EMA/379279/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sondelbay

International non-proprietary name: teriparatide

Procedure No. EMEA/H/C/005233/0000

Note

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

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

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

CS	Clinically significant
CV%	Coefficient of variation
dL	Decilitre
DNA	Deoxyribonucleic acid
E. coli	Escherichia coli
EC	European Commission
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FSH	Follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GCV%	Geometric CV%
GM	Geometric mean
GMR	Geometric mean ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
hr	Hour
HR	Heart rate
IB	Investigator´s brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
K3EDTA	Tripotassium ethylenediaminetetraacetic acid
k_{el}	Apparent terminal elimination rate constant
kg	Kilogram
kg/m2	Kilogram per metre square
L	Litre
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
ln	Natural log

LSM	Least-squares means
MedDRAsq	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
mIU	Million International Units
mL	Millilitre
mmHg	Millimetre of mercury
mmol	Millimole
msec	Millisecond
N	Sample size; number of observations
NCS	Not clinically significant
No.	Number
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	Interval between the P and R waves on the ECG
PTH	Parathyroid hormone
PTH (1-84)	Full-length parathyroid hormone
PTH1R	Parathyroid hormone-receptor-1
QA	Quality Assurance
QC	Quality Control
QRS	Value of the interval between the Q and S waves on the electrocardiogram tracing
QT	Value of the interval between the Q and T waves on the ECG
QTc	Corrected value of the interval between the Q and T waves on the ECG tracing using Bazett´s [QTcB] and Fridericia´s [QTcF] corrections
R^2	Coefficient of determination
REC	Research Ethics Committee
rhPTH (1-34)	Recombinant human parathyroid hormone 1-34
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SID	Screening identification number

SIV	Site initiation visit
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
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
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
WHO	World Health Organisation

1. CHMP Recommendation

Based on the review of the data on quality, safety, efficacy, the application for Sondelbay in:

- the treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture
- the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality

The manufacturing process for the automated assembly of the drug device combination has not been validated. As the manual assembly of the pen was linked to issues with reliability of dose delivery in supporting clinical studies, the automated assembly step is considered a critical manufacturing step. Validation data for a minimum of three production scale batches of the finished product as packaged in the multi-dose pen device is required to demonstrate that the automated assembly process is maintained in a state of control during routine commercial production.

Impurities are present in INTG8 but not the reference product. As these impurities may pose a safety concern, the levels should be measured using a suitably validated method and an appropriate specification should be registered for their control.

Benefit/risk

As the single dose Pharmacokinetic study 0425-17 was the sole clinical data supporting this application the integrity of the clinical trial data is essential for informing a positive benefit/risk assessment. A GCP inspection was requested for clinical study 0425-17. The pivotal study (0425-17) was found to be GCP non-compliant during an inspection at CRO site. Additionally, the GCP inspection confirmed that dysfunction of the manually assembled medical device used in study 0425-17 cannot be excluded. Therefore, it is not possible at the present time to justify that proper dose was administered to patients in study 0425-17.

In line with EMA position concerning the non-acceptability of replacement of pivotal clinical trials during the assessment of an application in the context of a marketing authorisation in cases of GCP non-compliance, it is not permissible to accept new study/data to replace the pivotal study on which the application is based. As the data from study 0425-17 is not GCP compliant the reliability of the data for bioequivalence is not accepted.

Inspection issues

GMP inspection

A GMP inspection was requested for the following site: Intas Pharmaceuticals Ltd Biopharma Division, Ahmedabad – 382213, Gujarat, India in order to provide further product specific information.

An updated GMP certificate NL/H/19/2014264 dated 13.12.2019 has been provided confirming GMP compliance of the manufacturer Intas Pharmaceuticals Ltd Biopharma Division, for manufacture of teriparatide.

GCP inspection

A GCP inspection was requested for clinical study 042517. The conclusions of the GCP inspection at CRO site indicate that there are significant concerns regarding the conduct and overall GCP compliance of the study.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Osteoporosis is a systemic disorder characterized 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.

2.1.2. Epidemiology

Not applicable for biosimilars.

2.1.3. Biologic features

Not applicable for biosimilars.

2.1.4. Clinical presentation, diagnosis

Not applicable for biosimilars.

2.1.5. Management

Not applicable for biosimilars.

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 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. The development programme/compliance with CHMP guidance/scientific advice

The clinical development consisted of one single dose three period three-way crossover PK study (Study 0425-17) in healthy volunteers comparing teriparatide (INTG8) with, EU sourced Forsteo and US sourced Forteo for bioequivalence and subsequently, biosimilarity.

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 for teriparatide (INTG8). The advice given in the clinical part 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). 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 0425-17 50 males and 49 post-menopausal women were recruited.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. General comments on compliance with GMP, GLP, GCP

GMP

For all manufacturing sites for drug substance and drug product except Intas Pharmaceuticals, India which was issued in April 2016. The Applicant was asked to provide an updated GMP certificate. An updated GMP certificate NL/H/19/2014264 dated 13.12.2019 has been provided confirming GMP compliance of the manufacturer Intas Pharmaceuticals Ltd Biopharma Division, Ahmedabad, Gujarat, 382213, India for manufacture of teriparatide.

GLP

The Study G17027 is being done in compliance with OECD principles of Good Laboratory Practice (GLP).

GCP

The clinical PK-study with teriparatide was study 0425-17.

According to the Applicant, the trial complied with all requirements regarding the obligations of investigators and all other pertinent requirements of ICH E6 (R2) 'Guideline on Good Clinical Practice', 2016; ICMR Guidelines for Biomedical Research on Human Subjects; Schedule Y (with subsequent amendments) of Drug and Cosmetics Rules, 1945 of CDSCO (Central Drugs Standard Control Organization), Ministry of Health and Family Welfare, Government of India; Declaration of Helsinki (Brazil, October 2013); and any other applicable regulatory requirements. Therefore, the Applicant concluded, that according to Article 8 (ib) of Directive 2001/83/EC it meets the ethical requirements of Directive 2001/20/EC. Concerns have been identified regarding the quality and validity of the reported data in study 0425-17 conducted by Lambda Therapeutic Research Ltd. A GCP inspection was requested as part of the clinical major objections during the procedure. The conclusions of the GCP inspection indicate that there are significant concerns regarding the conduct and overall GCP compliance of the study.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The application for INTG8, (teriparatide) has been submitted by Accord Healthcare S.L.U.(Spain) as a bio-similar application according to Article 10.4 of Directive 2001/83/EC as amended.

Biosimilarity

The chosen EU reference product is: Forsteo

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

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

This medicinal product is authorised in the EEA (EMEA/H/C/000425) on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended.

Orphan designation

Not Applicable.

Information on paediatric requirements

Not applicable.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as a solution for injection containing 600 micrograms per 2.4 mL (250 micrograms/ml) of teriparatide as active substance.

Other ingredients are: glacial acetic acid, sodium acetate anhydrous, mannitol, meta-cresol, Hydrochloric acid and/or sodium hydroxide (for pH adjustment) and water for injection.

The product is available in a cartridge assembled into a disposable pen. The pen is designed to deliver 28 daily doses of 20 micrograms/ 0.08 ml of drug substance.

3.1.2. Active Substance

General Information

The active substance Teriparatide (INN) is a recombinant, active N-Terminal 34 aa fragment of the endogenous human Parathyroid hormone (PTH). Binding of PTH to PTH-specific cell-surface receptor (PTHR1) mediates the biological action of PTH. The company name INTG8 is also used throughout the dossier to refer to active substance. The amino acid sequence corresponds to 4118 Da. Recombinant Teriparatide contains no glycosylation or other post translational modifications.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

An MO was raised as the EU GMP certificate for the active substance manufacturing and testing site was based on an inspection performed more than 3 years ago and therefore before production of the current product. A product-specific inspection was requested to resolve this MO. Following this inspection, an updated GMP certificate has been provided confirming GMP compliance of this site.

The active substance is expressed in *E. Coli* cells. Testing for both MCB and WCB includes tests for identity, bacteriophage testing, sequencing of plasmid DNA, testing for absence of contaminating fungi and testing for retention of the expression construct. The applicant has detailed how future working cell banks will be qualified.

The INTG8 DS manufacturing process is divided into Upstream and Downstream manufacturing. In general, the process is well described. The Upstream process consists of Seed Cultivation, Fermentation and Harvest, Cell Lysis and multiple Wash steps.

The Downstream process consists of Inclusion Body Solubilisation, Refolding and a series of chromatography and filtration steps. Reprocessing is proposed following filter integrity failure. Supporting data for this reprocessing step has been provided.

Each critical step is controlled through process parameters (PPs) as inputs and process attributes as outputs. An FMEA approach has been used to assign PPs as critical / non-critical and process characterisation studies have been performed to establish proven acceptable ranges for PPs.

For all raw materials used, a supplier has been listed along with in-house specifications and a representative Certificate of Analysis. There are no materials of animal origin. All components (Resins, filters and containers) used in the manufacture of DS are listed along with where in the process they are used.

Process Validation

An FMEA evaluation was used to assign risk to process parameters. Risk ranking was based on frequency of risk occurrence, detectability of risk and severity of risk. Parameters assigned a high-risk potential (potential CPPs) were studied experimentally

At-scale process validation (PPQ) was performed and the process described in S.2.2. The data adequately demonstrate that consistent process performance and acceptable product quality are achieved during routine commercial scale manufacturing. CPPs and non-CPPs were run within their acceptance criteria. PAs and QAs registered in S.2.2 and S.2.4 were monitored during the PPQ studies. All QAs and PAs monitored met the acceptance criteria as per S.2.2. All DS lots met release acceptance criteria. In these studies, the levels of HCP, hcDNA are cleared at each step to below the method LOQ.

Upstream and downstream hold times were validated, however a query is raised requesting batch data in support of proposed hold times.

Resin lifetimes have been validated at scale down. Testing encompasses purity, yield and impurities. The applicant has detailed the test methods that were employed. A protocol for validation of resin lifetimes at-scale has been provided. In relation to this, a query is raised requesting that HCP is evaluated with a quantitative limit.

Manufacturing process development

The upstream process was initially developed at a lower scale. This was subsequently scaled up to the clinical/commercial scale. Optimization work was also undertaken for the downstream, process which was initially developed at lower scale and subsequently scaled up. The clinical trial batches were produced using the same manufacturing process. For the first process validation campaign (PV1), there was a minor change in a process step compared to the clinical batches. For the PV2 batches there were some changes to set points, and ranges for CPPs and KPPs. The commercial process uses the same process as for PV2.

A comparability study was provided. The comparability data mainly comprises of a table of batch release data which supports the comparability claim. However, as outlined in ICH Q5E, the tests and analytical procedures chosen to define drug substance or drug product specifications alone are generally not considered adequate to assess the impact of manufacturing process changes since they are chosen to confirm the routine quality of the product rather than to fully characterise it. Therefore, the current comparability package is considered insufficient. Additional comparability data has been requested, including appropriate assay(s) to characterise primary and secondary structure, deamidated, truncated and succinimide forms, charge by CEX, high molecular weight species by SEC, binding kinetics by SPR.

A standard risk assessment approach has been used to stratify the quality attributes into high, medium and low risk. This ranking is further used in the biosimilarity studies. In order to assess the criticality of process parameters and decide which parameters should be investigated further in process characterisation studies, a failure modes and effects analysis (FMEA) was carried out. In general, a standard type of approach was used for the FMEA.

Process characterization studies were conducted using scale down models which were qualified on the basis of statistical equivalence with commercial scale batches. Further details of the commercial scale batches used for this comparison have been requested. For each manufacturing step, design of experiments (DoE) studies were performed which included both univariate and multivariate studies. A significant amount of data is provided for the multivariate studies which followed standard QbD principles. Where the studied range was not found to have an impact on the relevant outputs, the characterized 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 justification for assigning key process parameters (KPPs) versus critical process parameters (CPPs) has been sufficiently explained.

Characterisation

Teriparatide drug substance was characterised through evaluation of physico-chemical and functional product quality attributes. The data presented confirms the expected primary, secondary and tertiary structure of the drug substance. Functional characteristics, product variants, pharmaceutical properties and process related impurities have also been suitably evaluated for the DS. Taking into account the simple molecular structure of Sondelbay (34 amino acids and without disulphide bonds) and its expression in *E. coli* (no glycosylation or posttranslational modifications), the testing panel for characterization is acceptable. In general, the characterisation study was carried out using orthogonal analytical methods. The data supporting method qualification for the purpose of characterisation was provided. Further details of characterisation can be found in the biosimilarity section.

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

Specifications

The release specifications include tests for identity, purity, potency and safety related tests and are, in general, in accordance with ICH Q6B. There is no dedicated release test proposed to routinely control for charge variants in the drug substance, however further data are requested to support this conclusion. Tests are registered for the relevant process related impurities DNA and HCP. Specifications are also in place for endotoxin and bioburden and proposed limits are acceptable.

At Day 120, the applicant was requested to register a specification or IPC for certain impurities. In response, the applicant claimed that the SE-HPLC method was qualified to detect them. No data were provided to support these claims. The impurities may pose a risk in terms of immunogenicity. The presence of these impurities, which are in the biosimilar but not the reference product, could therefore result in an unfavourable safety profile of INTG8 compared to the reference product and this represents a Major Objection. The applicant has been requested to provide data to show that the SE-HPLC method is appropriately validated to detect these impurities. Furthermore, the levels of these impurities in clinical batches should be presented and an appropriate specification limit should be set. The limit of quantitation of the method should be justified in the context of the potential risk of increased immunogenicity caused by residual impurities.

The approach of using stability data to justify the release limit for total oxidation is not supported, the Applicant has been requested to tighten the acceptance criteria to the limits specified in the Ph. Eur. monograph for Teriparatide. The specification for potency is reasonably close to the actual batch data

and is acceptable. Specifications for the impurities DNA and HCP are sufficiently low and do not lead to any safety concern. The specification for endotoxin is within the required Ph. Eur. limit and the specification for bioburden is acceptable is acceptable for a biological drug substance.

Analytical procedures and reference standards

In general, a very detailed description in the form of SOP's was provided for the analytical method descriptions. All compendial methods are considered acceptable and were suitably qualified. In general, the methods have been validated according to ICH Q2. The method for identity and purity has been updated to include reporting of retention times for related proteins D and E, as per the teriparatide Ph. Eur. monograph. The relative potency assay method was validated for INTG8 DS and DP samples. The applicant is requested to update the method description to clearly state that the INTG8 reference standard should be used for the potency bioassay.

The methods for HCP and HCDNA quantitation in INTG8 DS samples are adequately described and validated in accordance with ICH Q2.

Additional in-process analytical methods were provided for purity and osmolality (Ph. Eur. 2.2.35) for DS in-process samples.

Batch analyses

Batch data are provided for 14 batches in total; all release tests were within the proposed acceptance criteria and it appears thus far that the process is capable of manufacturing batches of consistent quality. Three of the batches were used in the clinical study and six were PPQ batches. Batch data has been requested from the three new commercial batches which were manufactured using the updated storage conditions.

Reference standards

Details of the historical reference standards have been provided. A development reference standard was initially established from an R&D batch. A primary reference standard (PRS) was subsequently prepared from a clinical batch. The PRS was tested using a combination of release tests and extended characterization tests; SOPs have been provided for the analytical methods. A working reference standard was derived from the PRS. A protocol for the establishment of the future working reference standards has been provided.

Container closure

Appropriate specifications are registered for each container closure type and include tests for physical dimensions, endotoxin, sterility, biological reactivity and cytotoxicity. CoAs have also been provided for each container closure. The applicant has confirmed that the container closure systems conform to the relevant requirements of Ph. Eur. 3.2.2.1. Integrity testing was carried out by the supplier.

Stability

In the data provided to date for real time stability testing on PV batches, all tests are within acceptance criteria and no trends were observed for INTG8 DS within 12 months.

However, some major discrepancies in the reporting of results for each batch were noted.

The data from the results provided for the stability batches is not considered acceptable as sample analysis was not conducted at the proposed 3-, 6-, 9-, 12-month intervals in accordance with ICH Q1A. The applicant is asked to provide a justification to support how they are representative of the required testing frequencies as described in ICH Q1A.

Additionally, PV batches were removed from the stability study and it is not clear why they were removed. A query is raised to provided updated results on these batches.

The material for the container closure used for these stability studies is representative of the commercial container closure. Photostability testing was carried out in accordance with ICH Q1B. INTG8 DS is photosensitive on exposure to either UV or white light.

In general, the analytical methods used for stability testing are registered with appropriate stability acceptance criteria in S.4.1. The post-approval stability commitment to place INTG8 DS on stability for each calendar year that INTG8 DS is manufactured with adequate test methods, specifications, and testing intervals was provided and considered acceptable.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The drug product is supplied as a sterile solution in a multi-dose, class cartridge (600 microgram/2.4 ml) which is assembled into a pen injector. The drug-device combination contains treatment for 28 doses as a subcutaneous injection. The drug product formulation is based on that of the reference product and contains the following: teriparatide, glacial acetic acid, anhydrous sodium acetate, mannitol, meta-cresol, hydrochloric acid/ sodium hydroxide for pH adjustment and water for injection. There is no overage proposed, and no novel excipients are present.

Product development has been described in the dossier. Changes in manufacturing processes over the history of the product (engineering, clinical and PPQ batches) have been described and comparability established based on quality attributes of the in-process intermediates and drug product. A more comprehensive compatibility study has been requested to demonstrate comparability between the pivotal clinical and PPQ/ commercial scale batches. It is not clear that changes in analytical methods throughout product development have been evaluated or equivalency demonstrated. Range finding studies were performed to support the commercial formulation and preservative efficacy tests have been performed on small scale batches. Data on two commercial scale batches supports that at the lower end of the proposed target manufacturing range, preservative efficacy is maintained. The updated report, including a comment on compliance of methods with the Ph. Eur., is requested. The primary packaging consists of a glass cartridge, rubber stopper and aluminium seal. Primary packaging components are adequately described and supported by development studies. The glass cartridge is then assembled into the outer pen device and a major objection has been raised on this component of the finished product. The device has a CE mark and is supported by product development on the final drug-device combination including dose accuracy and functionality testing. In-use stability and real time stability data, as well as process validation data on the assembly process remains outstanding and must be provided before the use of this device can be accepted.

Manufacture of the product and process controls

A major objection was raised regarding finished product manufacturing site as the GMP certification provided was based on an inspection performed more than 3 years ago. A product-specific inspection at this multi-product facility has been performed and the updated GMP certificate submitted. Sites for sterilisation of primary packaging containers should also be registered in the dossier.

The manufacturing process for the glass cartridge is standard and involves the following steps: preparation of the formulation buffer, mixing with drug substance, sterile filtration, aseptic filling/stoppering, visual inspection and secondary packaging. Hold times for the formulation buffer and formulated bulk have been provided at commercial scale and support the proposed in-use hold times.

This is a photosensitive product and the applicant has described steps to ensure the drug substance is protected from light during the manufacturing process. The description of the manufacturing process has been updated to include reference to automated assembly of the drug device combination. However, this is considered a fundamental part of the manufacturing process and so must be appropriately validated. A major objection has therefore been raised on this aspect of the manufacturing process.

Overall the control strategy for the drug product is considered as adequate. The proposed target acceptance criteria and/or PARs are listed for both critical and non-critical parameters. Appropriate IPCs are in place and include filter integrity pre- and post-sterile filtration, and fill volume. The proposed limit for bioburden testing prior to sterile filtration should be tightened to NMT 10 CFU/100 ml. The control strategy for the automated assembly of the cartridge in the device has been provided. The manufacturing process validation is presented for PPQ batches at commercial scale and is acceptable and the process is demonstrated to be capable of producing batches of consistent quality. However, the process validation data for the automated assembly process with the proposed device at commercial scale remains outstanding and has been requested. A toxicological assessment of the results of extractable/leachable studies has been provided, one clarification on risk of nitrosamines remains. There is no design space formally requested and reference to both design space and prior knowledge have been removed from the dossier as neither have been supported by appropriate data.

No shipping validation has been provided and this has been requested for the product as packaged in the final drug device combination.

Product specification, analytical procedures, batch analysis

In general, the drug product specifications are considered sufficient. Additional tests for purity, impurities and aggregates have been included in the updated release specifications. In addition, specifications have been presented for the drug-device combination, including functional parameters for the pen assembly such as functionality testing and delivered dose accuracy. These are monitored both at release and over stability studies to demonstrate that the functionality of the pen device does not impact on the delivered dose over time.

Specification limits have been set based on ICHQ6B, ICHQ5C, the SmPC for Forteo, the EPAR for Forteo, currently available batch data from clinical and PPQ batches and available real time stability data. Stability specifications are the same as those proposed for release

In general, the descriptions of the analytical methods are considered adequate – some minor clarifications were provided. All validation reports for analytical methods have been generated and the applicant has confirmed that technical transfer to EU QC test facilities has been successfully performed.

Data from several drug product batches have been provided in order to justify the acceptance criteria. A risk assessment in accordance with ICHQ3D for elemental impurities has been provided.

Container closure

The primary container for the drug product consists of a cartridge. All components are supplied pre-sterilised. The applicant has been requested to register the sterilisations cycles to the dossier. Non-pharmacopoeial cycles have been appropriately validated Supplier certificates of conformance have been supplied for each of the primary packaging components and in-house specifications are registered to the dossier.

The secondary container is a pen injector, a plastic tray and disposable plastic carton. The pen consists of three components – pen cap, pen body and cartridge holder. Pens were manually assembled for the

clinical trials batches and lack of exposure was seen in 11 out of 99 subjects. The corrective action proposed is to use machine assembly of the pen device commercial product, hence this is considered a critical quality component of the manufacturing process and data to support this step was requested as a major objection. Dose accuracy studies have been performed and are appropriate. The automated assembly of the pen has been demonstrated on small scale studies to meet dose accuracy and functionality testing requirements, however the applicant has not provided validation data on commercial scale batches to support that the process remains in control and consistently produces product capable of meeting its release specifications (including device functionality testing which has been demonstrated to be a critical quality attribute of the finished product). This major objection is therefore retained.

Stability of the product

The proposed shelf life for INTG8 DP cannot be supported until sufficient stability data on commercial scale batches has been provided to support this proposal. The limited stability data submitted to date is not in accordance with the requirements of ICH Q5C and ICH Q1A(R2). At present the applicant has provided real time data for clinical batches. No real time data has been presented for commercial product with automated assembly of the cartridge into the device. The applicant is requested to provide sufficient real-time data on commercial product packaged in the drug-device combination to support the claimed shelf life.

Photostability studies conclude that the drug product is photosensitive and the primary container must be stored protected from light (either in secondary or tertiary packaging).

In-use stability tests should be repeated on the drug device combination. An in-use stability data to support that the device can be used for 28 daily injections over 28 days has been provided but it is not clear that this data has been generated on a pen which was assembled automatically. This has been requested.

Biosimilarity

Sondelbay has been developed as a biosimilar of EU approved Forsteo (marketing authorisation holder: Eli Lilly Nederland B.V.) containing the same active substance, teriparatide. The strength, presentation and composition of the proposed biosimilar is identical to the EU reference medicinal product (RMP). The Sondelbay clinical development program included one clinical study to demonstrate clinical similarity (PK and PD) between Sondelbay, Forsteo and Forteo (US product) in terms of clinical pharmacology efficacy and safety. All INTG8 lots used are representative of the commercial process. A number of the RMP batches were frozen prior to expiry and subsequently thawed for analytical testing during the similarity exercise, however these are included only as supportive information.

An overarching major objection was raised on the biosimilarity package on the basis that the use of expired reference product batches, which have been stored at an unapproved condition prior to testing (frozen – 80 °C), was not adequately justified with respect to demonstrating biosimilarity. This was successfully addressed by including additional batches in a revised biosimilarity exercise and including the frozen batches for information only. For all analytical tests, the final number of batches included in the biosimilarity exercise was justified as being sufficient to establish a suitable quality target profile for each attribute.

As part of the major objection, the Applicant was requested to justify the statistical approach. The Applicant clarified that the 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.

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.

While the overall biosimilarity program (analytical methods applied) is not very extensive, this can be attributed to the simple molecular structure of Sondelbay (34 amino acids and without disulphide bonds) and its expression in *E. coli* (no glycosylation or posttranslational modifications). 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)*.

Primary and higher order structure

The results of the primary and higher order structure evaluation support the claim of biosimilarity.

Product related variants

Product related impurities were evaluated. In terms of total purity, INTG8 can be considered comparable to the reference product. However, it is evident that INTG8 has a consistently higher content of oxidised peaks than the RMP. Given the low levels observed, it is not considered that they will have an impact on efficacy. However, currently an impact on safety cannot be ruled out.

Functional characteristics

Biological activity was evaluated using two different cell-based assays. Taken together, the data from both potency assays strongly supports the biosimilarity claim.

An SPR based method was also used to determine binding kinetics of teriparatide as part of the evaluation of functional characteristics. All INTG8 batches were within the min-max and mean ± 3 SD range of the EU RMP. This provides further evidence of comparable potency.

Pharmaceutical properties

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. The slight differences observed are not considered to impact on the claim of biosimilarity.

Comparative forced degradation study

In this study, different modes of stress were applied in a controlled manner to test samples to compare the degradation trend and nature of impurities. It is agreed that the stress applied lead to a comparable increasing trend of degradation impurities for all samples both qualitatively and quantitatively.

Post approval change management protocol(s)

Not applicable.

Adventitious agents

As the drug substance is generated in *E. coli* the risk of viral contamination of the cell line by viruses potentially harmful to humans is minimal. Therefore, no formal viral validation study is required.

The applicant has identified all materials of biological origin in manufacture of the drug substance, all are free of materials of human or animal origin with the exception of one raw material, obtained by acid hydrolysis of duck feathers. As per EMA/01/01 rev 01, birds are not susceptible to TSE and the certificate of origin and TSE/BSE statements are supplied. All other components are supported by certificates of analysis.

GMO

Not applicable.

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

The drug substance Teriparatide (INTG8) is manufactured according to a standard process in an *E. coli* cell line. Sufficient information has been provided on cell line development and characterisation. Comparability of the process and the final drug substance from the different production runs (engineering, clincial, PPQ) has been adequately described. Overall the control strategy appears to be appropriate with defined process parameters and IPCs in place. The FMEA study used to determine process parameters for evaluation during process characterisation been provided. The process validation presented is sufficient to support a consistent process. The drug substance is sufficiently characterised using a suite of appropriate analytical tests. The testing panel and proposed specifications for release of the drug substance is generally acceptable however there are some outstanding queries regarding oxidised impurities.

A Major Objection is raised on the presence of impurities which are present in INTG8 but not the reference product. As these may pose a safety concern, the levels should be measured using a suitably validated method and an appropriate specification should be registered for their control.

Analytical procedures are well described and validated, however some issues are to be clarified. Batch data is consistent, however some additional information is requested on the commercial batches. A two-tiered reference standard system is in place. Further details of the container closure system are required, as the proposed containers can cause oxidation of the drug substance. The claimed drug substance shelf life is currently not supported as discrepancies were noted in the reporting of results and data is missing for PV batches.

The development of the drug product formulation and manufacturing process has been extensive; a number of issues have been raised based on the information provided. A major objection is raised on the omission of validation data to support the automated assembly of the drug device combination, a critical step in the manufacturing process. This is requested to support the applicability of the proposed control strategy for this process, batch data for the DDC and stability data generated in product as packaged in the DDC.

The testing panel for release of drug product is generally acceptable but the applicant is requested to further tighten limits for total impurities. Analytical methods are adequately described. A total of nine batches has been analysed and the batch data is consistent. Additional batch data for clinical batches has been provided. The primary container closure system is acceptable. Additional information has been provided for the secondary packaging (pen device) components. The claimed drug product shelf life is not supported. Stability studies have commenced with the commercial product but no data has been presented for review. In addition, it is not clear that drug device combination product has been placed on stability, real time data is requested.

Sufficient data has been provided to support biosimilarity. The number of batches tested, the panel of analytical tests and the statistical approach used are all considered to be acceptable and in accordance with with biosimilar guidelines CHMP/437/04 Rev 1 and CHMP/BWP/247713/2012. An outstanding issue remains regarding the higher levels of oxidation in INTG8 compared with the reference product.

3.2. Non clinical aspects

3.2.1. Pharmacology

INTG8 is a recombinant 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), authorized in the EU.

In order to demonstrate similarity to the reference product the applicant has performed several in vitro studies.

The assessment of biosimilarity or not of INTG8 will be primarily based on the quality assessment of the appropriateness and acceptability of the in vitro comparability studies conducted and is discussed with the Quality AR. The submitted non-clinical in vitro studies do not suggest a significant difference between INTG8 and the reference products tested.

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

No secondary pharmacology, PD drug-drug interaction or safety pharmacology studies have been performed. This is considered acceptable for a biosimilar application.

3.2.2. Pharmacokinetics

No nonclinical assessment of the pharmacokinetics of INTG8 has been provided. The applicant has completed a 28-day repeat dose toxicity study in rats, Study G17027. In addition, it is noted that a clinical PK study has been performed. Given that INTG8 is a relatively simple peptide which 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.

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).

3.2.3. Toxicology

A GLP-compliant, comparative toxicity study was not deemed necessary. This is agreed and endorsed considering the well-established profile of the reference product and considering the principles of the 3R's for animal welfare. Furthermore, this is 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/42832/2005 Rev1). The study overall 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.

No genotoxicity, reproductive toxicology or carcinogenicity studies have been performed and as outlined in the relevant guidance, none are necessary for biosimilars (EMEA/CHMP/BMWP/42832/2005 Rev1). Local tolerance was to be assessed as part of the comparative repeat dose toxicity studies.

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

In addition, according to the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" (EMEA/CHMP/BMWP/42832/2005 Rev1) the impurities present may have an effect on immunogenic potential and the potential to cause hypersensitivity. The Applicant has presented chemical and biological data analysis on impurities profile differences that may cause immunogenic and hypersensitivity consequences of treatment with INTG8 compared to Forsteo. These data suggest similarity of INTG8 to the Forsteo in terms of immunogenic potential and the potential to cause hypersensitivity.

3.2.4. 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.

3.2.5. Discussion on non-clinical aspects

The nonclinical package to support the MAA, including the overview and written summaries, is very limited, however, this has to be considered in the context of 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. No in vivo studies have been performed and the in vitro studies alone are sufficient from a nonclinical perspective to attest to the absence of differences between INTG8 and the reference product, Forsteo. The absence of secondary PD, safety pharmacology or PD drug interactions in line the relevant guideline.

Pharmacokinetics

There is no information provided in relation to the nonclinical pharmacokinetics of INTG8. This can be considered 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 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. The proposed text for Sections 4.6 and 5.3 is in line with that of the reference product.

3.2.6. Conclusion on non-clinical aspects

The MAA is approvable from a nonclinical perspective.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Type of Study	Study Objective	Study Design	Test Product; Reference Product; Dose/ Regimen; Route of Administration	Study Population	No. of Subjects Age	Duration of Treatment	Status/Results
Study 0425-17 conducted in India under CDSCO-approved CTA (Indian clinical trial registry number: CTRI/2018/09/015697)	To demonstrate PK bioequivalence of INTG8 of Intas Pharmaceuticals Limited, India against Forteo® and Forsteo® following a 20 µg single SC injection	Randomized, three-treatment, three-period, crossover, assessor-blind, single-dose, bioequivalence study	**Test Product:** INTG8 (Intas, India); **Reference Products:** Forsteo (Eli Lilly Nederland B.V., The Netherlands) & Forteo (Lilly USA, LLC); Single dose (20 µg); SC administration.	Healthy men and postmenopausal women	99 dosed and completed (59 male, 40 female); 19 to 64 years old	Single dose	**Primary** **Completed** **Demonstrated PK Similarity (Teriparatide PK profile):** 90% CI of the primary endpoint parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within predefined acceptance limit (80%-125%) for T vs R1, T vs R2, and R2 vs R1. **Secondary** **Demonstrated PD Similarity (Baseline non-adjusted corrected total serum calcium levels)** The geometric LSM ratio values of $AUEC_{0-t}$ and E_{max}, of baseline non-adjusted corrected total serum calcium levels were within 80% to 125% and hence similar for the test and reference arms. **Exploratory** **Immunogenicity:** Of 98 subjects tested for immunogenicity, 2 subjects were confirmed ADA-positive; 1 subject in the R2TR1 sequence, and 1 subject in the R1R2T sequence (both were positive at the beginning

3.3.1. Methods

3.3.2. In general, the applicant has followed the principles of the EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1). Pharmacokinetics

As the Applicant claims INGT8 to be biosimilar to Forsteo they have not conducted dedicated studies to characterise the PK of teriparatide.

The INTG8 clinical development program included one comparative PK study (**study 0425-17**) in healthy subjects to demonstrate clinical similarity between INTG8, Forsteo, and Forteo in terms of clinical pharmacology, efficacy and safety.

The Applicant decided on a randomized, assessor-blind, three-treatment, crossover, single-dose PK and PD study of INTG8, Forsteo, and Forteo. with the primary focus of demonstrating overall similarity in PK between INTG8 and Forsteo and Forteo. and for the planning and conduct of this study relied on the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), which is in principle acceptable, provided that quality, non-clinical and clinical data show robust evidence for biosimilar comparability.

This is the only clinical study supporting this biosimilar application.

Study Design

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.

Sample Size

The sample size was calculated based on the total coefficient of variation (CV) of about 41% for the area under the concentration-time curve from time zero to time t (AUC0-t) obtained from the literature. The sample size was determined using the SAS® software by considering the following assumptions:

a) T/R ratio = 95.0% to 105.0%

b) CV ~ 41%

c) Significance Level = 5%

d) Power = 80%

e) Bioequivalence Limits = 80.00% to 125.00%

Based on the above estimates, 68 completers were required to obtain a sufficient power. Considering approximately 30% dropouts and/or withdrawals (anticipated to be high due to 3 consecutive periods), 99 subjects were to be enrolled in Study 0425-17.

99 healthy men and postmenopausal women entered the study and were randomised to either of the three treatment arms.

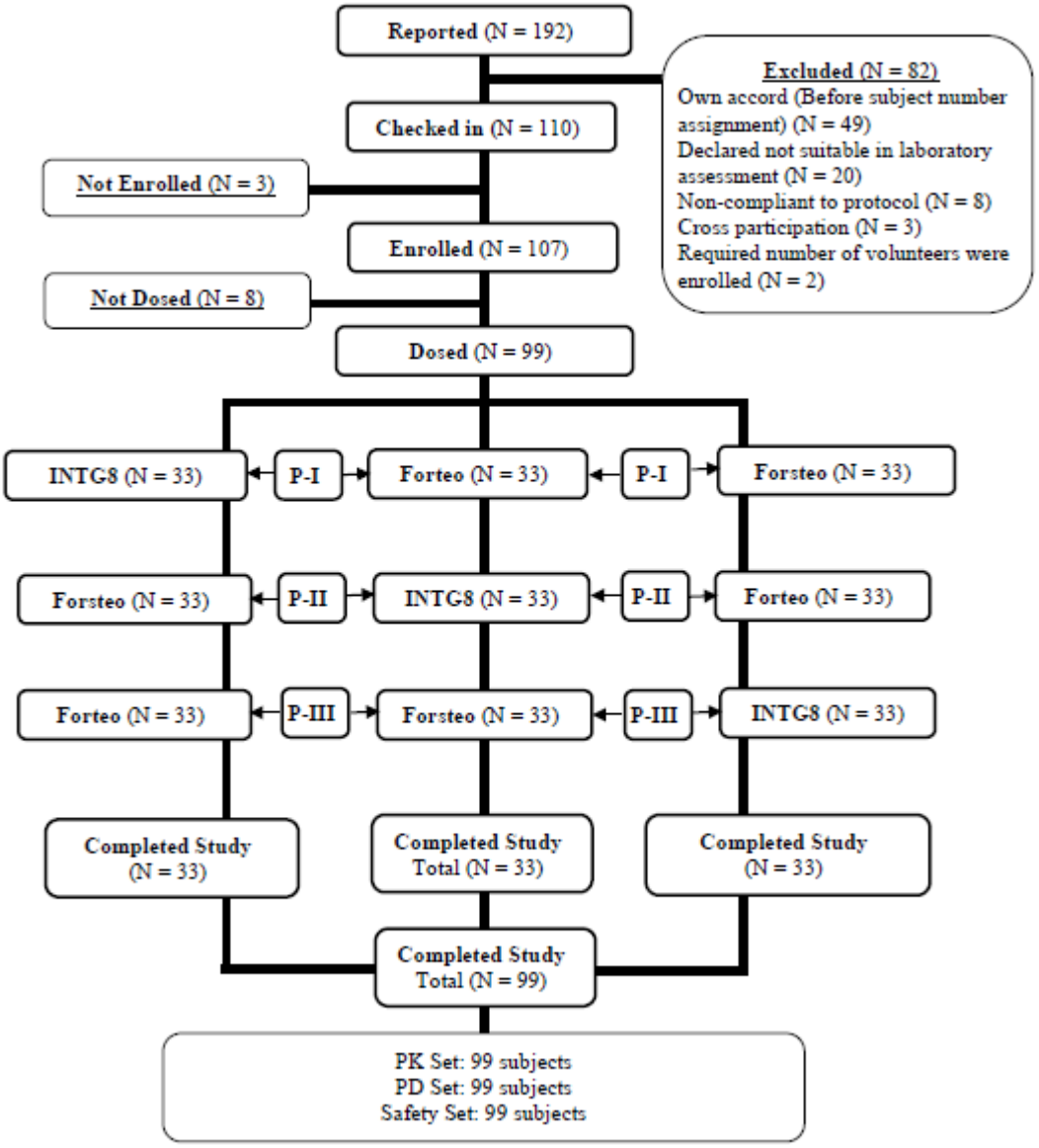
Study 0425-17 was conducted in Indian healthy men (aged 18–45 years) and postmenopausal women (aged 45–65 years).

Demographics and Other Baseline Characteristics

Parameters					**Total (N=99)**
		TR1R2 (N=33)	**R2TR1 (N=33)**	**R1R2T (N=33)**	
Age (years), Mean ± SD		39.9 ± 13.34	40.8 ± 13.28	38.5 ± 14.08	39.7 ± 13.46
Gender, N (%)	Male	20 (60.61%)	19 (57.58%)	20 (60.61%)	59 (59.60%)
	Female	13 (39.39%)	14 (42.42%)	13 (39.39%)	40 (40.40%)
Height (cm), Mean ± SD		160.5 ± 10.37	159.2 ± 10.84	161.9 ± 10.14	160.5 ± 10.41
Weight (kg), Mean ± SD		59.2 ± 8.97	59.6 ± 9.47	59.5 ± 9.00	59.4 ± 9.06
BMI (kg/m^2), Mean ± SD		23.03 ± 3.052	23.54 ± 3.178	22.73 ± 2.951	23.10 ± 3.049

Subjects were randomized to receive a single SC dose of 20 µg INTG8, Forsteo, and Forteo (via pre-filled pen) in crossover manner.

The sequence of administration of treatments i.e. "TR1R2" or "R2TR1" or "R1R2T" to the subjects were determined according to the randomization schedule.



Note: A washout period of 24 hours was maintained between the dosing days of any two consecutive periods.

For the characterization of the PK profile of teriparatide, venous blood samples were collected for determination of teriparatide serum concentration. The samples were collected at pre-dose and at 0.083, 0.167, 0.25, 0.333, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 4, 5, 6 hours following drug administration, in each period.

The primary objective was to demonstrate PK bioequivalence of INTG8 against Forteo and Forsteo following 20 µg single SC injection.

During the study, 48 blood samples (each of 3 mL) for pharmacokinetics (PK), were collected from each subject except for missing sample to evaluate the PK profiles of INTG8, Forsteo and Forteo.

The Device

Forsteo

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

Forsteo is supplied in siliconised Type 1 glass cartridges sealed with rubber closures and aluminium caps. Each cartridge is supplied in a prefilled delivery device (pen) that is not refillable (disposable), Ready to use device (No priming needed) with 6 steps to injection as mentioned in the Summary of Product Characteristics of Forsteo.

INTG8

INGT8 was supplied as teriparatide 20 µg/80 µL SC. solution for injection.

The INTG8 device used in Study 0425-17 was manually assembled, whereas the to-be marketed INTG8 pen device will be machine assembled.

The pen device of INTG8 will be a reusable device however, the applicant has outlined that the dose delivered would remain same as that of Forsteo.

Criteria for conclusion of bioequivalence

Bioequivalence of INTG8 with that of Forsteo was to be concluded, if the 90% CI for the ratio of geometric LSMs for the ln-transformed PK parameters Cmax, AUC0-t and AUC0-∞ fell within the acceptance range of 80% to 125%.

In the PK Study Bioequivalence is based on the comparisons of Test Product-T vs. Reference Product-R1 and Test Product-T vs. Reference Product-R2.

Pharmacokinetic Endpoints:

Primary PK Parameters	
Cmax	Maximum measured serum concentration
AUC0-t	Area under serum concentration versus time curve from time zero to the last measurable concentration
AUC0-∞	Area under the serum concentration versus time curve from time zero to infinity
Secondary PK Parameters	
Tmax	Time to reach maximum measured serum concentration
t1/2	Terminal half-life
Λz	Terminal rate constant
AUC_%Extrap_obs	Residual area in percentage
Vd	Volume of distribution
Cl	Total body clearance

1, 1.333, 1.667, 2, 2.5, 3, 4, 5, 6 hours following drug administration, in each period.

Number of subjects (planned and analyzed)

Enrollment (n=99)

Final PK analysis (n=99)

Pharmacokinetic and statistical Investigations

Subject No. 1012 (Period 1), 1016 (Period 2), 1023 (Period 3), 1032 (Period 2), 1050 (Period 2), 1051 (Period 1), 1053 (Period 2), 1060 (Period 3), 1072 (Period 3), 1094 (Period 2) and 2047 (Period 1) had no detectable concentrations of Teriparatide after administration of test product-T.

No such behaviour has been observed for other periods of the same subjects and for all periods of other subjects. For these subjects values of Cmax and AUC0-t were estimated as zero while AUC0-∞ parameter cannot be estimated.

To investigate the possible cause of no detectable concentration in few subjects in particular periods of the study, A detailed investigation was conducted by a team comprising of members from Clinical Pharmacology and Medical Affairs (CPMA), Bio-analytical (BA), Pharmacokinetics, Biostatistics and Programming (BP) of Lambda Therapeutic Research Ltd. This investigation report includes clinical, Bio-analytical, pharmacokinetic and statistical aspects of the study.

The Applicant has concluded that in absence of any evidence from clinical and bio-analytical investigations, subjects are included in the pharmacokinetic and statistical analysis in line with protocol. However, during the statistical analysis, zero values of Cmax and AUC0-t were automatically disregarded during analysis, due to ln-transformation.

Pharmacokinetic Results

The PK parameters of INTG8, Forsteo, and Forteo are summarized in the following table:

Source: Study 0425-17 report body page 9/459

Pharmacokinetic Parameters of INTG8, Forsteo, and Forteo (N=99)

Parameters (Units)	Mean ± SD (untransformed data)		
	INTG8 (N=96)	Forsteo (N=96)	Forteo (N=96)
T_{max} (h)*	0.250 (0.083 – 1.000)[a]	0.250 (0.083 – 1.333)	0.250 (0.083 – 1.333)
C_{max} (pg/mL)	104.500 ± 61.4114	125.894 ± 45.0302	120.881 ± 54.9993
AUC_{0-t} (pg.h/mL)	130.533 ± 80.9174[¥]	158.539 ± 60.3275[#]	163.874 ± 77.1427[$]
$AUC_{0-\infty}$ (pg.h/mL)	165.477 ± 71.0457[^]	180.406 ± 63.4572[#]	191.465 ± 107.5735[$]
λ_z (1/h)	0.998 ± 0.3075[^]	0.971 ± 0.3542[#]	0.931 ± 0.3130[$]
$t_{1/2}$ (h)	0.760 ± 0.2338[^]	0.885 ± 0.8415[#]	0.871 ± 0.6037[$]
AUC_%Extrap_obs (%)	12.096 ± 5.6319[^]	12.355 ± 10.8108[#]	12.763 ± 11.0177[$]
V_d (L)	157.736 ± 84.9041[^]	156.292 ± 145.3454[#]	151.532 ± 86.9291[$]
Cl (L/h)	149.215 ± 101.7220[^]	127.838 ± 57.5554[#]	126.496 ± 55.3318[$]

*T_{max} is represented as median (min-max) value.

[¥]N=95, [#]N=94, [$]N=91, [^]N=84 and [a]N=85.

Note 1: Subject Nos. 1012 (Period-I, INTG8), 1016 (Period-II, INTG8), 1023 (Period-III, INTG8), 1032 (Period-II, INTG8), 1050 (Period-II, INTG8), 1051 (Period-I, INTG8), 1053 (Period-II, INTG8), 1060 (Period-III, INTG8),1072 (Period-III, INTG8), 1094 (Period-II, INTG8) and 2047 (Period-I, INTG8) had all zero serum concentration. Hence, some of the pharmacokinetic parameters were not calculated for the same.

Note 2: Subject No. 1025 (Period-II, Forteo), 1027 (Period-III, Forsteo), 1029 (Period-I, Forsteo), 1035 (Period-II, Forteo) and 1083 (Period-I, Forsteo) had complete NR samples in their respective periods. Hence, none of the pharmacokinetic parameters were calculated for the same.

Note 3: Subject Nos. 1011 (Period-III, Forsteo), 1012 (Period-III, Forteo), 1037 (Period-I, Forteo), 1072 (Period-II, Forteo), 1077 (Period-II, Forteo), 1087 (Period-I, INTG8), 1088 (Period-I, Forsteo) and 1096 (Period-II, Forteo) had three consecutive non-reportable (NR) samples in the late phase. Hence, the same were excluded from AUC_{0-t} and other elimination phase-dependent pharmacokinetic parameters.

Note 4: Subject Nos. 1005 (Period-I, INTG8), 1036 (Period-III, Forteo), 1070 (Period-II, INTG8) and 1097 (Period- III, INTG8) were excluded based on the data review.

Summary of Statistical Comparisons of Pharmacokinetic Parameters

Source: Study 0425-17 report body page 10/459

(INTG8 vs. Forsteo) (N=99)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	INTG8 (T)	Forsteo (R1)	Ratio (T/R1)			
lnCmax	113.657$	121.392*	93.6	88.51 – 99.04	21.7	100.0
lnAUC0-t	135.041#	150.192^	89.9	83.47 – 96.85	28.4	99.9
lnAUC0-∞	153.050#	175.237^	87.3	81.56 – 93.53	26.0	100.0

*N=96, $N=85, ^N=94 and #N=84.

Subgroup Analysis

A Subgroup Analysis was performed which excluding the 11 subjects Subject No. 1012, 1016, 1023, 1032, 1050, 1051, 1053, 1060, 1072, 1094 and 2047 who were found to have zero concentration in either period Teriparatide 20 µg/80 µl recombinant human parathyroid hormone [1-34] Injection.

Summary statistics of pharmacokinetic parameters for Teriparatide (T vs. R1)

Source Study 0425-17 Table No. 14.2.1.15

Excluding Subject No. 1012, 1016, 1023, 1032, 1050, 1051, 1053, 1060, 1072, 1094 and 2047 had all zero concentration in either period Teriparatide 20 µg/80 µl recombinant human parathyroid hormone [1-34] Injection.

		Tmax (h)	Cmax (pg/mL)	AUC0-t (pg.h/mL)	AUC0-inf (pg.h/mL)
N		85	85	84	84
Mean		0.259	118.023	147.626	165.477
SD		0.1638	51.4796	69.7247	71.0457
CV(%)		63.2	43.6	47.2	42.9
Geometric Mean		0.226	109.438	132.591	151.156
Reference Formulation-R1					
N		85	85	83	83
Mean		0.316	122.379	153.915	176.314
SD		0.2102	38.7872	54.2014	58.0170
CV(%)		66.5	31.7	35.2	32.9
Geometric Mean		0.263	116.048	143.380	166.813
ANOVA p-value					
ln-transformed Group		-	0.0428	0.3826	0.1494
	Sequence	-	0.0334	0.0017	<0.0001
	Sequence*Group	-	0.5901	0.6469	0.1981
	Subject(Sequence*Group)	-	<0.0001	<0.0001	<0.0001
	Formulation	-	0.0548	0.0197	0.0015
	Period(Group)	-	0.0097	0.8174	0.5883
Geometric Least Squares Means					
ln-transformed Test-T		-	111.361	132.997	151.704
Reference-R1		-	118.940	147.919	173.695

Test Formulation-T

Ratio of Geometric Least Squares Means(%)(T/R1)					
ln-transformed			93.6	89.9	87.3
Intra Subject Variability(%)					
ln-transformed		-	21.7	28.4	26.0
Inter-Subject Variability(%)					
ln-transformed		-	29.4	35.8	30.2
90% Confidence Interval(T Vs. R1)					
ln-transformed	Lower	-	88.51	83.47	81.56
	Upper	-	99.04	96.85	93.53
	Power(%)	-	100.0	99.9	100.0

Treatment specification -> T: INTG8 and R1: Forsteo.

Sensitivity Analysis

Additional summary statistics and statistical comparisons containing data from excluded subjects based on the data review were generated as sensitivity analysis and provided.

Test V Forsteo:

Summary statistics of pharmacokinetic parameters for Teriparatide (Sensitivity Analysis; **T vs. R1)**

Source Table No. 14.2.1.5

		Tmax	Cmax	AUC0-t	AUC0-inf
		(h)	(pg/mL)	(pg.h/mL)	(pg.h/mL)
N		88	99	98	87
Mean		0.255	105.089	131.114	165.475
SD		0.1626	61.2155	79.9480	70.1305
CV(%)		63.7	58.3	61.0	42.4
Geometric	Mean	0.222	109.573	133.031	151.506
Reference	Formulation-R1				
N		96	96	94	94
Mean		0.320	125.894	158.539	180.406
SD		0.2026	45.0302	60.3275	63.4572
CV(%)		63.3	35.8	38.1	35.2
Geometric	Mean	0.270	117.915	145.894	168.939

ANOVA p-value

ln-transformed Group	-	0.0042	0.3545	0.1385
Sequence	-	0.4544	0.0166	0.0003
Sequence*Group	-	0.3689	0.2914	0.0325
Subject(Sequence*Group)	-	<0.0001	<0.0001	<0.0001
Period(Group)	-	0.0047	0.8279	0.5854
Geometric Least Squares Means				
ln-transformed Test-T	-	113.326	135.328	153.890
Reference-R1	-	121.501	150.325	175.351

Ratio of Geometric Least Squares Means(%)(T/R1)

ln-transformed		-	93.3	90.0	87.8
Intra Subject Variability(%)					
ln-transformed		-	21.6	27.8	25.6
Inter-Subject Variability(%)					
ln-transformed		-	31.1	37.2	31.7
90% Confidence Interval(T Vs.	R1)				
ln-transformed Lower		-	88.31	83.82	82.17
Upper		-	98.52	96.69	93.73
Power(%)		-	100.0	100.0	100.0

Note: N = 88 subjects were considered in all statistical calculations of Cmax and N = 87 subjects were considered in all statistical calculations of AUC0-t for Test formulation except mean, SD and %CV.

Treatment specification -> T: INTG8 and R1: Forsteo.

Human Factors Summative (Validation) Study

A summative study was conducted as a simulated use study in the form of one-to-one in-depth interviews.

The Applicant concluded that the summative study results demonstrated that the pen design did not contribute to any significant use errors. Therefore, there was no need to make any changes to the pen design. However, the results indicated that some improvement to the Instructions for Use (IFU) would eliminate or reduce the use errors observed in the study further. The Applicant was requested to re validate the IFU at least in a smaller number of individuals to test the refined IFU and demonstrate that the changes made have appropriately reduced usage errors associated with the device. As requested the Applicant has performed a bridging summative HF study, the results of which indicate that the IFU, which was refined following the summative study is effective in supporting the correct use of the Teriparatide Pen Injector and that the pen is safe and effective for the intended users, uses and use environments.

3.3.3. Pharmacodynamics

The Applicant submitted one PK/PD study 0425-17, which was a randomized, assessor-blind, three-treatment, crossover, single-dose study of INTG8, Forsteo, and Forteo.

Study 0425-17 assessed PD (corrected total serum calcium levels) similarity of INTG8, Forsteo and Forteo, as a secondary objective, after SC administration of a single 20 µg dose in healthy men and postmenopausal women.

In this study the Pharmacodynamic (PD) similarity of INTG8, Forsteo, and Forteo was assessed in consideration of the PD marker, corrected total serum calcium levels.

As the EMA SA outlined a PK/PD study would only suffice for demonstration of efficacy if a surrogate marker existed that would show efficacy acutely, during the PK/PD study. As no such marker is available for osteoporosis, the pharmacodynamic data from (Study **0425-17)** are considered as supportive only.

A total of 34 blood samples for the PD evaluation, at the time points specified in the protocol.

For the measurement of corrected total serum calcium levels, venous blood samples were collected at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours following drug administration in each period.

A total of 99 subjects were dosed in the study according to the randomization scheme.

All the 99 dosed subjects completed the study.

Pharmacodynamic Results

PD parameters were derived from the **baseline adjusted and non-adjusted corrected total serum calcium levels.** Dataset for the calculation of the PD parameters were prepared using Phoenix® WinNonlin® Version 6.4 (Certara L.P.).

Statistical Comparisons of Baseline-Adjusted Corrected Total Serum Calcium Levels

Parameters (INTG8 vs. Forsteo) (N=99)

Parameters	Geometric Least Squares Means			90% Confidence Interval	95% Confidence Interval	Intra Subject CV (%)	Power (%)
	INTG8 (T)*	Forsteo (R1)^	Ratio (T/R1)%				
lnEmax	0.300	0.318	94.5	79.98 - 111.74	77.41 - 115.46	74.2	71.0
lnAUEC0-t	1.461	1.527	95.6	70.80 - 129.19	66.75 - 137.02	177.0	33.5

*N=94 and ^N=93.

The 90% and 95% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed corrected total serum calcium level parameters AUEC0-t and Emax of INTG8relative to Forsteo, were not within the range of 80.00% to 125.00%. The Applicant has concluded- no meaningful differences in pharmacodynamic parameters were observed between INTG8, Forsteo and Forteo.

Statistical Comparisons of Baseline Non-Adjusted Corrected Total Serum Calcium Levels
Parameters (INTG8 vs. Forsteo) (N=99)

Parameters	Geometric Least Squares Means			90% Confidence Interval	95% Confidence Interval	Intra Subject CV (%)	Power (%)
	INTG8 (T)^	Forsteo (R1)	Ratio (T/R1)%				
lnEmax	9.461	9.487	99.7	99.47 - 99.99	99.42 - 100.04	1.1	100.0
lnAUEC0-t	213.818	214.794	99.5	97.47 - 101.67	97.07 - 102.09	8.8	100.0

^N=96.

The 90% and 95% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed corrected total serum calcium level parameters AUEC0-t and Emax of INTG8 relative to Forsteo, were within the range of 80.00% to 125.00%.

3.3.4. Discussion on clinical pharmacology

The INTG8 clinical development program included one comparative PK study (study 0425-17) in healthy subjects to demonstrate clinical similarity between INTG8, Forsteo, and Forteo in terms of clinical pharmacology, efficacy and safety.

This is the only clinical study supporting this biosimilar application.

In the PK Study bioequivalence is based on the comparisons of Test Product-T vs. Reference Product-R1 (Forsteo) and Test Product-T vs. Reference Product-R2 (Forteo)

As this is an EU centralised application the focus of this AR is on Test versus Forsteo, we have included some results of Test versus Forteo as supportive data.

The INGT8 device in Study 0425-17 was manually put together and the to-be-marketed device would be the same device, just manufactured differently (manual assembly versus machine manufactured.

The Rapporteur has major concerns regarding the INGT8 device used in the PK study.

There is a serious concern in relation to the reliability of the device to deliver the correct amount of drug product.

Overall at least 15 of the 99 participants (15%) had a documented failed or incomplete dose administration.

The question remains on whether or not the device worked correctly and if the other subjects in the study received the correct full dose i.e. if partial failure of the devices could have occurred.

The issues were identified by the applicant post hoc following the review of the exposure data which identified some patients had no exposure following administration of the test product.

As the device is a multiunit vial this could be more significant over time. The Applicant's proposed corrective action to assure accurate dosing is to only use machine assembled pen devices, for the to-be-marketed pen device." However, there is no evidence or data submitted to support the fact that this corrective action will address the issue and furthermore there is no bridging data to the single PK bioequivalence trial.

Regarding the PK data set it is unclear which subject data were included/excluded in the various analyses and how this may have impacted the results. throughout the dossier the Applicant's explanation of who were and were not included is vague and difficult to follow.

The numbers in the subgroup analysis and sensitivity analysis also need to be clarified.

In addition, the mean Cmax, AUC0-t, and AUC0-inf were 93.6%, 89.9% and 87.3% respectively in this subgroup analysis which excluded the 11 subjects who had no exposure to teriparatide. These numbers are exactly the same in the analysis of the full PK set of 99 subjects which seems implausible and may be an error where the report was meant to read in 88 patients.

Regarding 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 one (1)

This finding suggests that there is a statistically significant difference between formulations at a two-sided alpha=0.1 level.

However, we cannot conclude whether there is a statistically significant difference at a two-sided alpha=0.05 level.

The 95% CI would necessarily be wider than the 90% CI so it is possible that the 95% CI could contain one(1)

The Applicant is requested to discuss the fact that the 90% CI does not cross 1 and to justify that the observed differences in pharmacokinetic parameters are not clinically relevant.

The above issues bring into question the validity of this PK study and raises further concerns regarding using this dataset to support any clinical conclusions considering this is the only clinical study supporting this biosimilar application.

As the EMA SA outlined that A PK/PD study would only suffice for demonstration of efficacy a surrogate marker existed that would show efficacy acutely, during the PK/PD study.

As no such marker is available for osteoporosis, the pharmacodynamic data from Study are considered as supportive only.

In this study the Pharmacodynamic (PD) similarity of INTG8, Forsteo, and Forteo was assessed in consideration of the PD marker, corrected total serum calcium levels.

The comparison of the PD parameters was a secondary objective in this study.

The Applicant has concluded that the Mean ratios of ln-transformed pharmacodynamic parameters for baseline adjusted Emax and AUEC0-t were very close to unity (ranged between 94.1 to 102.9%).

Mean ratios of lntransformed parameters for baseline non-adjusted Emax and AUEC0-t also were very close to unity (ranged between 99.3 to 100.3%). Hence pharmacodynamic effects of all three formulations are comparable.

The Applicant concluded that no meaningful differences in pharmacodynamic parameters were observed between INTG8 and Forsteo however the 90% and 95% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed corrected total serum calcium level parameters AUEC0-t and Emax of INTG8 relative to Forsteo, were not within the range of 80.00% to 125.00%.

3.3.5. Conclusions on clinical pharmacology

As Study **0425-17,** a single Pharmacokinetic study is the sole clinical efficacy data supporting this application the integrity of the clinical trial data is essential informing a positive benefit risk assessment. There are a number of concerns regarding the robustness of the data submitted as a clear account of subjects has not been provided and number of patients were excluded, due to no dose of product was administered even though it was recorded that it was given by a HCP or insufficient amount of the test product provided.

The PK results reported by the applicant are exactly the same to 2 decimal places with 11 patients included or excluded which seems implausible.

Clarification on subgroup and sensitivity analysis is required.

Regarding 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 one (1)

While the data support that the product is bioequivalent to the reference product there are a number of concerns about the data set and exclusion of subjects, further reassurance regarding the validity of data is required.

Also the reliability of the device used in the PK study is a concern as there were a number of patients who failed to achieve any dose or an inadequate dose which were only identified after evaluation of the results.

The pharmacodynamic data from **Study 0425-17,** are considered as supportive only.

The Applicant has concluded that the Mean ratios of ln-transformed pharmacodynamic parameters for baseline adjusted Emax and AUEC0-t were very close to unity (ranged between 94.1 to 102.9%).

Mean ratios of lntransformed parameters for baseline non-adjusted Emax and AUEC0-t also were very close to unity (ranged between 99.3 to 100.3%). Hence pharmacodynamic effects of all three formulations are comparable.

The Applicant concluded that no meaningful differences in pharmacodynamic parameters were observed between INTG8 and Forsteo however the 90% and 95% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed corrected total serum calcium level parameters AUEC0-t and Emax of INTG8 relative to Forsteo, were not within the range of 80.00% to 125.00%.

These PD results need to be viewed in the context of the question mark over the PK data as outlined earlier in this Overview and the Clinical AR. The PD data could be considered supportive in demonstrating similarity of INTG8 versus Forsteo.

The conclusions of the GCP inspection indicate that there are significant concerns regarding the conduct and overall GCP compliance of the study. GCP compliance at this this particular study site is still considered to be a major objection. (MO)Therefore as a number of concerns have been raised at this time a conclusion on the bioequivalence of INTG8 versus Forsteo with respect to the rate and extent of the Teriparatide cannot be made.

3.3.6. Clinical efficacy

As outlined in the EMA SA (EMA/CHMP/SAWP/544758/2014) a phase III efficacy study is not regarded as necessary if INGT8 can be reliably shown to be highly similar to Forsteo. If this confirmation is not achieved, a Phase III therapeutic equivalence study would be required to demonstrate efficacy.

Dose-response studies and main clinical studies

Dose-response studies: not applicable for biosimilars.

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

Not applicable.

Clinical studies in special populations

Not applicable for biosimilars.

Supportive study(ies)

Not applicable.

3.3.7. Discussion on clinical efficacy

As per EMEA/CHMP/BMWP/118264/2007 Rev 01 guidelines clinical efficacy/safety studies will usually be required as a part of the comparability exercise unless similar efficacy of the biosimilar and the reference product can be convincingly deduced from the comparison of their physicochemical characteristics, biological activity/potency and PD fingerprint profiles, based on the use of highly sensitive and specific methods, then a dedicated efficacy trial may be waived.

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

Clarity as regards the impact of the device failure in the study is needed to judge the clinical relevance. A definite conclusion on comparability in terms of efficacy will depend on the outcome of such a discussion. For the assessment of the respective PK/PD -study, please see section Pharmacokinetics and Pharmacodynamics above.

3.3.8. Conclusions on clinical efficacy

Clarity as regards the impact of the device failure in the study is needed to judge the clinical relevance. A definite conclusion on comparability in terms of efficacy will depend on the outcome of such a discussion. The pivotal study (0425-17) was found to be GCP non-compliant during an inspection [GCP/2019/026] at CRO site EMA/13824/2017). In cases of GCP non-compliance submission of a new study/data during the clock stop, to replace the pivotal study on which the application is based is not permitted. The conclusions of the GCP inspection indicate that there are significant concerns regarding the conduct and overall GCP compliance of the study. GCP compliance at this this particular study site is still considered to be a major objection.

3.3.9. Clinical safety

The only safety data provided in support of this biosimilarity application was 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.

Patient exposure

The study was conducted in healthy male and postmenopausal women. A total of 99 subjects (59 male and 40 female) were dosed and completed the study. All 99 subjects were included in the safety analysis.

Adverse events

A total of 3 treatment emergent adverse events (TEAEs) were reported by 3 subjects (3.03%) during the study. Two AEs in 2 subjects (2.02%) were reported after administration of Forsteo (vomiting and glucose urine present) and 1 AE in 1 subject (1.01%) reported after administration of Forteo (dizziness). All 3 AEs were mild, and 2 of them were related to the study drug.

Serious adverse events and deaths

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

Laboratory findings

Laboratory assessments (including serum chemistry, haematology and urinalysis) were evaluated during the bioequivalence study. Laboratory tests of haematology and biochemistry (except random glucose, sodium, potassium, and chloride), immunology and urine analysis were performed at screening and at the end of the study (after 28 days from dosing of Period-III) rather than at the end of each period. Statistically significant changes in lipase and creatinine values were identified between screening and the end of the study. These changes were not considered by the applicant to be clinically significant. For creatinine the changes were minimal and were similar across all three periods. For lipase the mean value recorded for treatment sequence TR1R2 was higher than for the other two sequences. This is most likely a chance finding and is not considered to be clinically relevant. One adverse event of glucose urine positive was detected in the follow up period post study. This case was

reported as resolved during follow-up. Subjects were monitored for their serum calcium levels throughout the study. Changes in the calcium homeostasis can occur following a single treatment with teriparatide however there were no reports of hypercalcemia.

Immunological events

Immunogenicity was evaluated in PK study 0425-17 as an exploratory objective. Immunogenicity blood samples were taken at screening, before the first dose (0 hour), and 28 days after the last dose. (i.e., 28 days after Period 3 dosing). 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. However, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. Of the 98 subjects tested for immunogenicity, 8 subjects were found positive for ADA in the screening test. Of these 8 positive subjects, 2 subjects were confirmed positive for ADA in the confirmatory assay. Both subjects were positive for ADA at both the time points. No subject was tested positive for neutralizing antibodies. Titer of anti – PTH antibodies remained stable in one subject and increased from 1:2 to 1:4 titer in the other. None of these subjects had neutralizing antibodies. In the PK study there were no apparent clinically meaningful adverse events associated with either pre-existing antibodies or induced ADA following treatment with INTG8 (Teriparatide). There was no l difference in TEAEs in patients with a negative ADA result compared to those with a positive result. There were no reports of injection site reactions or hypersensitivity reactions.

Discontinuation due to AES

No subject discontinued from the study due to AEs.

3.3.10. Discussion on clinical safety

The only clinical safety data available for the biosimilar comparability exercise is from the comparative PK study (Study 0425-17). A major concern has been identified relating to the device used to administer INTG8 (teriparatide). Eleven subjects did not register serum levels of teriparatide. The failure to administer a dose was not detected at the time of the injection but was attributed in a retrospective review to imprecise positioning of the device plunger relative to the cartridge stopper due to manual assembly of the pen devices used in the clinical study. A further 4 patients were excluded from the PK/PD analysis due to inaccurate administration of study drug. It is unclear to what extent inaccurate dosing (under or over-dosing) may have occurred in the remaining patients. The applicant has indicated that the device intended to be commercialised will not involve manual assembly so this issue with inaccurate dosing should not be a problem. No data from the device due to be commercialised has been presented in this application. The pivotal study (0425-17) was found to be GCP non-compliant during an inspection [GCP/2019/026] at CRO site EMA/13824/2017). In cases of GCP non-compliance, submission of a new study/data during the clock stop, to replace the pivotal study on which the application is based is not permitted. Consequently, the concern that no clinical data in relation to use of the to-be marketed INTG8 pen device is unresolved. Concerns regarding the dosing of INTG8 in PK study 0425-17 have not been addressed. These concerns undermine the contribution of the safety and immunogenicity data to the comparability exercise supporting biosimilarity of INTG8 and Forsteo.

The TEAE reporting rate was very low. There were only three reports, two of which (nausea and dizziness) were reported in the first period in subjects treated with Forsteo and Forteo, both of which, were considered to be related and are commonly reported for the reference product Forsteo. The third report of urinary glucose occurred in the post treatment phase and was not related. All events resolved. Despite local injection site reaction being commonly reported for Forsteo, there were no reports of local injection site reactions associated with this product. The low rate of reporting of adverse events is noteworthy. The adverse event profile across all three treatment arms is not consistent with the known TEAE profile in other similar type studies or for the product. The applicant has commented further on the low reporting rates of adverse events and injection site reactions recorded in this study suggesting that study conduct where subjects were advised to follow a supine or semi-recumbent position during drug administration and till 4 hours' post dose administration strictly may have limited certain events. Regardless of explanations to explain the low rate of reporting of AEs the conclusions of the GCP inspection indicate that there are significant concerns regarding the conduct and overall GCP compliance of the study. GCP compliance at this this particular study site is still considered to be a major objection.

According to the Scientific Advice document supplied by the applicant, Intas Pharmaceuticals Limited's, INTG8 (Teriparatide) has been marketed in India under the brand name Terifrac following approval by the Drug Controller General of India in December 2010 for the treatment of osteoporosis in post-menopausal women who are at high risk of fracture. The applicant has provided an overview of the post marketing data collected in the 9 years since this product was authorised. The applicant has provided 5 PSURs covering the period from November 2010 to 31-Oct-2014. PSUR 1 (November 2010 to October 2011) and PSUR 2 (01-Nov-2011 to 31-Jul-2012) are identical. No PSUR is submitted after 31-Oct-2014. The applicant reports that the estimated patient exposure to INTG8 from India is approximately 64640 patient treatment. It is unclear how this number is calculated. The applicant reports that 88 spontaneous ICSRs (17 serious and 71 non-serious) resulting in 182 adverse events (27 serious and 155 non-serious)) were identified for INTG8 from India. The applicant indicates that these were submitted in in Appendix 06 in the application however this appendix could not be located. This data doesn't contribute any meaningful safety information in support of this application.

Laboratory tests of haematology and biochemistry (except random glucose, sodium, potassium, and chloride) and urine analysis were performed at the end of the study (after 28 days from dosing of Period-III). Clinical laboratory data was not collected at the end of each period. Data presented at the end of Period 1 may have been most informative. After cross-over, despite wash -out it is difficult to attribute events to INTG8 (Teriparatide) or Forsteo/Forteo. A number of metabolic adverse events are listed for Forsteo however these are generally associated with longer term repeat use (e.g. anaemia and hypercholesterolemia, (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. Changes in the calcium homeostasis can occur following a single treatment with teriparatide however there was no AE reports attributed to changes in calcium homeostasis in this study.

Statistically significant changes in lipase and creatinine values were identified between screening and the end of the study. These changes were not considered by the applicant to be clinically significant. For lipase the mean value recorded for treatment sequence TR1R2 was higher than for the other two sequences. The mean increase in lipase for treatment sequence TR1R2 is most likely a chance finding. No further action is required.

Head-to-head comparative immunogenicity studies (anti-teriparatide antibody) were assessed as an exploratory objective in Study 0425-17. Blood samples (10 mL each) were collected before the first dose and at the end of the study (i.e., 28 days after Period 3 dosing). This dosing schedule is not justified other than to say that it is in line with EU and US guidelines. Due to the short duration of the study, the crossover design, the problems with dosing in the study, the limited number of injections monitored and the relatively small sample size of tested subjects, antibody data from this study is of limited value.

Forsteo has low immunogenicity. The SmPC for Forsteo states that antibodies that cross-reacted with teriparatide were detected in 2.8 % of women receiving Forsteo. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. The two subjects who were confirmed positive for ADA in the confirmatory assay were positive for ADA at baseline and at day 28.

The limited characterisation of the immunogenicity of INTG8(Teriparatide) is a gap in the biosimilarity exercise. If INTG8 and Forsteo can be shown to have convincingly similar physicochemical, functional characteristics and PK and PD profiles immunogenicity of INTG8 could be expected to be similar to the reference product and further clinical immunogenicity data would not be required to support approval.

As part of a scientific advice clarification letter following direction from the CHMP to define a strategy to demonstrate potential immunogenicity of INTG8 (Teriparatide), 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. The applicant has indicated that they have not commenced the immunogenicity study based on advice from CHMP. The applicant's response refers to an extract from Scientific Advice in relation to the need for a phase 3 efficacy and safety study. The same the scientific advice clearly stated that the proposed comparative PK study may not be sufficient for assessing the immunogenicity of INTG8. The CHMP directed the applicant to define a strategy to demonstrate potential immunogenicity of INTG8. The applicant received a Scientific Advice Clarification letter regarding a proposed open label, single arm study on 100 post-menopausal women treated with daily subcutaneous doses of 20mcg INTG8 for a period of 12 months. CHMP indicated that the proposed strategy was acceptable with some recommendations regarding the power of the study and uncertainty regarding the impact of neutralisation on efficacy and safety due to the receptor structure with multiple binding sites in teriparatide. The applicant should justify why they did not proceed with the study requested by CHMP and outlined in the Scientific Advice Clarification Letter. A further study to characterise the potential immunogenicity of INTG8 over longer-term should be conducted to address this lack of data.

On the basis of the data presented, it is not possible to conclude on the biosimilarity from a quality perspective. An overarching quality major objection has been raised with respect to the demonstration of biosimilarity.

3.3.11. Conclusions on clinical safety

The safety data provided are from a single crossover bioequivalence study conducted comparing INTG8 (Teriparatide) and Forsteo and Forteo. This study was confounded by device failures resulting in inaccurate and failed dosing. The impact of inaccurate dosing on INTG8 exposure versus Forsteo and its subsequent impact on clinical safety and concerns regarding the validity of subject related data (adverse event profiles are not consistent with similar studies or the known profile for the product.) were corroborated by the findings of the triggered GCP inspection. Study 0425-17 was found to be GCP non-compliant during an inspection at CRO site.

Biosimilarity in terms of safety and immunogenicity data cannot be established from the clinical data presented in this application. The applicant's plans for post-marketing evaluation of immunogenicity should be clarified.

3.4. Risk management plan

3.4.1. Discussion on safety specification

The applicant refers to the RMP for a generic of Forsteo as the evidence source for safety concerns mentioned under Module SVIII. The applicant was requested to align the safety specification with the safety specification for the reference product Forsteo recently updated as part of (procedure EMEA/H/C/000425/II/0050/G). The applicant has indicated that the safety specification for the reference product Forsteo is not available.

As requested by the PRAC the applicant has added the 'Potential for medication errors due to wrong dose due device failure' as an important potential risk and 'Immunogenicity' as missing data.

3.4.2. Pharmacovigilance plan

The Applicant does not propose any additional pharmacovigilance activities.

The PRAC consider that the medication errors and immunogenicity issues of should be addressed. If the safety concerns are going to be listed as important potential risk and/or missing information the pharmacovigilance plan should be amended accordingly.

At this time, the PRAC, based on the submitted data, is of the opinion that the proposed post-authorisation pharmacovigilance development plan is not sufficient to identify and characterise the risks of the product and the applicant should propose pharmacovigilance studies in line with the safety concerns identified.

3.4.3. Risk minimisation measures

This section should be updated in accordance to the updated list of important safety risks and missing information.

3.4.4. Conclusion on the RMP

The RMP has to be updated in accordance to the response on medication errors and immunogenicity questions.

3.5. Pharmacovigilance system

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

Assessor's comments

Regarding the location of the Qualified Person for Pharmacovigilance (QPPV) and Pharmacovigilance System Master File (PSMF): This is currently acceptable. However, in the event of the UK exiting the European Union, the location of the QPPV and PSMF will need to be relocated to a Member State within the European Union.

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.

4. Biosimilarity assessment

4.1. Comparability exercise and indications claimed

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-Scientific Advice was generally taken into consideration and the development programme aligned accordingly however there were some deviations and omissions.

The applicant has made no reference in the dossier for INTG8 to the 12-month study outlined in a Scientific advice clarification letter. The applicant should clarify the status of this study.

4.2. Results supporting biosimilarity

Efficacy

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%.

However, the findings of the triggered GCP inspection of Study 0425-17 was found to be GCP non-compliant during an inspection at CRO site as a number of critical and major findings were reported. Therefore, the data cannot be supported as sufficient to conclude biosimilarity.

Safety

The incidence of treatment emergent adverse events (TEAE) was very low but comparable across all three treatment arms in the bioequivalence study. Only three TEAEs (none with INTG8,1 Forteo and 2 with Forsteo) were reported. All were classified as mild and resolved before the study concluded. Of 98 subjects tested for anti-PTH antibodies, 2 subjects showed confirmed ADA positive immune response in both pre-dose and end of the study samples. None of these subjects had neutralizing antibodies. There were no TEAES of injection site reactions or hypersensitivity reactions.

4.3. Uncertainties and limitations about biosimilarity

Efficacy

Device failures are not described adequately. The device failure in 11 subjects was not recorded by the HCPs who administered INTG8.

The documented device failure issue brings into question the validity of the PK study and raises concerns regarding using this dataset.

The impact of this lack of exposure on PK data is unclear because a comprehensive account of subjects in the study has not been provided. Overall it is unclear which data were included/excluded in the various analyses and how this may have impacted the results. The Applicant is therefore requested to present for each statistical analysis of the PK parameters (at least the three co-primary endpoints and selected key secondary endpoints) a list of excluded subjects with a description of the reason for exclusion and provide adequate justification that these exclusions did not affect the validity of the results.

The PK results reported by the applicant for the full dataset and the dataset excluding 11 patients are exactly the same to 2 decimal places, this needs to be clarified.

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 one (1). This finding suggests that there is a statistically significant difference between formulations at a two-sided alpha=0.1 level. The Applicant is requested to discuss the fact that the 90% CI does not cross one (1) and to justify that the observed differences in pharmacokinetic parameters are not clinically relevant.

Clarification on whether the PK study was sufficiently powered across the three co-primary endpoints jointly is required.

Although the pharmacodynamic data is being as considered as supportive data only the applicant concluded that no meaningful differences in pharmacodynamic parameters were observed between INTG8 and Forsteo however the 90% and 95% CIs of the geometric LSM ratios, derived from the analysis on the ln-transformed corrected total serum calcium level parameters AUEC0-t and Emax of INTG8 relative to Forsteo, were not within the range of 80.00% to 125.00%.

These PD results need to be viewed in the context of the question mark over the PK data as outlined earlier in this AR. The PD data could be considered supportive in demonstrating similarity of INTG8 versus Forsteo.

Safety

At least 15% of the study subjects received no or inaccurate dosing. There is an uncertainty regarding the dose received by the remaining subjects. The to-be-marketed device is the same device but is

manufactured differently (manual assembly versus machine manufactured) this is intended to mitigate the risk of device failure. However, no clinical data have been presented using the machine assembled to-be marketed device. The impact of device failure resulting in no or inaccurate dosing on the safety and immunogenicity data collected is a source of uncertainty.

The rates of TEAE was very low for all three treatments. The adverse event frequencies are not in line with similar type studies or the known profile of the product.

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 gap in the biosimilarity exercise. The emergence of ADAs and their impact of ADAs on safety over the longer term has not been adequately evaluated.

4.4. Discussion on 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.

The clinical biosimilar comparability exercise which comprised single PK and PD study is confounded by difficulties with the injector pen dosing device which resulted in 11 subjects receiving no dose and 4 other subjects receiving an incorrect dose. It is unclear if the remaining subjects received the intended dose.

The device used in the PK study was assembled manually which is purported to have resulted in device error resulting in the dosing inaccuracies. The device intended to be commercialised will be machine assembled. No clinical data have been presented for subjects dosed with the machine assembled device which presents a further gap in the biosimilarity exercise. The applicant should comment on the significance of this lack of data in the to be marketed device. Device related dosing errors should be included in the RMP as an important potential risk.

As a single Pharmacokinetic 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 are a number of concerns regarding the quality and validity of the reported data submitted.

A clear account of subjects has not been provided. A number of patients were excluded due to failure to receive a dose (11 patients), possible receipt of an incorrect dose (4 patients). A further 8 subjects with three NR samples and a further 5 subjects with a full profile as NR in particular period were not considered.

The Applicant was requested to present for each statistical analysis of the PK parameters (at least the three co-primary endpoints and selected key secondary endpoints) a list of excluded subjects with a description of the reason for exclusion and provide adequate justification that these exclusions did not affect the validity of the results. This data has been presented and are acceptable.

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 one (1). The Applicant was requested to discuss the fact that the 90% CI does not cross one (1) and to justify that the observed differences in pharmacokinetic

parameters are not clinically relevant. In their response the applicant has adequately discussed this observed difference.

Implausibility of analytical data submitted needs to be addressed- the PK results reported by the applicant for the full dataset and the dataset excluding 11 patients are exactly the same to 2 decimal places.

Clarification on whether the PK study was sufficiently powered across the three co-primary endpoints jointly was requested and a satisfactory response has been provided.

Device failures are not described adequately- There were significant concerns raised during the review of the PK study regarding device failure resulting in failed or inaccurate dosing. The manufacturer has conducted a retrospective investigation as to the cause of this rate of failure, as outlined in G8-RPT-62. In this assessment, the manufacturer determined that the root cause for failure of dose delivery in these 11 subjects was most likely due to the imprecise position of the device plunger relative to the cartridge stopper. This in turn was due to the devices used in the PK study being manually assembled. Device failure in these 11 subjects was not recorded by the HCPs who administered INTG8.

Due to these concerns regarding exclusion of subjects from some of the PK and statistical comparisons, implausible results and concerns regarding non-recording of device failure, and the GCP report findings of critical and major findings with the conduct of the study the major objection in relation to the Pivotal Study 0425-17 remains.

The Applicant has clarified that INGT8 is a self-priming device.

Analysis of safety data as part of the comparability exercise is limited by the crossover study design. The usefulness of a comparison of adverse events and immunogenicity data between INTG8 and Forsteo at the end of a three-way crossover study is questionable. Adverse event data collected after the first period which would have provided the most meaningful information.

However, the overall reporting rates of AEs for all three treatments in this study is remarkably low. There was one report each of vomiting and dizziness which are labelled as commonly occurring ADRs in the Forsteo SmPC. Local reactions are also commonly reported for Forsteo however despite all 99 subjects receiving injections during the study, and local tolerance being evaluated at 30 mins, 2, 6 and 12hrs after the injection in each period there were no reports of local injection site reactions in this study. The adverse event frequencies are not in line with similar type studies and the known profile of the product. This raises concerns regarding the validity of the subject related data and further supports the concerns regarding compliance with GCP at this study site.

Immunogenicity data was collected at baseline and at the end of the study. Of 98 subjects tested for immunogenicity, 2 subjects showed confirmed ADA positive immune response in both pre-dose and end of the study samples. Titre of anti – PTH antibodies remained stable in one subject and increased from 1:2 to 1:4 titer in the other. None of these subjects had neutralizing antibodies. There were no reports of hypersensitivity reactions or allergic reactions. The general immunogenic potential of Forsteo is low (Detection rate 2.8% in women treated with Forsteo generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy). If INTG8 and Forsteo can be shown to have convincingly similar physicochemical, functional and PK PD characteristics the immunogenicity of INTG8 is expected to be similar to the reference product. Therefore, for the purposes of approval, further clinical immunogenicity data may not be required. However as agreed in the scientific advice clarification letter immunogenicity over repeat doses up to one year should be evaluated. Immunogenicity should be included in the RMP as missing information until this information is made available.

In the scientific advice application, the applicant states INTG8 has been marketed in India under the brand name Terifrac following approval by the Drug Controller General of India in December 2010 for the treatment of osteoporosis in post-menopausal women who are at high risk of fracture. No post-marketing data has been presented in this application. Available post-marketing safety data should be provided for review.

From a quality perspective, the comparability exercise does not support a conclusion of biosimilarity. A major objection has been raised with respect to the demonstration of biosimilarity and a revised biosimilarity exercise has been requested.

GCP issues

The findings of the triggered GCP inspection of Study 0425-17 was found to be GCP non-compliant during an inspection at CRO site as a number of critical and major findings were reported.

The Applicant has submitted a new B/E study (study 0242-17).

However, in line with the EMA position paper (EMA/448853/2015) on non-acceptability of replacement of pivotal clinical trials during the assessment of an application in the context of a marketing authorisation in cases of GCP non-compliance, in case the application contains only one pivotal study which is found to be GCP non-compliant and reanalysis is not provided or not possible, this means that the application no longer contains any pivotal clinical data that can be used to support the safety and efficacy of the medicinal product in the context of the application in question.

Article 7(c) of Regulation (EC) No 726/2004 provides that, in order to prepare its opinion, the CHMP may allow the applicant to "supplement the particulars accompanying the application within a specific time period", but this does not mean that the applicant is allowed to replace pivotal studies on which the application is based, in case of GCP non-compliance.

Therefore, as critical findings were identified, the additional B/E study (study 0242-17) cannot be accepted as a replacement for the original pivotal study Study 0425-17.

4.5. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, INTG8 (teriparatide) is considered not biosimilar to the reference product. Therefore, a benefit/risk balance comparable to the reference product cannot be concluded.