufacture clinical batches was also used for the process validation batches and will be used for manufacture of commercial batches. Changes to the manufacturing process throughout development are limited to increases in scale and minor modifications, so an extensive comparability exercise is not required. However, the applicant has provided a comparison of release and in-process testing results across the different processes and results are similar.

Process development studies were performed to evaluate compatibility with manufacturing process aids, to estimate hold times for process intermediates and for stirring speed studies. Process characterisation studies were performed to confirm criticality and to establish the control strategy.

Process parameters, operating ranges and process performance criteria were evaluated for each individual step of the manufacturing process, with ranges defined based on the results of the ranging studies, and release data for clinical and developmental batches. CPPs, KPPs and NKPPs have been identified for all operating and performance parameters for the finished product manufacturing process. Overall the classifications of parameters are considered reasonable and many are run at set point.

Container closure

The primary container consists of a Type 1 Ph. Eur. siliconised glass cartridge, a siliconised rubber stopper and a bromobutyl lined aluminium seal. Specifications are included in the dossier and are acceptable and supported by certificates of analysis (in-house and vendor), technical drawings of all components have also been included in the dossier

The selection of materials for the container closure system is supported by relevant studies. All container closure components (glass cartridges, bromobutyl rubber stopper, aluminium seal) comply with their respective Ph. Eur. monographs. Data has been provided to demonstrate that these is no fragmentation of the rubber stopper during normal in-use conditions over 28 days. Extractable/leachable studies have been performed to evaluate volatile and non-volatile substances. Risk assessments for elemental impurities and nitrosamines have been provided. All elemental impurities above the limit of quantitation are supported by a risk assessment confirming that levels detected were well below the PDE as per ICH Q3D or ICH M7.

The pen device and pre-filled glass cartridge are presented as a single integral drug-device combination product and the applicant has correctly identified that this is governed by Directive 2001/83/EC, and classified as a medicinal product. The application is supported by a checklist confirming compliance with the Essential Requirements of Annex 1 of the Medical Devices Directive 93/42/EEC. This is accepted as the Medical Device Directive was still in force at the time of submission and validation of this MAA.

Manufacture of the product and process controls

Accord Healthcare Polska Sp. z.o.o., Pabianice, Poland and Accord Healthcare BV Netherlands, Utrecht, NL are the sites of EU batch release.

Valid EU GMP documents have been provided for the sites responsible for finished product manufacture, testing and release. During the procedure a major objection was raised in relation to the lack of a Manufacturing and Importation Authorisation (MIA)/GMP certificate covering sterility testing for a proposed QC testing site. The relevant updated documentation was provided by the applicant in their responses and the major objection therefore considered resolved.

The sites of sterilisation for the primary container closure components have been registered in the dossier. Confirmation of ISO standards has been confirmed therefore GMP certificates for these sites is not required.

The manufacturing process for the finished product is an aseptic filling process with sterile filtration prior to filling.

Overall the description of the manufacturing process is sufficiently detailed and includes the automated assembly of the cartridges into the pre-filled pens. Labelling is a manual process but there is 100% verification of label application. A clarification was sought on the potential splitting/ pooling of cartridge batches prior to assembly and the applicant has confirmed that there is no pooling of cartridge batches and that traceability is ensured for each lot of pre-filled pens. As the active substance is light sensitive and prone to oxidation the applicant has confirmed that the active substance is protected from light during the thawing process. There is no reprocessing permitted during routine manufacture. The product is sterile filtered with control of bioburden prior to filtration and filter integrity confirmed pre- and post-filtration.

Process validation was performed on process validation batches manufactured at commercial scale. All PPQ batches (for cartridges and automated assembly pens) met the pre-defined acceptance criteria as per the validation protocol and support that the manufacturing process for finished product is in a validated state. The applicant has used a traditional approach for process validation, testing unit operations at the set point of the range for relevant process parameters. Process verification will continue throughout the lifecycle of the product. Acceptance ranges for CPPs and KPPs have been proposed based on development studies. There is no reference to design space in the dossier.

A filter validation study supports the use of the proposed filter. Media fill studies support the proposed filling time.

Shipping validation data is not yet available. The applicant has provided the results of a simulated qualification study on three process validation batches to evaluate the impact of the proposed commercial shipping route, and determines that there is no impact on quality of the finished product (including functionality testing of the device) during simulated transportation. The product-specific shipping validation report shall be completed post-approval and should be made available onsite for review during inspection.

Overall it is considered that the applicant has adequately described the manufacturing and control of this appropriately validated manufacturing process for both the cartridge and the prefilled pen

Product specification, analytical procedures, batch analysis

The applicant has presented a panel of release tests which are in accordance with ICHQ6B, Ph. Eur. 04/2015:0520 Parenteral Preparations and are based on the Ph. Eur. monograph for Teriparatide 01/2017:2829. The specifications include tests for physical characteristics, identity, purity, potency and safety related tests. Each method has a reference to the monograph where relevant, and includes a unique code linking to the laboratory method.

Specifications have been set based on the batch data and for the most part are considered justified based on the mean ± 3SD approach. However, some tightening of specifications was requested during review.

No additional impurities were identified other than those in the active substance. 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. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

During the procedure, a major objection was raised in relation to the absence of a comprehensive nitrosamine risk evaluation on potential risk factors for nitrosamine formation in the active substance, finished product solution and primary packaging process. In response, the applicant provided a risk evaluation concerning the presence of nitrosamine impurities, applying the principles outlined in the "Assessment report Procedure under Article 5(3) of Regulation EC (No) 726/2004" (EMA/369136/2020)". No nitrosating agents are detected in the active substance or components of the finished product and the risk evaluation supports that in the event of any risk of presence of nitrosamines during manufacture, subsequent steps would be capable of removing them. Therefore, no additional control measures are deemed necessary. The major objection was considered adequately resolved.

Analytical methods

Analytical procedures are described in the dossier. Pharmacopoeial methods are described with reference to their Ph. Eur. monograph. Descriptions of non-pharmacopoeial methods for both release and in-process testing are adequate. Non-compendial methods have been validated in accordance with ICH Q2 (R1). Compendial methods have been verified as appropriate for use. Analytical method transfer protocols (with pre-defined acceptance criteria) have been provided to support the transfer of all biological, immunological and immunochemical analytical methods from IPL to the EU testing site and the applicant has confirmed that all test transfers will be completed prior to the end of the procedure.

Batch analysis

Batch data has been presented for a number of batches manufactured from the different manufacturing processes. The manufacturing processes are closely aligned between the different scales and while a formal comparability study has not been provided in accordance with ICH Q5E, comparative batch date demonstrates that results are broadly similar. Analytical methods have not changed over process development (change in method numbers only). Therefore, it is considered that the number of batches provided is acceptable and supports the proposed specifications.

Reference materials

Reference is made to the active substance section.

Stability of the product

The applicant claims a shelf life of 24 months at 2-8ºC based on stability studies performed in accordance with ICH guidelines, using container closure systems identical to those registered for routine storage. The analytical methods used in the stability monitoring programme are the same as those used for release testing. The stability indicating nature of the tests has been verified and testing intervals registered in the dossier are in accordance with ICH Q5A and are acceptable.

The shelf life is supported by real time stability data for representative batches. In addition data for batches stored under accelerated conditions have been provided.

As comparability of the active substance from the different manufacturing process iterations has been accepted, the approach to base stability of commercial material using data from an earlier process can be endorsed. All results are within acceptance criteria for all batches at all timepoints. Overall it is agreed that the stability of the finished product over long term storage conditions has been demonstrated and support the claimed shelf life of 24 months.

An in-use stability study has been performed on a representative batch of finished product, towards the end of its shelf life to support the 28-day in-use shelf life at 2-8ºC. A second in-use stability study supports temporary excursions from 2-8ºC for a maximum of 3 days at 25ºC. The in-use conditions are appropriately reflected in the SmPC.

Photostability was assessed on one representative batch and demonstrates that the finished product is considered as light sensitive and should be protected from light. Direct exposure to light is minimised by holding cartridges in a black bag prior to assembly into the prefilled pen.

In conclusion, the applicant has demonstrated a logical and comprehensive approach to evaluation of stability of the finished product under real time and in-use storage conditions. It is concluded that the requested shelf life of 24 months at 2-8ºC can be supported.

Biosimilarity

Sondelbay has been developed as a biosimilar of EU approved Forsteo (marketing authorisation holder: Eli Lilly Nederland B.V.). The strength, presentation and composition of the proposed biosimilar is identical to that of the EU reference medicinal product. The Sondelbay clinical development program included one clinical study (study 0258-20) to demonstrate clinical similarity (PK and PD) between Sondelbay, Forsteo and Forteo (US comparator) in terms of clinical pharmacology efficacy and safety. The analytical similarity study included side-by-side analysis of various lots of Sondelbay against the EU sourced reference medicinal product (Forsteo). In addition, the analytical similarity study also included batches of the US product, Forteo, as a comparator in order to gather supporting data that can bridge Sondelbay with both the EU reference product and the US product (supportive data only). A comprehensive package is presented which supports the biosimilarity of Sondelbay to the EU reference product.

Depending on the phase of product and method development as well as the availability of reference product lots, analysis for analytical similarity assessment was conducted at different time intervals. The suitability of the analytical methods used during the analytical similarity exercise is supported by appropriate method qualification.

Multiple lots of Sondelbay and the EU reference product are used for the analytical similarity assessment. Clinical study lots of Sondelbay, Forsteo and Forteo were part of the biosimilarity studies. All batches of Sondelbay included in the biosimilarity exercise are representative of the proposed commercial process for active substance and finished product. Lots of different age for all products were included in the studies to represent the entire product shelf life. All batches (Sondelbay and reference product) were within shelf life and stored at the approved or proposed storage conditions. Overall, the suitability of the batches included in the biosimilarity exercise is agreed.

An overview of the analytical similarity exercise is presented in Table 1. The analytical similarity of Sondelbay was assessed at multiple levels beginning with primary and higher order structure, product variants and purity, functional characteristics and finally, pharmaceutical properties of the finished product. The testing panel is considered to be appropriate. The techniques applied are state of the art and the principle of orthogonality is generally applied in line with EMA/CHMP/BWP/247713/2012 (Guideline on similar medicinal products containing biotechnology-derived proteins as active substance: quality issues). The evaluation of the similarity of various product attributes was based on both qualitative and quantitative data assessments and linked to critical quality attributes identified as part of a risk assessment. Quality attributes were analysed based on potential clinical implications and viewed through process and analytical uncertainty/sensitivity for each of the analytical techniques. The risk/criticality assigned to each test method informs the number of lots tested with that method and the level of statistical rigor applied in the biosimilarity exercise. The risk evaluation is endorsed. The data from the reference product from the biosimilarity study serves as the QTPP range which is acceptable. The statistical approach is broken down into (i) within-specification claims, (ii) one-sided non-inferiority, (iii) two-sided similarity/equivalence, and (iv) descriptive/graphical comparison. Overall, the number of batches tested per quality attribute and the assessment criteria (statistical rigor) applied are considered to be appropriate.

Table 1: Summary of Analytical Similarity Exercise

Critical Quality Attribute	Analytical Test	Conclusion
Primary structure	N-terminal sequencing	• Obtained sequence of the first 15 amino acids of INTG8 and Forsteo is observed to be identical • The sequence is identical to published sequence of Ph. Eur.
	Amino acid sequencing using LC-MS and MS/MS	• Peptide mapping profiles of INTG8 and Forsteo is highly comparable • Obtained sequence of amino acids of INTG8 and Forsteo is observed to be identical • The sequence is identical to published sequence of Ph. Eur.
	Intact mass (LC-MS)	• Average molecular weight of INTG8 and Forsteo is same : 4117.2 Da • Average molecular weight of INTG8 and Forsteo (4117.2 Da) is similar to expected theoretical mass (4117.7 Da) • The min-max range of molecular weight is same
	Peptide mapping (HPLC)	• Peptide mapping profiles of INTG8 and Forsteo are highly comparable
	cIEF	• Average pI values of INTG8 and Forsteo is same which is 7.5 • The min-max range of pI is same

Critical Quality Attribute	Analytical Test	Conclusion
Higher Order Structure	1 D NMR Spectroscopy	• NMR spectra of INTG8 and Forsteo are comparable
	2 D NMR Spectroscopy	• NMR spectra of INTG8 and Forsteo are comparable
	CD (far UV) spectropolarimetry	• CD spectral profiles of INTG8 and Forsteo are highly comparable • The min-max range of observed minima is highly comparable
	FTIR	• Spectral profiles of INTG8 and Forsteo are comparable • The min-max range of Amide I minima is comparable
	Fluorescence spectroscopy	• Spectral profiles of INTG8 and Forsteo are comparable • The min-max range of λ max is overlapping
Product related variants	RP-UPLC	• The impurity levels in 100 % of the lots tested are $\leq \mu + 3*\sigma R$ of impurities in Forsteo • Chromatographic profiles of INTG8 and Forsteo are comparable
	CEx-HPLC	• Total impurity levels in 100 % of INTG8 lots tested are $\leq \mu + 3*\sigma R$ of impurities in Forsteo • Chromatographic profiles of INTG8 and Forsteo are comparable
	SE-HPLC	• Total impurity levels in 100 % of INTG8 lots tested are $\leq \mu + 3*\sigma R$ of impurities in Forsteo (No HMWs detected) • Chromatographic profiles of INTG8 and Forsteo are comparable
	SDS-PAGE	• The electropherogram profile of INTG8 samples are similar to Forsteo
Functional characteristics	SPR	• K_D of 100 % INTG8 lots tested is within $\leq \mu \pm 3*\sigma R$ of Forsteo
	UMR-106 cell based assay	• The % relative potency of all INTG8 lots is within $\leq \mu \pm 3*\sigma R$ of Forsteo • 90 % confidence interval (-6.907, 1.495) falls entirely within the equivalence margin, %, (-12.29, +12.29) and therefore INTG8 is equivalent to Forsteo in terms of UMR-106 cell-based assay
	Saos-2 cell based assay	• The % relative potency of 100 % INTG8 lots is within $\leq \mu \pm 3*\sigma R$ of Forsteo • 90 % confidence interval (-1.574, 11.908) falls entirely within the equivalence margin, %, (-16.57, +16.57) and therefore INTG8 is equivalent to Forsteo in terms of Saos-2 cell-based assay
Pharmaceutical properties	Protein concentration by UPLC	• The protein concentrations obtained is within the Intas drug product specification range i.e. ± 10% of claimed strength of the product for all samples. • 90 % confidence interval (3.606, 11.279) falls entirely within the equivalence margin, %, (-16.25, +16.25) and therefore INTG8 is equivalent to Forsteo in terms of protein concentration by UPLC
	Physical appearance	• Physical appearance of INTG8 and Forsteo samples is comparable in appearance – clear and colourless liquid
	pH	• The pH results obtained are comparable for INTG8 and Forsteo i.e. are within Intas drug product specification range 4.0 ± 0.2

Critical Quality Attribute	Analytical Test	Conclusion
	Osmolality	• Osmolality values obtained are comparable for INTG8 and Forsteo i.e. are within Intas drug product specification range 293 mOsmol/kg of water ± 29 mOsmol/kg of water
	Excipient- m-cresol	• M-cresol content obtained are comparable for INTG8 and Forsteo i.e. are within Intas drug product specification range 2.7 to 3.3 mg/mL

Primary and higher order structure

Primary structure was evaluated using N-terminal sequencing, amino acid sequencing, intact mass analysis, peptide mapping and determination of isoelectric point (cIEF). Higher order structure was evaluated using UV Circular dichroism, FTIR, fluorescence spectroscopy, 1D NMR and 2D NMR. The results of primary and higher order structure analysis support the conclusion of biosimilarity.

Product variants

Product variants were evaluated by RP-UPLC, CEX-HPLC, SE-HPLC and SDS-PAGE.

RP-UPLC

The first Sondelbay lots showed higher levels of % oxidation compared to Forsteo batches. In order to address this, the applicant introduced refined handling and storage conditions for Sondelbay active substance which resulted in a reduction in levels of % oxidation. Data is presented comparing the Sondelbay batches (refined storage conditions) against Forsteo batches. The sum of % area of oxidised peaks for Sondelbay is slightly higher than for Forsteo. The % purity of Sondelbay is within the range of the reference product. Similiarly, the total % area of peaks due to related proteins for Sondelbay is within the range for the reference product and is also $\leq \mu + 3*\sigma R$ total impurities in Forsteo. Minor differences in the levels of % oxidised impurities and individual named impurities have been justified on the grounds that individual impurities for Sondelbay are within or only slightly higher than the reference product and also considering the data from functional tests and clinical safety/efficacy. The results of stability trending analysis support that the age of the batches at the time of testing do not impact on the biosimilarity conclusion.

CEX- HPLC

The average % total impurities of Sondelbay are below the value of mean + 3 SD for Forsteo. While results for Sondelbay deviate slightly by comparison to the range for the EU reference product, the differences are not considered to be significant in the context of the similarity assessment. Results of stability trending analysis indicate that impurity levels do not change significantly with batch age and, thus, differences in batch age at the time of testing do not impact on the biosimilarity the conclusion.

SE-HPLC and SDS-PAGE

The results of both SE-HPLC and SDS PAGE support the conclusion of biosimilarity. The presence of HMW variants was not detected in Sondelbay or EU reference product using either method.

Functional characteristics

Biological activity

Biological activity was evaluated using two different cell-based assays, one using a rat sarcoma cell line (UMR-106) and the other using a human osteosarcoma cell line (Saos-2). The % relative potency for Sondelbay lies within the min-max range for the EU reference product or overlaps significantly. Furthermore, the % relative potency of all Sondelbay lots lies within $\mu \pm 3*\sigma R$ of Forsteo. According to the stability trending analysis, there is no significant impact of age on % relative potency. As such, it is accepted that the age differences at the time of testing do not adversely impact the conclusion on biosimilarity. The data presented regarding biological activity support the conclusion of biosimilarity.

An SPR based method was used to determine the binding kinetics of teriparatide samples to rh PTH1R. The range of KD (equilibrium dissociation constant) values of Sondelbay lots fall inside the min-max range observed for the Forsteo lots.

Pharmaceutical properties
Pharmaceutical properties evaluated during the analytical similarity exercise include protein concentration (RP-HPLC), dose accuracy, physical appearance, pH, osmolality and m-cresol levels (RP-HPLC). Most of the attributes evaluated for Sondelbay lots either fall within the min-max range observed for the EU reference lots or are slightly outside the range but meet specification. The data presented with respect to pharmaceutical properties is sufficient to support a conclusion of biosimilarity.

Comparative forced degradation

From the RP UPLC, SE HPLC and mass spectroscopic analysis results, it is agreed that temperature stress, acidic stress and oxidation stress lead to a comparable increasing trend of degradation impurities for all samples both qualitatively and quantitatively. Comparable stability profiles have been demonstrated for Sondelbay versus Forsteo.

Conclusion

The analytical similarity of Sondelbay was assessed at multiple levels beginning with primary and higher order structure, product variants and purity, functional characteristics and finally, pharmaceutical properties of the finished product. Overall, the analytical similarity program is appropriate and supports a conclusion of biosimilarity against the EU reference product, Forsteo.

Adventitious agents

As the active substance is generated in *E. coli* it is acknowledged that the risk of viral contamination of the cell line by viruses potentially harmful to humans is minimal. Therefore, no formal viral validation study in accordance with ICH Q5A is required.

The applicant has identified all materials of biological origin in manufacture of the active substance, all are free of materials of human or animal origin with the exception of one material. As per EMA/01/01 rev 01, its origin is not a species susceptible to TSE and the certificate of origin and TSE/BSE statements are supplied. All other components are supported by certificates of analysis.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is manufactured using a standard approach for *E. coli* derived medicinal products. The manufacturing process is sufficiently well described. Appropriate controls have been registered which have been supported by appropriate development data. The control strategy is comprehensive and underpinned by process development studies. Sufficient information has been provided on cell line development and characterisation. Several manufacturing processes were used throughout development, supported by

appropriate comparability studies. The process was validated in process validation campaigns, and the data show the process to be under control.

The active substance is sufficiently characterised using a suite of appropriate analytical tests and the impurities have been sufficiently addressed. The proposed active substance release specifications and acceptance criteria are acceptable. Analytical procedures are well described and validated. Batch data has been provided to shows batch to batch consistency. A two-tiered reference standard system is in place. The container closure system is acceptable. The proposed active substance shelf life is adequately supported by real time data.

The finished product is presented as a solution for injection in a pre-filled pen at a concentration of 20µg/ 80µl. The product is formulated using widely used excipients and includes m-cresol as preservative. A comprehensive overview has been provided detailing the pharmaceutical and development of the product. The product is manufactured under GMP and the process consists of receipt and mixing of formulated active substance and sterile filtration and filling. The process is well characterised. Process validation data supports the proposed process, including automated assembly of the prefilled pen device. Release and stability specifications of the finished product have been appropriately justified and are acceptable. Impurities are described and controlled. It is considered that the process control strategy sufficiently guarantees consistent and satisfactory quality/performance of the product. The analytical methods are suitably validated. The primary packaging is adequately described and the cartridges are supplied sterile. The product is stable over the proposed shelf life of 24 months at 5°C and for 28 days at 2-8ºC for sub-cutaneous injection. One temporary excursion to 25ºC for up to 3 days within the in-use period is supported. The device is appropriately supported by an EC certificate under Directive 93/42/EEC Annex II and has met the requirements of ISO 13485:2016.

The analytical similarity of Sondelbay was assessed at multiple levels beginning with primary and higher order structure, product variants and purity, functional characteristics and finally, pharmaceutical properties of the finished product. Overall, the analytical similarity program is appropriate and supports a conclusion of biosimilarity.

Two major objections were raised during the procedure, in relation to the absence of a risk evaluation for nitrosamine impurities and to the lack of MIA/GMP certificate covering sterility testing for the proposed QC testing site. These issues were resolved as the applicant provided an appropriate risk evaluation for nitrosamine impurities and the requested documentation for the QC testing site.

2.4.4. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

INTG8 is a recombinantly produced fragment of the endogenous human parathyroid hormone, which contains the identical sequence of the 34 N-terminal amino acids (the biologically active fragment) of the 84-amino acid human PTH. It has been developed as a biosimilar to the reference product Forsteo (teriparatide; Eli Lilly Nederland BV), authorised in the EU.

In order to demonstrate similarity to the reference product the applicant has performed several *in vitro* studies. Surface plasmon resonance measurements were performed to measure the binding kinetics of INTG8 to recombinant human PTH1 receptor. Similar measurements were also performed for the reference product Forsteo. The calculated KD values for INTG8 were within μ ± 3*σR of those measured for Forsteo.

Subsequent to this, cell-based potency assays in a rat (UMR-106) and a human (Saos-2) cell line were performed in which cAMP levels were measured as a surrogate for the binding of Teriparatide to the PTH1 receptor expressed in both of these cell lines. In both cell lines, the relative potencies measured for INTG8 were within the range of μ ± 3*σR of the reference Forsteo suggesting similarity.

Biological activity of INTG8 and Forsteo in terms of their effect on bone pharmacodynamic parameters in axial and appendicular bones was also be evaluated as part of Study G17027. A dose dependent increase in BMD and BMC in both sexes was observed at two cancellous sites (femur metaphysis and lumbar vertebra) by INTG8 and EU-Forsteo. At cortical site (femur diaphysis), EU-Forsteo was found to be inhibitory while INTG8 remained ineffective. However, BMD and BMC were increased in INTG8 group at 30 and 100 μg/kg and in EU-Forsteo group at 100 μg/kg in female rats. The significance of these differences is unclear in the absence of measured exposure levels of INTG8 and the reference product, Forsteo.

The assessment of biosimilarity of INTG8 are primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted. The submitted non-clinical studies do not suggest a significant difference between INTG8 and the reference products tested.

No secondary pharmacology, PD drug-drug interaction or safety pharmacology studies have been performed. This is considered acceptable for an application under Article 10(4) of Directive 2001/83/EC, as amended.

2.5.3. Pharmacokinetics

No nonclinical assessment of the PK of INTG8 has been provided. The serum samples for toxicokinetics in the 28-repeat dose toxicity study were not analysed due to repeated failure of selectivity in haemolysed serum during analytical method validation. Given that INTG8 is a relatively simple peptide that lacks post-translational modifications, there is no scientific rationale to suggest that the nonclinical PK of INTG8 will differ significantly from the reference product, provided that biosimilarity can be demonstrated. It is also noted that a clinical PK study has been performed.

There were no distribution, metabolism, excretion or PK interaction studies conducted as part of this application, and none are required in line with biosimilar development guidelines (EMEA/CHMP/BMWP/42832/2005 Rev1).

2.5.4. Toxicology

A GLP-compliant, comparative 28-day repeat-dose study in SD rats was performed to compare toxicity, TK and immunogenicity of INTG8 and Forsteo.

Differences were seen between INTG8 and Forsteo in some of the pharmacodynamic bone endpoints as well as some haematological parameters. No differences in the NOAEL between INTG8 and Forsteo were observed; however, no toxicokinetics could be performed because of a failure to be able to detect Teriparatide in haemolysed serum. As outlined in the CHMP scientific advice, this study was not deemed necessary to support the MAA from a nonclinical perspective.

In vitro and *in vivo* assessment of immunogenicity suggest that the immunogenic potential of INTG8 is low, and comparable with that of Forsteo.

No genotoxicity, reproductive toxicology or carcinogenicity studies have been performed and, as outlined in the relevant guidance, these are not necessary for biosimilars (EMEA/CHMP/BMWP/42832/2005 Rev1).

2.5.5. Ecotoxicity/environmental risk assessment

The applicant has provided a justification for not submitting ERA studies on the basis that Teriparatide is a peptide, which is in line with the EMA guidance (EMEA/CHMP/SWP/4447/00 corr 2).

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.

2.5.6. Discussion on non-clinical aspects

The nonclinical package to support the MAA includes *in vitro* assays (receptor-binding studies, cell-based bioassays and an immunogenicity study) as well as an *in vivo* comparative nonclinical 28-day repeat dose toxicity study of INTG8 and Forsteo in rats. Data are considered in the context of the legal basis of the application.

Pharmacology

Several *in vitro* studies have been performed to demonstrate the comparability and similarity of INTG8 compared to Forsteo to: (i) bind with similar affinity to the PTH1 receptor; and (ii) induce downstream biological activity in both rat and human cells. Bone pharmacodynamic parameters in axial and appendicular bones were also evaluated in the comparative 28-day repeat dose toxicity study in rats, and some differences in PD endpoints were observed between INTG8 and Forsteo. However, analysis of toxicokinetic could not be performed due to haemolysis of the serum samples and therefore exposure levels of INTG8 and Forsteo could not be compared. As conduct of the *in vivo* comparative 28-day repeat dose toxicity study was not deemed necessary to support an MAA, the *in vitro* studies are sufficient from a nonclinical perspective to attest to demonstrate similarity between INTG8 and the reference product, Forsteo. The absence of secondary PD, safety pharmacology or PD drug interactions is in line the relevant guideline.

Pharmacokinetics

There is no information provided in relation to the nonclinical pharmacokinetics of INTG8. This can be considered to be acceptable provided the biosimilarity to the reference product is proven. As a relatively simple 34 amino acid peptide which lacks any post-translational modifications the PK profile it is unlikely to

differ significantly from the reference product. Furthermore, the clinical PK study is of much more relevance than any nonclinical PK data.

Toxicology

A GLP compliant 28-day repeat dose toxicity study reported no differences in the NOAEL between INTG8 and Forsteo, however, no toxicokinetics could be performed because of a failure to be able to detect teriparatide in haemolysed serum. The results of this study were not considered necessary from a nonclinical perspective to support the MAA. *In vitro* and *in vivo* assessment of immunogenicity suggest that the immunogenic potential of INTG8 is low, and comparable with that of Forsteo. However, nonclinical immunogenicity data may not be predictive of the clinical situation. The proposed text for Sections 4.6 and 5.3 of the SmPC are in line with that of the reference product.

ERA

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.

2.5.7. Conclusion on the non-clinical aspects

The marketing authorisation application is approvable from a nonclinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In this application, the applicant has submitted a new PK/PD study, Study 0258-20, which took place from 7 December 2020 to 22 January 2021, at the same Lambda Therapeutic Research Ltd site at Ahmedabad.

A study specific GCP inspection is not considered necessary for the new study submitted with this application, Study 0258-20. A number of GCP related other concerns were raised with respect to Study 0258-20 and were satisfactorily resolved by the applicant.

There was a recent remote GCP inspection of the same site (Lambda Therapeutic Research Ltd, Ahmedabad, India - June 2021) of another study arising from another application from the same applicant. The inspection was entirely focused on the qualification and safe operation of a critical computerised system used by the CRO during the conduct and reporting of the trial. The inspection team have concluded that although there were a number of critical and major findings, they do not impact the data integrity and reliability and thus there is no reason not to recommend accepting the trial data.

In addition, there was also an on-site inspection conducted in October 2021 at the bioanalytical site (Lambda Therapeutic Research Ltd, Ahmedabad, India) for another application from the same applicant. The preliminary inspection report does not highlight any critical findings and the major findings raised do not

affect the quality of data generated for the inspected study.

- **Tabular overview of clinical studies**

Table 2: Summary of Study Design and Objectives of INTG8 Clinical Study

Type of Study	Study Identifier	Location of Study Report	Study Objective	Study Design	Test Product; Dosage Regimen; Route of Administration	Study Population	No. of Subjects; Age	Duration of Treatment	Study Status; Type of Report
Phase I PK/PD study (Pivotal Study)	0258-20	5.3.1.2	**Primary Objective:** To demonstrate pharmacokinetic bioequivalence of INTG8 of Intas Pharmaceuticals Limited, India against Forteo® (Lilly USA, LLC) and Forsteo® (ELI LILLY NEDERLAND B.V., THE NETHERLANDS) following 20 µg single subcutaneous injection in healthy men and postmenopausal women. **Secondary Objectives:** To assess and compare local tolerance, safety, and tolerability of INTG8 of Intas Pharmaceuticals Limited, India against Forteo® (Lilly USA, LLC) and Forsteo® (ELI LILLY NEDERLAND B.V., THE NETHERLANDS) following 20 µg single subcutaneous injection in healthy men and postmenopausal women. And	An assessor-blind, randomized, three-treatment, three-period, single-dose, crossover, bioequivalence study in healthy men and postmenopausal women after subcutaneous (SC) administration under fasting conditions	**Test Product-T:** Teriparatide 20 µg/80 µL recombinant human parathyroid hormone [1-34] Injection (r-DNA origin); **Reference Product-R1 (EU Product):** Forsteo® Teriparatide 20 µg/80 µL Injection **Reference Product-R2 (US Product):** Forteo® Teriparatide 20 µg (rDNA origin) Injection **Dosage Regimen:** Single dose (20 µg/80 µL); **Route of Administration:** Subcutaneous	Healthy men and postmenopausal women	105 dosed and completed (62 male, 43 female); 19 to 63 years old	Single dose	Completed; Full report
			To assess and compare pharmacodynamic of INTG8 of Intas Pharmaceuticals Limited, India against Forteo® (Lilly USA, LLC) and Forsteo® (ELI LILLY NEDERLAND B.V., THE NETHERLANDS) following 20 µg single subcutaneous injection in healthy men and postmenopausal women.						

PK: pharmacokinetics; PD: pharmacodynamics; SC: subcutaneous

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioanalytical methods

Validation data is presented for the analytical method for corrected total calcium in human serum using the Vitros Chemistry Analyser system. This is a spectorphotometic system which measures both calcium and albumin. The method has been validated for precision and accuracy. As this is a widely used commercial

system for diagnostic testing and the analysis was carried out in an accredited laboratory, it is considered acceptable that fully validation according the EMA Guideline on Bioanalytical Methods is not presented. In any case, since the method is a direct estimation method and does not include any processing, evaluation of selectivity, matrix effect and calibration curve is not feasible.

Teriparatide is measured in human serum using a Sandwich ELISA. Validation data has been presented for precision, accuracy, selectivity, specificity, dilution linearity, stability and robustness. The assay uses a pre-treatment step to deplete endogenous PTH (1-84) and it has been demonstrated that the assay is specific to PTH (1-34) and that there is no interference from endogenous PTH (1-84). Details of incurred sample reanalysis have been provided. Data on the tolerance of the assay for anti-teriparatide antibodies was not provided. However, teriparatide has a short half-life and is eliminated from circulation in about 6 hours, whereas it would take several days to generate a sufficient level of ADAs to impact the bioavailability of teriparatide. Therefore it is acceptable that assay tolerance for ADAs was not investigated. The applicant assumed an LLOQ concentration of 10 pg/ml, which is about 10% of the Cmax value. The applicant presented a discussion regarding the LLOQ used in the BEQ study. The applicant performed the additional analyses to demonstrate the lack of influence of the adopted level of LLOQ (5 pg/ml) on the 0258-20 study results. The simulations performed did not show any significant changes in the results obtained. Changes in Cmax and AUC0-t and AUC0-inf values were minor and did not affect the conclusion regarding bioequivalence. In addition, the applicant conducted a sensitivity analysis from which all subjects with Cmax <50 pg/ml were excluded. The observed change in geoLMS of Cmax, AUC0-t and AUC0-inf was <7%. The T/R ratios were comparable, and the 90% confidence intervals met the acceptance criteria for bioequivalence. In addition, in study 0258-20, a carry-over effect was also not observed. Furthermore, no case was found with a pre-dose concentration > 5% for any period. Considering the totality of the data and the applicant's explanation, it appears that the assumed higher LLOQ does not affect the bioequivalence inference.

The immunogenicity studies followed a standard three-tiered approach of screening, confirmation and titre. Sufficient details of the assay are provided in the validation report and in the bioanalytical report. The screening assay is based on an indirect ELISA where plates are coated with the biosimilar to capture ADAs. The approach to establishing cutpoints is considered standard and in line with relevant published guidance. The ADA assay has been suitably validated. The sensitivity of the assay was shown to be 39.9 ng/ml for the screening assay and 16.2 ng/ml for the specificity assay. This is considered to be an acceptable level of sensitivity for an assay of this nature. The assay showed acceptable precision. The assay has been shown to tolerate up to 200 pg/ml of biosimilar teriparatide which is considered acceptable. Data was provided to show that the positive control antibodies could be detected at a comparable level when either the biosimilar, Forsteo, or Forteo were used as the capture reagent. Furthermore, ADAs against either of the three products were confirmed to be positive in the confirmation assay when biosimilar teriparatide was used as an inhibitor. These data confirm that the ADA assay is suitable for detection of ADAs against the biosimilar and the reference product.

The NAb assay is based on inhibition of teriparatide induced cAMP generation in UMR 106 cells. The assay cut point was established using 36 healthy serum samples using a 1% false positive rate. Sufficient details of the statistical approach are provided. The sensitivity of the assay was shown to be 156 ng/ml which is considered sufficiently sensitive for a NAb assay. The inter- and intra-assay precision results were below 24% which is also considered acceptable. The tolerance of the assay was 400 pg/ml, which is above the recorded Cmax in the PK study. Assay specificity was shown using human IgG. Sufficient stability data has been provided. Finally the assay was shown to give comparable results for INTG8, Forsteo and Forteo.

Study # 0258-20

The study was an assessor-blind, randomised, three-treatment, three-period, single-dose, crossover, bioequivalence study in healthy men and postmenopausal women after subcutaneous (SC) administration under fasting conditions. During the study, blood samples for pharmacokinetics (PK), for pharmacodynamics (PD) and for immunogenicity were collected from each subject to evaluate the immunogenicity, PK and PD profiles of INTG8, Forsteo and Forteo.

Mean serum teriparatide concentrations were similar following a single SC dose of INTG8, Forsteo or Forteo. Peak mean concentration was reached at similar time following a single SC dose of INTG8, Forsteo and Forteo.

The statistical comparison of serum teriparatide PK parameters for INTG8 vs. Forsteo is summarised in Table 3. The 90% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed Cmax, AUC0-t and AUC0-∞ of INTG8 relative to Forsteo were within the acceptance range of 80.00% to 125.00%.

Table 3: Summary of Statistical Comparisons of Pharmacokinetic Parameters (INTG8 vs. Forsteo) (N=105)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	INTG8 (T)	Forteo (R1)	Ratio (T/R1)%			
lnC_{max}	106.634	94.875	112.4	107.78 - 117.20	18.4	100.0
$lnAUC_{0-t}$	126.363	115.958	109.0	103.74 - 114.48	21.7	100.0
$lnAUC_{0-\infty}$^	144.851	137.245	105.5	100.92 - 110.38	19.5	100.0

^N=103.

Group effect was found to be statistically significant for ln-transformed pharmacokinetic parameter Cmax, AUC0-t and AUC0-∞ of INTG8 vs. Forsteo. As the present study satisfies all the scientific and statistical criteria, and the 90% CI for the primary pharmacokinetic parameters are within the acceptance range, the significant ANOVA effect can be ignored.

Sequence effect was found to be statistically significant for ln-transformed pharmacokinetic parameters AUC0-t and AUC0-∞ of INTG8 vs. Forsteo. The cause for significant sequence effect may not be found with certainty. Therefore, under special circumstances the significant sequence effect can be ignored. This study was a single dose study; had an adequate washout; and used appropriate design and analysis. Hence, this sequence effect is most likely, accidentally statistically significant and can be ignored.

Sequence*Group effect was found to be statistically significant for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of INTG8 vs. Forsteo. The cause of the significance of Sequence*Group could not be identified with certainty; however as the present study satisfies all the scientific and statistical criteria, and the 90% CI for the primary PK parameters are within the acceptance range for Cmax, AUC0-t and AUC0-∞ of INTG8 vs. Forsteo, the statistically significance of Sequence*Group effect can be ignored.

Formulation effect was found to be statistically significant for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of INTG8 vs. Forsteo. Formulation effect is found to be statistically significant for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of INTG8 vs. Forsteo and Cmax and AUC0-t of INTG8 vs. Forteo for Teriparatide. The significant formulation effect might be contributed one-sided 90% confidence interval obtained in the study. As, the decision of equivalence is based on the 90%

confidence interval by Schuirmann two one sided 't' test which is within the acceptance criteria i.e. 80.00% to 125.00%. This significant formulation effect for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of INTG8 vs. Forsteo is just statistically significant and can be ignored.

Period (Group) effect was found to be statistically significant for the ln-transformed PK parameter Cmax of INTG8 vs. Forsteo for teriparatide. In the study, clinical conditions were kept identical in both the period of the study, and there were no pre-dose concentrations observed. Hence, appearance of Period (Group) is insignificant in nature. The decision of equivalence is based on the 90% confidence interval by Schuirmann two one sided 't' test which is within the acceptance criteria i.e. 80.00% to 125.00%. Hence, this significant period effect for ln-transformed pharmacokinetic parameters Cmax of teriparatide is just statistically significant and can be ignored.

Subject (Sequence*Group) effect was found to be statistically significant for the ln-transformed PK parameters Cmax, AUC0-t and AUC0-∞ of INTG8 vs. Forsteo. Since each subject is assigned only one sequence within the group, subjects are said to be nested within Sequence*Group. This Subject (Sequence*Group) effect is tested by the residual and should be highly significant. This significance is an indication that the purpose of using crossover design has been realised in that the between-subject variance is significantly larger than the residual. This significant Subject (Sequence*Group) effect for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of INTG8 vs. Forsteo is just statistically significant and can be ignored.

2.6.2.2. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

PD was assessed in the healthy volunteer study 0258-20. The mean corrected total serum calcium levels profiles (both baseline-adjusted and non-adjusted) were similar following a single SC dose of INTG8, Forsteo or Forteo.

The statistical comparison of the corrected total serum calcium level parameters for INTG8 vs. Forsteo is summarised in Table 4. The geometric LSM ratios for baseline-adjusted Emax and AUEC0-t were 102.4% and 98.1% for INTG8 vs. Forsteo. The geometric LSM ratios for baseline non-adjusted Emax and AUEC0-t were 99.9% and 100.1% for INTG8 vs. Forsteo.

Table 4. Summary of Statistical Comparisons of Corrected Total Serum Calcium Levels Parameters (INTG8 vs. Forsteo)

Parameters	Geometric Least Squares Means			90% Confidence Interval	95% Confidence Interval	Intra Subject CV (%)	Power (%)
	INTG8 (T)	Forsteo (R1)	Ratio (T/R1)%				
Baseline-adjusted (N=96*)							
lnE_{max}	0.307	0.300	102.4	87.33 - 119.99	84.66 - 123.78	71.5	74.9
$lnAUEC_{0-t}$	1.664^	1.696^	98.1	72.54 - 132.66	68.39 - 140.72	185.6	33.3
Baseline non-adjusted (N=105)							
lnE_{max}	9.831	9.845	99.9	99.59 - 100.12	99.54 - 100.17	1.2	100.0
$lnAUEC_{0-t}$	227.007	226.687	100.1	99.01 - 101.28	98.79 - 101.51	4.9	100.0

N=92.

ANOVA p-values and inter-subject CV of baseline adjusted and non-adjusted corrected total serum calcium levels for INTG8 vs. Forsteo are summarised in Table 11-13.

Group, Sequence*Group, Period(Group) and Subject (Sequence*Group) effects were found to be statistically significant for the ln-transformed Emax of baseline non-adjusted corrected total serum calcium levels.

Subject (Sequence*Group) effect was found to be statistically significant for the ln-transformed AUEC0-t of baseline non-adjusted corrected total serum calcium levels.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Since investigation of similarity aims at excluding significant differences between two substances, a study population as homogenous as possible is recommended.

There is no data suggestive of a difference in PTH receptor density between osteoporotic and healthy individuals. A biosimilar application does not need to establish the PK for each population again. Homogeneity and reduction of variability are the most important requirements to find differences between test and reference products in comparative Biosimilar-studies.

This approach is also in compliance with the EMA-Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**).

The inclusion and exclusion criteria are acceptable. The population recruited to the study is in line with the guidelines. There are no differences in PK expected with age as mentioned in reference product Forsteo SmPC. It is accepted that healthy subjects who were enrolled into the study are a more appropriate population to use in a crossover study. The demographic characteristics are equally distributed between treatment arms and are thus seen as appropriate.

The randomisation schedule where subjects received the three treatments in either sequence in a cross-over manner is supported. Overall, the study is fully supported to have provided an outcome being unbiased by any blinding issues.

The single dose administration of 20 µg teriparatide by SC injection in the abdomen irrespective of age, weight or other medical conditions, corresponds to the only approved daily dose of the originator Forsteo. Additionally, standard treatment duration with teriparatide involves no dose adjustment, and teriparatide exhibits linear PK over a tested dose range of 20 µg to 60 µg. Therefore, the single fixed 20-µg dose is deemed acceptable.

A washout period of 24 hours was maintained between the dosing days of any two consecutive periods. This washout is acceptable, as it comprises more than the (BE guideline) recommended 5 half-lives of teriparatide. The Primary and secondary endpoints are acceptable.

There were no substantial amendments to the protocol, only 2 minor errata.

Overall, the trial was a very similar design to the initial study performed with the previous Sondelbay submission, EMEA/H/C/005233/0000 and the trial design is acceptable.

The ethnicity of the proposed study population was Asian and Indian only. It is relevant to discuss what is known of pharmacokinetic and pharmacodynamic properties of teriparatide in different ethnic populations and in both genders. However as outlined in the EMA SA the pharmacokinetics and pharmacodynamics of the reference teriparatide product Forsteo have not been extensively studied in different ethnic populations. The available data on Caucasian, Japanese and Chinese women do not indicate that there would be clinically significant differences among different ethnic groups.

All subjects that were dosed completed the study. All subjects were fully treatment compliant and none had any concomitant medications during the study. This is not unexpected given the short duration of the study and the short wash-out periods.

No major protocol deviations occurred. All subjects had minor deviations for auxiliary body temperature instead of oral body temperature, which was part of a COVID-19 viral infection prevention policy and is not expected to impact on results. Deviations also included pre-dose housing, post-dose vital, pre-dose sample, washout and sample processing deviations, however these deviations were minor in nature and unlikely to impact results.

The 90% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed Cmax, AUC0-t and AUC0-∞ of INTG8 relative to Forsteo were within the acceptance range of 80.00% to 125.00%. A number of concerns were originally raised for this data, however they were mainly resolved in responses by the applicant. Bioequivalence was also demonstrated for other comparisons including the US reference product (INTG8 vs. Forteo and Forteo vs. Forsteo).

A small number of samples had NR readings, the majority of which were haemolysed. These samples are unlikely to have any impact on the data results.

The EMA clinical biosimilarity guideline outlines that *observing 90% CIs of ratios of biosimilar to reference product within a pre-specified, justified acceptance range may not, by itself, be sufficient. The location and the width of the confidence interval should also be taken into account in the interpretation of similarity.* The 90% CI does not cross 1 for any of the PK parameters however given that no major objections were raised on the PK data the observed differences in pharmacokinetic parameters are unlikely to be clinically relevant**.**

While bioequivalence criteria were met for the comparison of INTG8 vs. Forsteo, results demonstrated statistically significant group, sequence, group*sequence, formulation, period and subject (sequence*group) effects between the test and EU reference product. The statistically significant differences in pharmacokinetic parameters are not clinically relevant.

Description statistics were provided for secondary endpoints Tmax, λz, Vd, Cl and t1/2, which did not raise any concerns.

Pharmacodynamics:

For baseline non-adjusted data, data from all 105 subjects were included. The geometric mean ratios of the INTG8/Forsteo for corrected calcium levels are close to unity: 99.9 and 100.1 for lnEmax and lnAUEC0-t. The 90% and 95% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed corrected total serum calcium level parameters Emax and AUEC0-t of INTG8 relative to Forsteo were within the bioequivalence limits of 80.00% to 125.00%.

For baseline adjusted data, data from 9 (8.6%) subjects has been excluded for Emax and data from 13 (12.4%) subjects have been excluded for AUEC0-t. The geometric mean ratios of the INTG8/Forsteo for

corrected calcium levels are also close to unity: 102.4 and 98.1 for lnEmax and lnAUEC0-t. The 90% and 95% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed corrected total serum calcium level parameter Emax of INTG8 relative to Forsteo were within the range of 80.00% to 125.00%. However the 90% and 95% CIs of the geometric LSM ratios for AUEC0-t of INTG8 relative to Forsteo were not within the range of 80.00% to 125.00%. As a secondary end-point, the study was not powered to compare baseline adjusted data of total Serum Calcium Levels Parameters (INTG8 vs. Forsteo). The T/R ratio of AUEC0-t and Emax are well within 80.00 to 125.00% limits and close to 1. In addition, the PK data which is more reliable and sensitive and robust for this application. Overall while the PD data raise some uncertainty, the data can be accepted.

2.6.4. Conclusions on clinical pharmacology

Overall the pharmacology results support the claim that Sondelbay is a biosimilar of Forsteo.

2.6.5. Clinical efficacy

2.6.5.1. Main study(ies)

Study 0258-20

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 5. Summary of Efficacy for Trial 0258-20

Title: An assessor-blind, randomized, three-treatment, three-period, single-dose, crossover, bioequivalence study of INTG8 of Intas Pharmaceuticals Limited, India to Forteo (Lilly USA, LLC) and Forsteo (ELI LILLY NEDERLAND B.V., THE NETHERLANDS) in healthy men and postmenopausal women after subcutaneous administration	
Study identifier	0258-20 (Protocol Version Number 1.0)
Design	This study was an assessor-blind, randomised, three-treatment, three-period, single-dose, crossover, bioequivalence study in healthy men and postmenopausal women after SC administration under fasting conditions. Subjects were sequentially assigned a subject number as per the arrival sequence number, which was allotted on the basis of the subject's reporting time to the facility on the day of check-in and compliance to the requirements of the protocol. Subjects who discontinued/was withdrawn prior to the dose administration and sampling were replaced with the extra subjects available during the dosing. Subjects received INTG8, Forsteo or Forteo as per the randomisation schedule. The randomisation schedule was generated using SAS version 9.4 by the biostatistician. The sequence of administration of treatments i.e. "TR1R2" or "R2TR1" or "R1R2T" to the subjects were determined according to the randomisation schedule. Equal allocation of subjects in each sequence was ensured. This was an assessor-blinded study so coded treatment blinding was not required. The study staff taking care of subject's safety and the laboratory personnel doing the sample analysis of PK, PD, and immunogenicity data were blinded.

	Duration of main phase:		Clinical phase: Group-I: 07 December 2020 to 12 January 2021 Group-II: 11 December 2020 to 22 January 2021 Group-III: 17 December 2020 to 17 January 2021
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Equivalence Testing		
Treatments groups	Test Product-T (INTG8)		Treatment: Teriparatide 20 µg/80 µL recombinant human parathyroid hormone [1-34] Injection. Duration: After overnight fast of at least 10 hours, a single SC dose was administered on abdomen in supine position to each subject in each period with the help of pen device. Number randomised: All 105 subjects received a single dose of INTG8, Forsteo or Forteo in Period I, II & III as per the randomisation schedule.
	Reference Product-R1 (EU Product) (Forsteo)		Treatment: Forsteo Teriparatide 20 µg/80 µL Injection. Duration: After overnight fast of at least 10 hours, a single SC dose was administered on abdomen in supine position to each subject in each period with the help of pen device. Number randomised: All 105 subjects received a single dose of INTG8, Forsteo or Forteo in Period I, II & III as per the randomisation schedule.
	Reference Product-R2 (US Product) (Forteo)		Treatment: Forteo Teriparatide 20 µg Injection. Duration: After overnight fast of at least 10 hours, a single SC dose was administered on abdomen in supine position to each subject in each period with the help of pen device. Number randomised: All 105 subjects received a single dose of INTG8, Forsteo or Forteo in Period I, II & III as per the randomisation schedule.
Endpoints and definitions	Primary endpoint	Primary PK Parameters	Cmax, AUC0-t and AUC0-∞ of teriparatide
	Secondary endpoint	Secondary PK Parameters	AUC_%Extrap_Obs, Tmax, λz, Vd, Cl and t1/2 of teriparatide
	Secondary endpoint	Secondary PD Parameters	Tmax, Emax and AUEC0-t of baseline-adjusted and non-adjusted corrected total serum calcium levels
	Other endpoint	Immunogenicity Parameter	Anti-teriparatide antibodies
Database lock	02/February/2021		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	PK set: All subjects with available concentration data and for whom the PK profile can be adequately characterised (specific criteria defined). These subjects should not have any major protocol deviations or other clinical observations that can impact the PK (primary endpoint).			
Descriptive statistics and estimate variability	Treatment group	INTG8	Forsteo	Forteo
	Number of subjects	105	105	105
	Cmax pg/mL (mean)	116.703	105.684	107.019
	SD	44.8492	43.8711	45.9865

	AUC0-t pg.h/mL (mean)	139.868	128.957	126.513
	SD	67.4246	64.8885	60.3965
	AUC0-∞ pg.h/mL (mean)	154.118	148.023	160.372
	SD	65.5887	64.0065	178.9181
Effect estimate per comparison	lnCmax pg/mL	Comparison groups	INTG8 vs. Forsteo	
		GLSMR (%)	112.4	
		90% CI	107.78 - 117.20	
		Intersubject CV%	18.4	
	lnAUC0-t pg.h/mL	Comparison groups	INTG8 vs. Forsteo	
		GLSMR (%)	109.0	
		90% CI	103.74 - 114.48	
		Intersubject CV%	21.7	
	lnAUC0-∞ pg.h/mL	Comparison groups	INTG8 vs. Forsteo	
		GLSMR (%)	105.5	
		90% CI	100.92 - 110.38	
		Intersubject CV%	19.5	
	lnCmax pg/mL	Comparison groups	INTG8 vs. Forteo	
		GLSMR (%)	110.5	
		90% CI	105.18 - 116.07	
		Intersubject CV%	21.7	
	lnAUC0-t pg.h/mL	Comparison groups	INTG8 vs. Forteo	
		GLSMR (%)	109.5	
		90% CI	104.48 - 114.83	
		Intersubject CV%	20.8	
	lnAUC0-∞ pg.h/mL	Comparison groups	INTG8 vs. Forteo	
		GLSMR (%)	104.4	
		90% CI	98.15 - 111.11	
		Intersubject CV%	27.2	
	lnCmax pg/mL	Comparison groups	Forteo vs. Forsteo	
		GLSMR (%)	101.7	
		90% CI	96.78 - 106.91	
		Intersubject CV%	22.0	
	lnAUC0-t pg.h/mL	Comparison groups	Forteo vs. Forsteo	
		GLSMR (%)	99.5	
		90% CI	95.23 - 103.95	
		Intersubject CV%	19.3	
	lnAUC0-∞ pg.h/mL	Comparison groups	Forteo vs. Forsteo	
		GLSMR (%)	100.6	
		90% CI	94.74 - 106.90	
		Intersubject CV%	26.5	
	lnCmax pg/mL	Comparison groups	Forsteo vs. Forteo	
		GLSMR (%)	98.3	
		90% CI	93.53 - 103.33	
		Intersubject CV%	22.0	
	lnAUC0-t pg.h/mL	Comparison groups	Forsteo vs. Forteo	
		GLSMR (%)	100.5	
		90% CI	96.20 - 105.01	
		Intersubject CV%	19.3	
	lnAUC0-∞ pg.h/mL	Comparison groups	Forsteo vs. Forteo	
		GLSMR (%)	99.4	
		90% CI	93.55 - 105.56	
		Intersubject CV%	26.5	
Analysis description	**Secondary Analysis**			

Analysis population and time point description	PD set: All subjects with available concentration data (corrected total serum calcium) and for whom the PD profile can be adequately characterised. These subjects should not have any major protocol deviations or other clinical observations that can impact the PD.			
Descriptive statistics and estimate variability	Treatment group	INTG8	Forsteo	Forteo
	Number of subjects	105	105	105
	Tmax h (median)	0.167	0.250	0.250
	min-max	0.083 - 4.500	0.083 - 1.000	0.083 - 3.500
	λz 1/h (mean)	0.999	0.961	0.939
	SD	0.3428	0.3376	0.3646
	t1/2 h (mean)	0.779	0.868	1.129
	SD	0.2820	0.6832	2.8841
	AUC_%Extrap_ obs % (mean)	12.371	14.463	14.568
	SD	8.5318	11.2934	12.0314
	Vd L (mean)	181.107	201.030	204.181
	SD	128.4001	153.2457	127.6071
	Cl L/h (mean)	156.198	160.884	164.039
	SD	73.7876	70.4043	78.5273
	Tmax h, baseline adjusted (median)	4.000	4.017	4.000
	min-max	0.000 - 24.000	0.000 - 24.017	0.000 - 23.933
	Emax mg/dL, baseline adjusted (mean)	0.365	0.359	0.323
	SD	0.1969	0.1848	0.1487
	AUEC0-t mg.h/dL, baseline adjusted (mean)	2.927	2.771	2.134
	SD	3.6491	2.5701	1.9975
	Tmax h, baseline non-adjusted (median)	4.000	4.017	4.000
	min-max	0.000 - 24.000	0.000 - 24.017	0.000 - 23.933
	Emax mg/dL, baseline non-adjusted (mean)	9.791	9.806	9.800
	SD	0.2853	0.2903	0.2629
	AUEC0-t mg.h/dL, baseline non-adjusted (mean)	225.688	225.574	222.851
	SD	9.5818	12.4198	16.8498
Effect estimate per comparison	lnEmax pg/mL	Comparison groups	INTG8 vs. Forsteo	
		GLSMR (%) Baseline-adjusted; Baseline non-adjusted	102.4 99.9	
		90% CI Baseline-adjusted; Baseline non-adjusted	87.33 - 119.99 99.59 - 100.12	
		Intersubject CV% Baseline-adjusted; Baseline non-adjusted	71.5 1.2	
	lnAUEC0-t pg.h/mL	Comparison groups	INTG8 vs. Forsteo	
		GLSMR (%) Baseline-adjusted; Baseline non-adjusted	98.1 100.1	
		90% CI Baseline-adjusted; Baseline non-adjusted	72.54 - 132.66 99.01 - 101.28	

		Intersubject CV% Baseline-adjusted; Baseline non-adjusted	 185.6 4.9
	lnEmax pg/mL	Comparison groups	INTG8 vs. Forteo
		GLSMR (%) Baseline-adjusted; Baseline non-adjusted	106.8 99.9
		90% CI Baseline-adjusted; Baseline non-adjusted	93.80 - 121.53 99.65 - 100.16
		Intersubject CV% Baseline-adjusted; Baseline non-adjusted	 56.5 1.1
	lnAUEC0-t pg.h/mL	Comparison groups	INTG8 vs. Forteo
		GLSMR (%) Baseline-adjusted; Baseline non-adjusted	121.7 101.6
		90% CI Baseline-adjusted; Baseline non-adjusted	91.54 - 161.72 100.09 - 103.12
		Intersubject CV% Baseline-adjusted; Baseline non-adjusted	 164.7 6.5
	lnEmax pg/mL	Comparison groups	Forteo vs. Forsteo
		GLSMR (%) Baseline-adjusted; Baseline non-adjusted	91.9 99.9
		90% CI Baseline-adjusted; Baseline non-adjusted	79.38 - 106.28 99.72 - 100.17
		Intersubject CV% Baseline-adjusted; Baseline non-adjusted	 66.3 1.0
	lnAUEC0-t pg.h/mL	Comparison groups	Forteo vs. Forsteo
		GLSMR (%) Baseline-adjusted; Baseline non-adjusted	73.0 98.6
		90% CI Baseline-adjusted; Baseline non-adjusted	53.51 - 99.67 96.92 - 100.25
		Intersubject CV% Baseline-adjusted; Baseline non-adjusted	 206.1 7.4
	lnEmax pg/mL	Comparison groups	Forsteo vs. Forteo
		GLSMR (%) Baseline-adjusted; Baseline non-adjusted	105.8 100.1
		90% CI Baseline-adjusted; Baseline non-adjusted	91.77 - 122.00 99.83 - 100.28
		Intersubject CV% Baseline-adjusted; Baseline non-adjusted	 66.2 1.0
	lnAUEC0-t pg.h/mL	Comparison groups	Forsteo vs. Forteo
		GLSMR (%) Baseline-adjusted; Baseline non-adjusted	136.9 101.4
		90% CI Baseline-adjusted; Baseline non-adjusted	103.40 - 181.32 99.75 - 103.18
		Intersubject CV% Baseline-adjusted; Baseline non-adjusted	 170.8 7.4
Analysis description	**Other; immunogenicity analysis**		

Analysis population and time point description	Safety Set: All subjects who received at least one dose of any IMP and immunogenicity analysis was done on the safety set. A total of 51 blood samples were collected for the PK evaluation, 34 blood samples for the PD evaluation, and 2 blood samples for the immunogenicity evaluation at the time points specified in the protocol. Standard non-compartmental PK and PD parameters were derived for teriparatide and corrected total serum calcium levels (baseline-adjusted and baseline non-adjusted data), respectively.			
Descriptive statistics and estimate variability	Treatment group	TR1R2	R2TR1	R1R2T
	Number of subjects	105	105	105
	Anti-teriparatide antibodies, pre-dose (ADA-positive)	1	1	3
	Anti-teriparatide antibodies, end of study (ADA-positive)	0	0	2
	ADA-neutralising, pre-dose	0	0	0
	ADA-neutralising, end of study	0	0	0

2.6.5.2. Supportive study(ies)

Medical Devices aspects in relation to the Usability Engineering File for Teriparatide pen injector (Sondelbay)

The submission was supported by a human factors summative study.

Assessments of known use problems with similar devices were conducted in accordance with the FDA Human Factors Guidance - Applying Human Factors and Usability Engineering to Medical Devices: Guidance for Industry and Food & Drug Administration Staff (February 2016). Furthermore, a Use Failure Mode, Effects and Criticality Analysis (uFMECA) has been carried out on the device as has an IFU refinement study. The applicant has also applied the device harmonised standard for usability, IEC 62366-1:2015 - Application of usability engineering to medical devices and the Technical Report IEC 62366-2:2016 – Guidance on the application of usability engineering to medical devices.

For the summative human factors study, overall 46 participants were enrolled consisting of three distinct user groups (15 HCPs, 16 osteoporosis patients and 15 healthy volunteers). The applicant has reported no significant patterns of differences in performance amongst the three user groups.

The study assessed approximately twenty-four Safety Critical Tasks and eighteen Essential Tasks, and while a number of use errors were observed between both task types, none of these were deemed to be of unacceptable risk. The results of this summative usability study were then used to improve the associated Instructions for Use (IFU) for the device. The summative HF results are presented with respect to the user tasks (use steps). Summative study results are presented for safety critical tasks (tasks required for safe and effective use of Teriparatide Pen Injector. The main reason for participants committing the use errors was them not reading IFU attentively. Following the summative HF study, some improvements were made to the IFU, especially to make some of the instructions stand out so that they are easy to locate and follow.

However, it is noted that in the Participant Performance for Safety Critical Tasks that 10 participants failed the following:

"If the empty circle sign does not appear.. do not inject a second time on the same day. Instead, reset the pen (S)"

In the Participant Performance for Essential Tasks 7 participants again failed this.

The applicant then provides the following rationale in relation to this failure:

"In the summative HF study, two types of use errors were observed. Some participants did not notice in the IFU that they needed to reset the pen if the empty circle sign did not appear in the dose setting window following an injection. Others did not notice that they should not inject a second time on the same day. This again was primarily because they had not noticed this information in the IFU. Therefore, making the information more noticeable is considered to be important.

In order to communicate the instruction more effectively and prominently:

- The information regarding resetting the pen and not taking another dose (located within troubleshooting Step D and referred to in Step 5 of the IFU) was put in a box with a low opacity background colour.
- The conditional sentence, "If the empty circle sign does not appear in the dose setting window", was put in a chevron-box with slightly higher opacity to guide users to read the following instructions.
- The two pieces of information had been split into bullet points."

Following queries, the applicant has clarified that the empty circle sign does not appear in the Human Factor study, and no participant injected a second time on the same day after failing to see the empty circle sign. The main difference between the studies was that participants in the Bridging Summative study were asked to read through the IFU prior to simulating the use of Sondelbay pen, while participants in the Summative study were not encouraged or required to read the IFU. Thirty-seven out of 46 participants (80%) correctly understood that they should not take another dose on the same day in the Summative Study. The remaining participants had not seen the information in the IFU because they were rushing, skim-reading, or focusing on the main use steps to deliver their dose. However, once the Instructions for Use (IFU) was refined following the Summative Study, and participants were asked to read through the IFU prior to simulating the use of Sondelbay pen, all 29 out of 29 participants (100%) understood that they should not take another dose on the same day in the Bridging Summative Study.

2.6.6. Discussion on clinical efficacy

No dedicated efficacy study has been performed, which is acceptable for teriparatide in principle. Biosimilarity testing at the clinical level is based on the comparative PK study performed in healthy subjects and serum calcium as PD parameter was also assessed (under Pharmacokinetics section). Biological activity of INTG8 and Forsteo in terms of their effect on bone pharmacodynamic parameters in axial and appendicular bones was also evaluated as part of non-clinical study (under Pharmacology section). The assessment of biosimilarity of INTG8 are primarily based on the quality assessment of the appropriateness and acceptability of the *in vitro* comparability studies conducted. Overall results are supportive of similar efficacy of the biosimilar and the reference product Forsteo.

2.6.7. Conclusions on the clinical efficacy

Described under Conclusion on clinical pharmacology and Discussion on Benefit/Risk.

2.6.8. Clinical safety

The main safety data provided in support of this biosimilarity application is from a single, three treatment, three period, single dose crossover bioequivalence study comparing INTG8 (Teriparatide) with the reference products Forsteo (EU reference product) and Forteo- Study 0258-20.

2.6.8.1. Patient exposure

The study was conducted in healthy male and postmenopausal women. A total of 105 subjects (62 male and 43 female) were dosed and completed the study. All 105 subjects were included in the safety analysis, and all cases subjects received all 3 formulations.

2.6.8.2. Adverse events

Overall, the rate of AEs reported was low. In total 19 adverse events were reported by 13/105 (12.38%) of subjects. Of these 19 AEs, 11 were reported following the administration of the investigational medicinal product INTG8, with 5 reported following Forsteo (EU) and 3 following Forteo (US).

All reported 19 AEs were mild as per mild-moderate- severe categorisation, and Grade 1 as per CTCAE grading. While the number of AEs following INTG8 was somewhat higher than for both reference products (11 v 5 and 3); in terms of related AEs, there was a very similar rate reported following all 3 formulations, approximately 3% in each case. 12/19 AEs were considered to be related, and are reported evenly across the 3 treatments.

An overall summary of the 19 AEs reported is provided in Table below:

Table 6: Overall Summary of Adverse Events

	INTG8 (N=105) n (%) e	Forsteo (N=105) n (%) e	Forteo (N=105) n (%) e	Total (N=105) n (%) e
At least one post-dose AE	8 (7.62%) 11	4 (3.81%) 5	3 (2.86%) 3	13 (12.38%) 19
At least one AE leading to discontinuation	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0
At least one related AE	4 (3.81%) 4	4 (3.81%) 5	3 (2.86%) 3	9 (8.57%) 12
AE Severity				
At least one mild AE	8 (7.62%) 11	4 (3.81%) 5	3 (2.86%) 3	13 (12.38%) 19
At least one moderate AE	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0
At least one severe AE	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0
AE Toxicity Grading				
At least one Grade 1 AE	8 (7.62%) 11	4 (3.81%) 5	3 (2.86%) 3	13 (12.38%) 19
At least one Grade 2 AE	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0

	INTG8 (N=105) n (%) e	Forsteo (N=105) n (%) e	Forteo (N=105) n (%) e	Total (N=105) n (%) e
At least one Grade 3 AE	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0
At least one Grade 4 AE	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0
At least one Grade 5 AE	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0
At least one SAE	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0	0 (0.00%) 0

The detail of the 19 AEs reported after each formulation administration are displayed in Table below.

Table 7: Summary of Adverse Events by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	INTG8 (N=105) n (%) e	Forsteo (N=105) n (%) e	Forteo (N=105) n (%) e	Total (N=105) n (%) e
Gastrointestinal disorders				
Nausea	1 (0.95%) 1	2 (1.90%) 2	2 (1.90%) 2	5 (4.76%) 5
General disorders and administration site conditions				
Injection site reaction	0 (0.00%) 0	1 (0.95%) 1	0 (0.00%) 0	1 (0.95%) 1
Investigations				
Blood triglycerides increased	1 (0.95%) 1	0 (0.00%) 0	0 (0.00%) 0	1 (0.95%) 1
Glucose urine present	2 (1.90%) 2	0 (0.00%) 0	0 (0.00%) 0	2 (1.90%) 2
Neutrophil count increased	2 (1.90%) 2	0 (0.00%) 0	0 (0.00%) 0	2 (1.90%) 2
White blood cell count increased	2 (1.90%) 2	0 (0.00%) 0	0 (0.00%) 0	2 (1.90%) 2
Musculoskeletal and connective tissue disorders				
Back pain	2 (1.90%) 2	1 (0.95%) 1	1 (0.95%) 1	4 (3.81%) 4
Nervous system disorders				
Headache	1 (0.95%) 1	1 (0.95%) 1	0 (0.00%) 0	2 (1.90%) 2
Total	**8 (7.62%) 11**	**4 (3.81%) 5**	**3 (2.86%) 3**	**13 (12.38%) 19**

2.6.8.3. Serious adverse event/deaths/other significant events

No deaths or serious adverse events (SAEs) were reported during the study.

2.6.8.4. Laboratory findings

Laboratory tests of haematology and biochemistry and urine analysis were performed at the end of the study (after 28 days from dosing of Period-III). The laboratory reports were reviewed by a physician and were found to be clinically acceptable (including all the out of reference range reports) for all the subjects.

Four subjects had abnormal laboratory values during post-study, and these were attributed to the period 3 treatment, which in each case was reported for INTG8, which seems to reflect a conservative approach.

- One subject: Increase in blood triglycerides and Glucose present in urine
- One subject: Glucose present in urine
- Two subjects: Increase in white blood cell count and neutrophil count

However, the subjects did not report for their post-study safety assessment follow-up despite repeated efforts. Hence, adverse events were recorded for these lab abnormalities and they were considered as lost to follow-up.

Beyond looking at changes in laboratory values on an individual basis, each parameter was also evaluated and is summarised by treatment and time-point of collection. For quantitative laboratory data, descriptive statistics (count, mean, standard deviation, median, minimum and maximum) were calculated. Qualitative laboratory data were calculated and presented by categories using number and percentages. Statistically significant changes in mean WCC, neutrophil and lipase values were identified between screening and the end of the study in each of the 3 treatment sequences. For WCC/neutrophils the changes were minimal and were similar across all three sequences. For lipase the mean value recorded for treatment sequence R1R2T was higher than for the other two sequences.

Subjects were monitored for their serum calcium levels throughout the study. Although changes in the calcium homeostasis can occur following a single treatment with teriparatide there was no AE reports of hypercalcaemia.

2.6.8.5. Safety in special populations

Section not applicable for biosimilars.

2.6.8.6. Immunological events

Immunogenicity (anti-teriparatide antibody) was assessed as an exploratory objective in Study 0258-20. Blood samples were collected twice, once before the first dose of the first treatment, and once and at the end of the study (after all 3 treatments, i.e., 28 days after Period 3 dosing).

Of the 105 dosed subjects, 105 subjects were evaluated for immunogenicity. The samples were analysed to screen, confirm, and report a relative anti-drug antibody (ADA) concentration (titre). Confirmed positive samples were also characterised for neutralising activity.

A summary of ADA detection following INTG8, Forsteo, and Forteo is provided in Table 8, below. Of the total of 13 screening-positive subjects, 5 subjects were confirmed-positive for ADA in *either* pre-dose or end of the study samples.

Only 2 subjects were positive for ADA at the end of study visit, and in the case of both subjects, each had been confirmed positive at screening in advance of starting the study. Amongst these subjects none of the subject was found positive for neutralising antibodies at pre-dose or end of the study.

Table 8. Study 0258-20: Serum Anti-Teriparatide Antibody Detection Summary

Immunogenicity Test	Number of Subjects (ADA-Positive)							
	Pre-dosing visit				End of study visit			
	TR1R2	R2TR1	R1R2T	Total	TR1R2	R2TR1	R1R2T	Total
Screening test	2	5	6	13[a]	5	3	6	14[c]
Confirmatory test	1	1	3	5[b]	0	0	2	2[d]
Neutralizing test	0	0	0	0	0	0	0	0

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

Not applicable for biosimilars.

2.6.8.8. Discontinuation due to adverse events

No subject discontinued from the study due to AEs.

2.6.8.9. Post marketing experience

INTG8 has been marketed in India under the brand name Terifrac (marketing authorisation holder: Intas Pharmaceuticals Limited, India) following approval in India on 01 November 2010 for the treatment of osteoporosis in post-menopausal women who are at high risk of fracture.

It has been clarified by the applicant that the Terifrac device is not the same device as proposed for INTG8 in the EU. The applicant has provided a high-level summary of the post marketing safety data that has arisen in that context up to July 2021. It is agreed that there is no apparent safety trend or signal arising from the Indian post marketing data provided, and almost all of the SAEs are listed with a frequency of just 1.

Table 9. Post marketing Serious Adverse Events with Teriparatide (from 01-Nov-2010 to 31-Jul-2021)

MedDRA System Organ Class	Preferred Term	Number of Serious Adverse Events
Cardiac disorders	Myocardial infarction	1
Eye disorders	Blindness	1
Gastrointestinal disorders	Abdominal discomfort	1
	Abdominal distension	1
	Diarrhoea	1
	Rectal haemorrhage	1
General disorders and administration site conditions	Abasia	1
	Death	2
	Pain	1
Hepatobiliary disorders	Hepatomegaly	1
Infections and infestations	Dysentery	1
	Tuberculosis	1
Investigations	Blood alkaline phosphatase increased	1
	Blood creatinine increased	1

MedDRA System Organ Class	Preferred Term	Number of Serious Adverse Events
	Blood pressure increased	1
Musculoskeletal and connective tissue disorders	Muscle twitching	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	1
	Neoplasm malignant	1
	Plasma cell myeloma	1
Nervous system disorders	Dizziness	1
	Migraine	1
	Movement disorder	1
Renal and urinary disorders	Nephrolithiasis	1
	Renal disorder	1
Respiratory, thoracic and mediastinal disorders	Asthma	1
Skin and subcutaneous tissue disorders	Erythema	1
	Pruritus	1
	Skin burning sensation	1
Vascular disorders	Hypotension	1

2.6.9. Discussion on clinical safety

Data provided, exposure, patient population

The therapeutic indications, posology and route of administration proposed for INTG8 are identical to those for Forsteo, to which similarity is claimed by the applicant. The safety assessment of INTG8 was carried out in the Study 258-20 in 62 healthy men and 43 postmenopausal women, comparing to the safety of Forsteo and Forteo (US). This was a short-term three-way crossover single dose comparative bioequivalence study. Safety data was collected at the end of each of the three periods and 28 days after period III dosing. In the case of all 3 formulations INTG8 was delivered subcutaneously from a prefilled pen device to the abdomen; the same injector pen as is proposed product for market.

The safety population includes all subjects that received at least one dose of teriparatide, n=105. A total of 105 subjects received treatment, and in all cases the subjects received all 3 formulations. The safety population is acceptable in the context of a biosimilar application.

The overall demographic breakdown of the participants' notes that 59% were male, and just under 41% were female. The age range is reasonably broad from 19-63 years (mean age is 41 years), which is not unexpected given that the study deliberately sought to include post-menopausal women, in recognition that this is the age group of women most likely to be prescribed this therapy, and as such is more useful when

assessing safety. All participants are Asian, and specifically were of Indian descent. As this is a biosimilar assessment, focussing primarily on PK and PD endpoints, the patient population is considered acceptable.

Limitations of the design of Study 258-20 with regard to safety

The safety data from Study 258-20 is somewhat limited, in that only 105 subjects were dosed, and all subjects had one dose of each formulation (one test, and 2 reference products) over 3 consecutive days. While such a short wash out is appropriate for PK analysis for teriparatide, it does limit the ability to relate an AE to a specific formulation. The fact that only 1 dose of each formulation was given to each patient also limits the ability to draw meaningful conclusions on the safety of the proposed chronic daily dosing posology. It is also relevant that the only post treatment laboratory measurements were 28 days after the third treatment (clinical laboratory data was not collected at the end of each period), and so could feasibly be unrelated to any of the formulations.

Overall this study is unlikely to be able to detect certain types of adverse reactions such as rare adverse reactions, those with a long latency, those caused by prolonged or cumulative exposure, and the development of anti-drug antibodies (ADAs).

Overall view of the safety profile of INTG8

Within the confines of the data provided, the overall rate of AEs reported is low. In total 19 adverse events were reported by 13/105 (12.38%) of subjects. All were mild, or grade 1. While 11 of these 19 AEs are reported for the test product, INTG8, as already mentioned the design of the study does make it difficult to identify the treatment to which an AE might relate, when all 3 formulations were administered consecutively over 3 days. All reported 19 AEs were mild as per mild-moderate- severe categorisation, and Grade 1 as per CTCAE grading.

While the number of AEs following INTG8 was numerically higher than for both reference products (11 v 5 and 3); in terms of related AEs, there was a very similar rate reported following all 3 formulations, approximately 3% in each case. 12/19 AEs were considered to be related, and are reported evenly across the 3 treatments. Those AEs considered related were nausea (5AEs), back pain (4 AEs), headaches (2 AEs) and injections site reaction (1 AE).

The most common AE reported overall was nausea (5 events reports in 5 subjects, 4.76%), followed by back pain (4 events in 4 subjects, 3.81%), and then by headache (2 events in 2 subjects, 1.9%); and in each case there is no trend to an increased rate across the 3 formulations. It is noted that nausea and headache are listed as common AEs for Forsteo.

Injection site reaction was only reported once, and this was after the administration of the Forsteo reference product, and there were no other allergic type AE reported. The remaining AEs almost entirely relate to laboratory abnormalities, with no more than 2 cases for each abnormality, and were all reported for INTG8, see later discussion.

No subject discontinued from Study 0258-20 due to AEs.

There were no SAEs and no deaths in Study 0258-20.

No signal of immunogenicity was apparent, however, the study design is not sufficient to fully characterise this risk, see later discussion.

Laboratory abnormalities

Adverse events:

As already outlined, the design of the study (whereby patients received one dose of each formulation over 3 consecutive days), and the blood monitoring schedule (whereby subjects had only screening bloods, and a once off recheck of blood measurements 28 days after the end of treatment) very much limits the ability to characterise the safety of INTG8 in depth.

7 investigation/laboratory AEs were reported in 4 subjects, and in each case were reported for INTG8. These AEs concerned raised WCC, raised neutrophils, raised triglycerides, and glucose detected in urine; and in each case were graded as mild in severity These laboratory related AEs were reported for INTG8 because INTG8 had been given in period 3 for these 4 subjects, and so was the last treatment before blood sampling was taken 28 days later. Blood sampling was not taken after period 1 and period 2. Given the design of Study a conservative interpretation with respect to INTG8 and laboratory based AEs was needed. It should also be noted that in each case the investigator considered the AE to be unrelated to treatment, and that the abnormality was picked up a whole 28 days after the administration of the third and final formulation.

Also, the 7 investigation/laboratory AEs were not necessarily deemed clinically significant in each case- but the reason they were reported as AEs was that the 4 subjects concerned were lost to follow up as they did not return for post study safety assessment, despite best efforts.

Group trends in laboratory values:

Statistically significant changes in mean WCC, neutrophil and lipase values were identified between screening and the end of the study in each of the 3 treatment sequences. For WCC/neutrophils the changes were minimal and were similar across all three sequences.

For lipase the mean value recorded for treatment sequence R1R2T was higher than for the other two sequences. The applicant has provided the lipase values for patients that had the sequence R1R2T. Only 2 of these patients had lipase greater than the upper limit of normal (300 U/L), one had follow up level of 319, and the other 310. These are not significantly raised lipase values, and it is agreed that these are unlikely to be of any significance.

A number of metabolic adverse events are listed in the product information for Forsteo and do not seem to have occurred in this study; however these are generally associated with longer term repeat use (e.g. anaemia and hypercholesterolaemia, (common), hyperuricaemia and hypercalcaemia exceeding 2.76 mmol/L, (uncommon), and hypercalcaemia beyond 3.25 mmol/L (rare), alkaline phosphatase increased. These are unlikely to be detected in the context of a bioequivalence study.

Subjects were monitored for their serum calcium levels throughout the study. Although changes in the calcium homeostasis can occur following a single treatment with teriparatide there was no AE reports of hypercalcaemia.

Vitals/ECG

In Study 0258-20, subjects with orthostatic hypotension were not included in the study. Blood pressure, respiratory rate, radial pulse rate and temperature were measured during each clinical examination, at pre-dose and at 1, 3, and 10 hours' post-dose in each period. None of the subjects had any clinically significant abnormalities related to vital signs.

In study 0258-20, a 12-lead ECG recording was performed at screening, at 5 hours (±1 hour) post-dose in each period and at the end of the study (i.e., 28 days after dosing of Period-III). None of the subjects had any clinically significant abnormalities.
The commonest finding was bradycardia, and in all cases these were assessed as not clinically significant.

Immunogenicity

Assessment of immunogenicity was an exploratory objective of Study 0258-20. There were no also AEs associated with induced ADA. There were no reports of injection site reactions or allergic type reactions. Only 2/105 were ADA+ post study (at day 28), and in both cases the subjects had already been ADA+ during the screening period. None of the samples were positive for neutralising antibodies at D28 post period 3.

However, the duration of observation was very short; only one post dosing sample taken 28 days after the administration of the 3rd treatment, and therefore the possibility of an antibody-formation with INTG8 cannot be disregarded. The interpretation of any meaningful conclusions with regards to immunogenicity is further hampered by the fact that this is a cross over design, in that all patients received all 3 treatments on 3 consecutive days.

The general immunogenic potential for Forsteo the reference product is considered low; the SmPC for Forsteo states that antibodies that cross-reacted with teriparatide were detected in 2.8 % of women receiving Forsteo. While it is understood that the structure of INTG8 is relatively noncomplex (in that it is a small molecule and is not glycosylated, reducing the risk of ADA formation), the data provided are not enough to entirely reassure that ADA will not be more of an issue with INTG8 versus the reference product with continued, more long term use.

The need to more thoroughly characterise the immunogenic potential of INTG8 was discussed with the applicant in CHMP scientific advice, and was also raised in the previous submission. The additional *in vitro* immunogenicity data provided and discussed in the Preclinical AR is not sufficient to rule out the scenario that INTG8 could have a more immunogenic profile than Forsteo. The applicant plans to perform a post approval study in post-menopausal women, and to monitor for ADA, including neutralising antibodies for up to one year. While the post marketing immunogenicity study will not be a condition of approval, there is no objection to the applicant carrying out this study post approval, and submitting the data for assessment. The applicant also proposed to add the potential for immunogenicity to the safety specification of the RMP, under Missing Information.

2.6.10. Conclusions on the clinical safety

The safety database for INTG8 is limited to one crossover, single dose bioequivalence study, which only followed up for 28 days. Overall no new safety or immunogenicity concerns were identified in this study. The

study is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, and immunogenicity.

As the quality comparison of INTG8 to Forsteo is robust there is reassurance on the longer term safety/ immunogenicity potential of INTG8 compared to Forsteo, which itself has a low risk for immunogenicity. However, the applicant plans to perform a post marketing immunogenicity study in post-menopausal women with osteoporosis to more thoroughly characterise the risk of immunogenicity with INTG8. While the post marketing immunogenicity study will not be a condition of approval, there is no objection to the applicant carrying out this study post approval, and submitting the data for assessment.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

Important identified risks	• None
Important potential risks	• None
Missing Information	• Potential for immunogenicity

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to further characterise the safety concerns of the product.

2.7.3. Risk minimisation measures

Routine risk minimisation measures are considered sufficient to mitigate the safety concerns of the product.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

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

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

The analytical similarity of Sondelbay was assessed at multiple levels beginning with primary and higher order structure, product variants and purity, functional characteristics and finally, pharmaceutical properties of drug product. The study included side-by-side analysis of various lots of Sondelbay against the EU sourced reference medicinal product (Forsteo). The testing panel is considered to be appropriate. The techniques applied are state of the art, the principle of orthogonality is applied, and the methods have been appropriately qualified. The evaluation of the similarity of various product attributes was based on both qualitative and quantitative data assessments and linked to critical quality attributes identified as part of a risk assessment. Quality attributes were analysed based on potential clinical implications and viewed through process and analytical uncertainty/sensitivity for each of the analytical techniques. The risk/criticality assigned to each test method informs the number of lots tested with that method and the level of statistical rigor applied in the biosimilarity exercise. In general, the number of batches tested per quality attribute and the assessment criteria (statistical rigor) applied are considered to be appropriate. The suitability of the batches used in the biosimilarity exercise is agreed.

INTG8 (Teriparatide) has been developed as a biosimilar teriparatide using Forsteo as a reference product and is intended to be used in the same indications as the reference product. The applicant is proposing the following indication in adults.

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

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

The clinical development consisted of one single dose PK study in healthy volunteers comparing three formulations of teriparatide (INTG8, EU sourced Forsteo and US sourced Forteo) to evaluate the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of INTG8 compared to EU Forsteo.

The development plan followed respective EMA guidelines and the advice given in the clinical part of the EMA-SA was generally taken into consideration and the development programme aligned accordingly however there were some deviations and omissions.

3.2. Results supporting biosimilarity

Analytical similarity

The results from the following assays support the conclusion on biosimilarity: N-terminal sequencing, amino acid sequencing, intact mass analysis, peptide mapping, determination of isoelectric point, UV Circular dichroism, FTIR, fluorescence spectroscopy, 1D NMR, 2D NMR, RP-UPLC, CEX-HPLC, SE-HPLC, SDS-PAGE, cell-based bioassays (UMR-106 and Saos-2 cell lines), SPR. In addition, pharmaceutical properties were also evaluated during analytical similarity. The results of comparative forced degradation indicate that Sondelbay and Forsteo have comparable stability profiles.

PK/PD

For PK, the 90% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed Cmax, AUC0-t and AUC0-∞ of INTG8 relative to Forsteo were within the acceptance range of 80.00% to 125.00%. Bioequivalence was also demonstrated for other comparisons including the US reference product (INTG8 vs. Forteo and Forteo vs. Forsteo).

For PD, for baseline non-adjusted data, the geometric mean ratios of the INTG8/Forsteo for corrected calcium levels are close to unity: 99.9 and 100.1 for lnEmax and lnAUEC0-t. The 90% and 95% CIs of the geometric LSM ratios were within the bioequivalence limits of 80.00% to 125.00%. For baseline adjusted data, the geometric mean ratios of the INTG8/Forsteo for corrected calcium levels are also close to unity: 102.4 and 98.1 for lnEmax and lnAUEC0-t. The 90% and 95% CIs of the geometric LSM ratios were within the range of 80.00% to 125.00% for Emax.

Description statistics were provided for secondary endpoints Tmax, λz, Vd, Cl and t1/2, which did not raise any concerns.

Safety

Within the confines of the data provided, the overall rate of AEs reported is low. In total 19 adverse events were reported by 13/105 (12.38%) of subjects. All were mild, or grade 1. While 11 of these 19 AEs are reported for the test product, INTG8, as already mentioned the design of the study does make it difficult to identify the treatment to which an AE might relate, when all 3 formulations were administered consecutively over 3 days. In terms of related AEs, there was a very similar rate reported following all 3 formulations, approximately 3% in each case.

Injection site reaction was only reported once, and this was after the administration of the Forsteo reference product, and there were no other allergic type AE reported.

No subject discontinued from Study 0258-20 due to AEs.

There were no SAEs and no deaths in Study 0258-20.

Of 105 subjects tested for anti-PTH antibodies, only 2/105 were ADA+ post study (at day 28), and in both cases the subjects had already been ADA+ during the screening period. None of these subjects had neutralising antibodies.

3.3. Uncertainties and limitations about biosimilarity

Analytical similarity

Overall, biosimilarity is supported by the analytical similarity exercise. Minor differences in the levels of % oxidised impurities and individual named impurities have been justified on the grounds that all impurities for Sondelbay are within or only slightly higher (0.1%) than the reference product and also considering the data from functional tests and clinical safety/efficacy. There is data for only 7 DP batches manufactured using DS after storage refinement. As these are independent lots, produced consecutively, n = 7 is considered sufficient to conclude on similarity taking into account that the data from Sondelbay lots before DS refinement can also be considered as supportive of similarity for most impurities. The results of stability trending analysis support that the age of the batches at the time of testing do not impact on the biosimilarity conclusion.

PK/PD

The 90% CI does not cross 1 for any of the PK parameters, suggesting there may be some differences in pharmacokinetic parameters. The PK profiles of a small number of subjects were questioned including: Terminal rate constant (lambda_z) cannot be estimated, a spike in IMP concentration, no recordable plasma test concentration at certain timepoints, non-readable (NR) concentrations, subjects whose data had AUC extrap >20%. Statistically significant differences in pharmacokinetic parameters were identified but were not considered to be clinically relevant.

For PD, for baseline adjusted data, the 90% and 95% CIs of the geometric LSM ratios were not within the range of 80.00% to 125.00% for AUEC0-t and a number of subjects had pre-dose values as NR or had zero calcium levels leading to their data being excluded from the baseline adjusted analysis. Statistically significant differences in pharmacodynamic parameters were identified, however this data is more variable than PK and demonstration of biosimilarity assures that the efficacy and safety should be similar to that of the reference Teriparatide.

Safety

Overall the rates of TEAE was very low for all three treatments (19 AEs reported by 13/105 (12.38%) of subjects, and all were mild), and certainly seems much less than seen in other teriparatide studies. However, the safety data from Study 258-20 is somewhat limited, as only 105 subjects were dosed, and all subjects had one dose of each formulation (one test, and 2 reference products) over 3 consecutive days. This crossover, short washout design limits the ability to relate an AE to a specific formulation. The fact that only 1 dose of each formulation was given to each patient also limits the ability to draw meaningful conclusions on the safety of the proposed chronic daily dosing posology. It is also relevant that the only post treatment

laboratory measurements were 28 days after the third treatment (clinical laboratory data was not collected at the end of each period), and so could feasibly be unrelated to any, or none, of the formulations. Overall this study by design is unlikely to be able to detect certain types of adverse reactions such as rare adverse reactions, those with a long latency, those caused by prolonged or cumulative exposure, and the development of anti-drug antibodies (ADAs). However review of the quality of this product and its demonstration to be bioequivalent to the reference Teriparatide assures that the efficacy and safety can be expected to be similar.

Immunogenicity data were collected at baseline and at day 28 after period 3 dosing after the study had concluded. Due to the short duration of the study, the limited number of injections monitored and the relatively small sample size of tested subjects, antibody data from this study can only be considered as exploratory. The limited characterisation of the immunogenicity of INTG8 is still a relative gap in the biosimilarity exercise. The emergence of ADAs and their impact of ADAs on safety over the longer term has not been evaluated in Study 0258-20.

3.4. Discussion on biosimilarity

The analytical similarity program is acceptable and supports a conclusion of biosimilarity.

The benefit risk for INTG8 depends on successful demonstration of similarity to Forsteo in terms of physicochemical and biological terms and confirmation of comparable clinical performance. A confirmatory clinical trial was not submitted with this application. 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.

PK/PD:

As a single PK/PD study is the sole clinical data supporting this application the integrity of the clinical trial data is essential for informing a positive benefit risk assessment. There were a number of concerns regarding the data submitted, most of which have been resolved.

The Natural log (ln)-transformed PK parameters Cmax, AUC0-t, and AUC0-∞ the 90% Confidence Intervals (C.I.) for T vs R1 (Forsteo) are within the acceptance range of 80 – 125% however, it is noted that the C.I. does not cross 1. The PK profiles of a small number of subjects were questioned, as were the statistically significant differences in pharmacokinetic parameters. PD data is considered supportive. PD endpoints were secondary objectives and the PD data generally was more variable than PK data. For baseline adjusted data, the 90% and 95% CIs of the geometric LSM ratios were not within the range of 80.00% to 125.00% for AUEC0-t and a number of subjects had pre-dose values as NR or had zero calcium levels leading to their data being excluded from the baseline adjusted analysis. Statistically significant differences in pharmacodynamic parameters were identified, however PK similarity is predictive of PD effects, therefore it can be accepted that there should not be any relevant difference form the reference Teriparatide.

Safety:

Immunogenicity data was collected at baseline and at the end of the study, at 28 days after period 3. At day 28 of 105 subjects tested for immunogenicity, 2 subjects showed confirmed ADA positive immune response in both pre-dose and end of the study samples. None of these subjects had neutralising antibodies. Apart from one injection site reaction graded as mild there were no other reports of hypersensitivity reactions or allergic reactions. Despite there being no signal of increased immunogenicity risk, this data is very short

term, and it is not sure if the immunogenic potential of INTG8 could be greater than that of Forsteo if given for longer and if the patients are followed for longer. Since the general immunogenic potential of Forsteo is acknowledged to be low and because the quality comparison of INTG8 to Forsteo is sufficiently similar, there is sufficient reassurance on the longer-term safety/ immunogenicity potential of INTG8 compared to Forsteo to enable authorisation. However, the applicant intends to perform an immunogenicity study in the post approval setting to further characterise the potential for immunogenicity with INTG8. While the post marketing immunogenicity study will not be a condition of approval and therefore is not requested by CHMP. However if the applicant wishes to proceed there is no objection to the applicant carrying out this study post approval, and submitting the data for assessment.

3.5. Extrapolation of safety and efficacy

N/A

3.6. Additional considerations

N/A

3.7. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Outcome

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

Sondelbay is indicated in adults.

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

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

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The 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.