27 March 2025
EMA/131611/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Osvyrti

International non-proprietary name: denosumab

Procedure No. EMEA/H/C/006399/0000

Note

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

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Table of contents

List of abbreviations

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
anti-HCV	hepatitis C antibody
$AUC_{0\text{-}CT}$	Area under serum concentration versus time curve from time zero to cutoff time
$AUC_{0\text{-}inf}$	Area under the concentration versus time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the concentration versus time curve from time zero to the last measurable concentration
$AUC_{CT\text{-}t}$	Area under serum concentration versus time curve from cutoff time to last measurable concentration time
$AUEC_{0\text{-}t}$	Area under the % reduction from baseline versus time curve from time zero to the last measurable concentration
BMD	Bone mineral density
CDSCO	Central Drugs Standard Control Organization
CFB	Change from baseline
CHMP	Committee for Evaluation of Human Medicinal Products
CI	Confidence interval
CL	Clearance
CL/F	Total body clearance
C_{max}	Maximum measured serum concentration
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Serum cross-linked C-telopeptide of type I collagen
CV	Coefficient of variation
DSM-V	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
DXA	Dual-energy X-ray absorptiometry
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency

Abbreviation	Definition
Emax	Maximum % reduction from baseline
EOS	End of study
EU	European Union
FDA	Food Drug Administration
GCP	Good clinical practice
GMP	Good manufacturing practice
h	Hour
HBsAg	Hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator brochure
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG2	Immunoglobulins G2
IM	Immune
IMP	Investigational medicinal product
INTP23.1	Denosumab biosimilar
ITT	Intent-to-treat
IWRS	interactive web response system
LOCF	Last observation carried forward
LSM	Least squares mean
M	Missing
MAH	Marketing authorisation holder
MAR	Missing at random (MAR)
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
N/A	Not applicable
NAb	Neutralising antibodies
ng/mL	Nanogram per millilitre
NR	Non reportable
P1NP	Procollagen type I N-propeptide
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)

Abbreviation	**Definition**
PL	Package leaflet
PMO	Postmenopausal osteoporosis
PP	Per-protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
PTH	Parathyroid hormone
QA	Quality assurance
R	Reference
RANKL	Receptor activator of nuclear factor kappa-B ligand
ref	Reference
RMP	Risk management plan
RMPs	Reference medicinal products
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SERMs	Selective estrogen receptor modulators
SmPC	Summary of product characteristics
SOC	System organ class
T	Test
$t_{1/2}$	The terminal half-life
TEAE	Treatment emergent adverse events
T_{max}	Time to reach the maximum measured serum concentration
US	United States
V_d	Volume of distribution
V_d/F	Volume of distribution
λ_z	First order rate constant associated with the terminal (log-linear) portion of the curve. This parameter was calculated by linear least squares regression analysis using at least last three or more non-zero serum concentration values.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 6 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Osvyrti, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication(s):

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.

Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures.

Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see section 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

The application submitted is:

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA:

- Product name, strength, pharmaceutical form: Prolia 60 mg solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 26-05-2010
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/10/618/003

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

- Product name, strength, pharmaceutical form: Prolia 60 mg solution for injection in pre-filled syringe
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 26-05-2010
- Marketing authorisation granted by:

- Union
- Marketing authorisation number: EU/1/10/618/003

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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

Date	Reference	SAWP co-ordinators
12 December 2019	EMEA/H/SA/4311/1/2019/III	Elina Rönnemaa, Andrea Laslop

The applicant received scientific advice on the development of denosumab biosimilar (INTP23) for the treatment in the same indications as the reference product Prolia/Xgeva from the CHMP on 12/12/2019 (EMEA/H/SA/4311/1/2019/III). The Scientific Advice pertained to the following quality, non-clinical, and clinical aspects:

- Analytical similarity assessment; analytical and functional tests; planned differences in formulation composition between the reference product and INTP23; development of additional presentations of INTP23 compared to the authorised presentation of the reference product; omission of in vivo non-clinical studies.
- Adequacy of the overall clinical development programme; design of a comparative, single-dose PK, PD, and immunogenicity study of INTP23 and Xgeva in healthy volunteers including study population, dose, and endpoints; design of a comparative clinical study comparing PK, PD, and immunogenicity of INTP23 with Prolia in postmenopausal women with osteoporosis including study population, dose, endpoints, use of US-sourced reference comparator; choice of pharmacodynamic biomarker and in vitro diagnostic method to determine the biomarker in serum; extrapolation of clinical study results to other authorised indications of the reference product; ELISA-based pharmacokinetic measurement assay for detection of INTP23 and denosumab in clinical serum samples; overall approach to immunogenicity assessment including development of an immunogenicity assay for detection of anti-drug antibodies and an neutralizing antibody assay.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Jayne Crowe

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Mari Thorn

The application was received by the EMA on	6 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	17 June 2024
The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	1 July 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	27 June 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 July 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	13 September 2024
The following GMP and GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the quality/safety/efficacy assessment of the product:	
– GCP inspections at two investigator sites, the CRO site and the BE clinical and bioanalytical facility, located in India between 9-14 December 2024. The outcome of the inspection carried out was issued on.	20 February 2025
– A pre-authorisation GMP inspection was caried out at the manufacturer of the active substance and finished product: Intas Pharmaceuticals Limited, India. – Following the inspection a GMP certificate was issued on	4-8 March 2024 21 June 2024.
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	21 October 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	31 October 2024

The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	14 November 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	25 February 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	12 March 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Osvyrti on	27 March 2025

2. Scientific discussion

2.1. Problem statement

Not applicable for biosimilars.

2.2. About the product

Osvyrti was developed as a biosimilar product to Prolia (INN: denosumab), marketed by Amgen and was developed with the same strength and presentation:

• Prolia: 60 mg/mL pre-filled syringe (PFS)

Denosumab is a genetically engineered fully human monoclonal IgG2 antibody specific for RANKL, a transmembrane or soluble protein that plays a significant role in osteoclast-mediated bone resorption. Denosumab prevents the RANKL/RANK interaction and thus inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and cancer induced bone destruction.

The applicant is claiming all the approved indications of the reference product.

The claimed therapeutic indications are:

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.

Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

2.3. Type of application and aspects on development

The overall clinical programme was planned in line with the EMA scientific advice.

INTP23.1 60 mg/mL pre-filled syringe (PFS), Osvyrti is developed as a proposed biosimilar product to EU approved Prolia. In parallel, INTP23.1 120 mg/1.7 mL vial is developed as a proposed biosimilar product to EU approved Xgeva. The similarity exercise was designed to integrate the characterisation of both formulations of INTP23.1 to demonstrate overall biosimilarity of INTP23.1 to the RMPs. This is found acceptable and in line with a previous central scientific advice (EMEA/H/SA/4311/1/2019/III).

GCP compliance:

Phase I study:

The applicant stated that study 0568-19 was carried out in accordance with the protocol, relevant SOPs and was compliant with all the requirements regarding the obligations of investigators and all other pertinent requirements of New Drugs & Clinical Trial Rules, 2019 of CDSCO (Central Drugs Standard Control Organization), Ministry of health and family welfare, Government of India, 'National Ethical Guidelines for Biomedical and Health Research Involving Human Participants', ICMR [Indian Council of Medical Research (2017)], ICH (The International Council for Harmonization of Technical

Requirements for Pharmaceuticals for Human Use) E6 (R2) 'Guideline for Good Clinical Practice' (2016), Declaration of Helsinki (Brazil, October 2013) and any other applicable regulatory requirements.

The applicant did also submit information regarding inspection status of the clinical and bioanalytical facility.

Phase III study:

The applicant reported that 4 sites in in India were terminated because DXA scans had been falsified and patient eligibility criteria had been violated. According to *Listing 16.2.1.2 Study completion status*, these sites had randomised a total of 30 patients.

Falsifying data is a serious violation of good clinical practice and constitutes scientific misconduct, yet the applicant initially provided limited information about this problem. The following information can be found Clinical Study Report (Module 5.3.5.1 of Study 0774-19, *Section 10.1 Disposition of patients*):

> "Due to non-compliance of study eligibility criteria and falsified submission of DXA Scans to Lambda's DiaSoft-D platform by Site No.; all ongoing study patients were withdrawn as per sponsor discretion and further recruitment at these sites were stopped with immediate effect. Refer Appendix No. 16.3.2 for further details."

However, no further information on this issue was found in Appendix No. *16.3.2 Other CRFs submitted*. Similarly, no information about falsification is contained in *Appendix 16.1.8 Audit certificates*. During the procedure, the applicant was requested to clarify how the falsification of DXA scans was discovered and submitted monitoring reports. In addition, a triggered GCP inspection was performed to investigate the falsification of data and to verify the overall reliability of the trial data submitted in support of this application (Integrated inspection report EMA/IN/0000224311 and EMA/IN/0000224313). Departures from GCP compliance were identified, however those are unlikely to impact the overall quality of the data or the reliability of the data. Despite the findings observed, overall, the trial was conducted in an ethical manner and the level of compliance with GCP was sufficient to conclude that the data reported are of acceptable quality.

GMP compliance:

The inspection report from the pre-approval GMP inspection of the manufacturer Intas Pharmaceuticals Limited Plot No. 423/P/A, Sarkhej-Bavla Highway, Moraiya, Ahmedabad, Gujarat 382 213, India has been finalised on 19.6.2024 and concludes that the site operates in compliance with GMP for the manufacture of denosumab. A GMP certificate has been issued on 21.6.2024.

2.4. Quality aspects

2.4.1. Introduction

Denosumab is a fully human IgG2 monoclonal antibody (mAb) specific to receptor activator of nuclear factor kappa-B ligand (RANKL). Denosumab directly inhibits the RANK/RANKL signalling pathway, which is known to be vital for osteoclast activation, function, and survival and thereby decreases bone resorption. By blocking RANKL binding to its receptor, denosumab reduces formation and activity of

osteoclasts. This reduces loss of bone and maintains bone strength, making bones less prone to fractures.

The product INTP23.1 (Osvytri) is developed as a proposed biosimilar product to EU approved Prolia. INTP23.1 was extensively characterised, and the analytical similarity was assessed at multiple levels beginning with primary structure, higher order structure, product variants/impurities and purity, functional characteristics, particulates, and aggregates and finally with respect to pharmaceutical properties of finished product (FP).

The finished product, INTP23.1, is presented as a single-use pre-filled syringe containing 60 mg denosumab in 1 mL solution for injection as active substance (AS).

Other ingredients are:

- Acetic acid, glacial
- Sorbitol (E 420)
- Polysorbate 20
- Sodium hydroxide (for pH adjustment)
- Water for injections

The product is available in pack sizes of one pre-filled syringe.

2.4.2. Active substance

2.4.2.1. General information

Denosumab is a fully human IgG2 monoclonal antibody specific to receptor activator of nuclear factor kappa-B ligand (RANKL) consisting of two heavy chains, and two light chains of the kappa subclass. Denosumab contains a total of 36 cysteine residues, which are involved in both intra-chain and inter-chain disulfide bonds. Depending on the disulfide pattern, three main isoforms are present (see Figure S.1.2-2). The desired main species is the so-called IgG2-B, which is also the most stable isoform. Each heavy chain of denosumab contains an N-linked glycan at the consensus glycosylation site at Asparagine 298 and the main form lacks the heavy chain C-terminal Lys residues. The primary form of denosumab (G0F/G0F without C-terminal Lys) has a molecular weight of approximately 147 kDa. Three different isoforms of denosumab are illustrated.

Denosumab directly inhibits the RANK/RANKL signalling pathway by blocking RANKL binding to its receptor, which is vital for osteoclast activation, function, and survival, and thereby decreases bone resorption. This results in reduced formation and activity of osteoclasts, which reduces loss of bone, maintains bone strength, and makes bones less prone to fracture.

2.4.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Denosumab, INTP23.1 active substance, is produced in a fed-batch process using CHO-S cells in a 2000 L disposable production bioreactor. The purpose and setup of each of the steps of the upstream process from working cell bank (WCB) thawing to production are in general described in sufficient detail. Following harvest clarification, the downstream process consists of ten steps including three

chromatographic steps, viral inactivation/removal (low pH incubation and nanofiltration) and a redox reaction step to enrich the desired isoform (IgG2-B) of denosumab. AS is formulated, filtered, and dispensed into flexible freeze and thaw bags and stored at -20°C. Operational details and purpose of each downstream step have been provided.

Active substance (AS) and finished product (FP) manufacture take place at the same facility. Thus, it is acknowledged that no AS shipment validation study has been performed. INTP23.1 AS manufacture does not involve any reprocessing steps. Hold times of AS intermediates and materials of storage containers have been provided. Satisfactory demonstration of GMP requirements has been provided.

Flow charts and a narrative description of each step of the process for INTP23.1 AS manufacture have been provided and descriptions of process parameters have been included.

One batch of AS is defined as the amount of AS produced from the harvest of one 2000 L production bioreactor. Information on batch size and batch numbering system have been acceptably provided.

Resin and filter sanitation procedures, storage conditions and resin lifetime/re-use studies have been provided.

Control of materials

Raw materials, resins, filters, membranes, and containers used in the INTP23.1 AS manufacture have been listed. It is stated that all raw materials used in the upstream and downstream manufacturing process in contact with INTP23.1 are animal and human component free.

The compendial- and non-compendial raw materials used in the INTP23.1 AS manufacturing process have been satisfactorily described.

Sufficient information on qualitative compositions have been provided for proprietary media used in the manufacture of INTP23.1 AS.

The stepwise construction of the expression vector carrying the heavy- and light chains of denosumab has been sufficiently described.

All newly manufactured master cell banks (MCBs) and WCBs are qualified using defined specifications in accordance with recommendations in ICH Q5B and Q5D. The cell line history and production of the cell banks has been described in acceptable detail.

Safety information for biologically sourced materials and the risk of contamination by adventitious agents is provided in Module A.2.

Critical steps and intermediates

The denosumab manufacturing process is controlled by process parameters with defined targets/limits and in-process controls/process monitoring with defined acceptance criteria or expected ranges. The process parameters have been categorised into critical process parameters (CPPs), key process parameters (KPPs) and MPs (monitored parameters) based on their impact on the variability of the process performance. If a KPP exceeds the defined acceptance criteria an investigation is initiated, and appropriate action is taken. A batch is rejected if a CPP exceeds the defined proven acceptable range or acceptance criteria. The control strategy and acceptance criteria for defined process parameters have been described in acceptable detail.

The applicant presented the microbial control strategy applied during the denosumab manufacturing process. The endotoxin testing method was shown to be suitable for samples taken at various steps of the upstream- and downstream process.

Compendial methods are used for pH and osmolality. Denosumab concentration of in-process AS samples is measured by an in-house Protein A affinity chromatography method. Reference samples of internal standard or reference medicinal products Xgeva/Prolia are used to prepare a standard curve for sample quantification.

Process validation and/or evaluation

Process performance qualification has been performed with three consecutive AS batches produced at the 2000 L intended commercial scale. The process does not include any reprocessing steps. Criticality of each process step has been evaluated based on the CQAs and a justification for the classification is provided.

All process parameters in the upstream process were within normal operating range (NOR) and all process performance attributes met acceptance criteria. The defined process parameters, classifications and acceptance criteria for the seed generation steps are considered acceptably validated.

Taken together, results from the three process performance qualification (PPQ) runs, and validation protocol demonstrate a high reproducibility and comparable levels for all measured attributes for all process steps. It is agreed that the manufacturing process is robust, reproducible, and shown to efficiently remove process- and product related impurities.

The proposed hold conditions for intermediates and process buffers in specified storage containers are found acceptable. A resin reusability study was conducted at small scale. The applicant has committed to provide supportive data for the validation of proposed number of reuse cycles of chromatographic resins and UF/DF membranes at the manufacturing process scale.

In conclusion, the validation of the denosumab manufacturing process is considered adequate.

Manufacturing process development

Comparability data have been provided for eight batches produced with the intended commercial process. Results from batch analyses are consistent for all batches and fulfil the defined acceptance criteria. Consistent product quality between clinical trial material and intended commercial manufacturing process has been acceptably demonstrated.

Manufacturing process characterisation for INTP23.1 AS was performed using a Design of Experiments (DoE) approach with qualified scaled-down models. A risk ranking tool was used to assess the CQAs for denosumab. Process Failure Mode and Effects Analysis (FMEA) was used to identify process parameters with significant impact.

In conclusion, the applicant properly addressed the history of development of manufacturing process and discussed the impact on comparability.

Characterisation

Elucidation of structure and other characteristics

Characterisation of INTP23.1 was performed with respect to general properties, primary structures, higher order structure, functional characteristics, particulates and aggregates and product variants. Four different AS batches were used for characterisation, and all of these can be regarded as representative for the commercial process. In general, it is agreed that state-of-the-art methods were applied and that most relevant characteristics have been evaluated. However, specific comments are provided below. The applicant is reminded that the objective of the characterisation section is to demonstrate the main characteristics of the active substance rather than to show comparability between batches.

Impurities

The process-related impurities evaluated for INTP23.1 are host cell proteins (HCP), host cell DNA (HCD), Leached Protein A (LPA), Benzyl alcohol, cysteine hydrochloride, cysteine dihydrochloride, antifoam C and antifoam ADCF. It is sufficiently demonstrated that these impurities are reduced and cleared during the downstream purification process. The provided information is found acceptable.

2.4.2.3. Specification

A comprehensive set of relevant tests to cover general characteristics (appearance, pH, osmolality), quantity (protein concentration by OD280), identity (peptide mapping, pI by icIEF and antigen binding), potency (ELISA), purity (SE-HPLC, icIEF, reducing- and non-reducing CE-SDS), process-related impurities (HCP, residual DNA and leached Protein A), safety (endotoxin and bioburden) and product-related variants (glycan- and disulphide variants) has been included in the INTP21.1 AS specification. Appropriate Ph. Eur. references or in-house method identification numbers have been included for all compendial- and non-compendial methods, respectively.

Defined acceptance criteria for release and, if applicable, end of shelf-life testing have been provided. The parameters included in the specification are found adequate to control the quality of INTP23.1 denosumab. The same acceptance criteria apply for testing at release and end of shelf-life for all test parameters that are tested at both instances.

As previously requested, the applicant has revised the limits for HMW species as measured by SE-HPLC and the LMW species as measured by non-reducing CE-SDS as well as provided a sufficient justification for maintaining the proposed acceptance criteria for the total charge variants and purity as measured by icIEF. These proposals are found sufficient and acceptable, and the AS and FP specifications have been aligned.

Analytical procedures and reference standards

Compendial and non-compendial methods are used for release and stability testing of denosumab AS. Several of the described analytical methods are also used at FP release. The compendial analytical procedures are performed in accordance with the relevant pharmacopoeia at the time of testing. Non-compendial methods are briefly described and associated with method identification numbers that link them to the specification and respective validation. Non-compendial methods are described in sufficient detail.

As previously requested, the applicant has provided a sufficient and acceptable justification for the use of CpB treatment in the preparation of samples for release test and identity of charge variants by icIEF.

Overall, the analytical methods appear adequate for their intended purpose. The capability of the stability indicating methods to detect product degradation/modification has been evaluated by forced degradation studies.

Reference standards for INTP23.1 were prepared from representative INTP23.1 AS batches. For the commercial process, a two-tiered reference standard system is used including a primary reference standard (PRS) and a working reference standard (WRS).

Extensive information on the characterisation of the current WRS and PRS is provided. All characterisation results comply with the pre-defined acceptance criteria. Assignment of potency is clearly described. It is agreed that the current WRS and PRS are adequately qualified to be used as reference standards for INTP23.1.

The storage condition for both WRS and PRS is -80°C ± 5°C, and the shelf-life is assigned to 24 months. The shelf-life and storage conditions are based on data from the current and historical PRS, which is found representative for both WRS and PRS. Stability testing of WRS and PRS will continue at intervals of 6 months according to appended protocols. This is found acceptable. Furthermore, a freeze thaw study was conducted. Three freeze thaw cycles, i.e., freezing at -80°C and thawing at 2°C - 8°C were evaluated with a hold at 2°C - 8°C for 15 days post 3 freeze thaw cycles. The obtained results are found acceptable.

Validation of analytical procedures

The compendial methods used for physical appearance, pH and osmolality can be considered validated. Validation reports for all non-compendial analytical procedures applied for active substance and finished product have been provided. In conclusion, relevant parameters have been validated, in line with ICH guideline Q2 (R1).

Batch analyses

Eleven batches of INTP23.1 AS manufactured at the same Intas Pharmaceuticals site that will be used for the intended commercial manufacturing using the same process (except the addition of a redox reduction step in batches P23.1-BM-0002 an onwards) and scale (2000 L) are included in the batch analysis. All batch analysis results met acceptance criteria of specifications that were effective at the time of testing.

Analytical changes and changes to the specifications introduced during development are sufficiently described and reported batch analysis results indicate that the process is consistent.

Justification of specification

Specifications have been established based on ICH Q6B guidelines and presented batch data from AS batches produced at the intended commercial scale with the intended commercial process. The considered batches include batches used for clinical trials, PPQ and representative batches. Data from release and stability at real time condition up to 18 M have been used to judge variability and potential changes upon storage. As no relevant changes of quality attributes (QAs) have been observed during storage of AS at long-term conditions, the applicant proposes identical acceptance criteria for those parameters tested at release and for stability. This is found acceptable.

The proposed acceptance criteria are all agreeable.

Container closure

INTP23.1 active substance is filled aseptically into 12 L Celsius FFT (Flexible Freeze Thaw) bags and is stored at -20 ± 5ºC. The Celsius FFT bag is constructed from S71 film, a multi-layer co-extruded high gas barrier film containing EVAM (ethylene vinyl acetate copolymer, mono-material) as fluid contact layer and EVOH (ethylene vinyl alcohol) as gas barrier layer. The components of the bag and the material of the components are well described. A representative image and a schematic drawing are included. Specifications for the bag are stated and an example of the vendor certificate is provided. The contact layer of S71 film conforms with Ph.Eur. 3.1.7 (Polyethylene- Vinyl-Acetate) and complies with US FDA 21 CFR 177.1350. This is found acceptable. The stability samples are stored in 5 mL and 50 mL Flexboy bags which are considered representative of full-scale storage container closure system.

An extractable and leachable assessment study was performed. The results are presented in a separate report. In conclusion, it is agreed that the study supports the use of the 12 L Celsius FFT bags with respect to extractables and leachables.

2.4.2.4. Stability

Stability testing of AS has been performed in line with recommendations in relevant ICH guidelines. The included batches encompass three clinical batches, three PPQ batches as well as two developmental- and two representative batches.

No significant decrease in AS quality occurs during the proposed storage period, at the intended condition (-20°C ± 5°C). Hence, the supplied data supports the proposed shelf life of 18 months, which therefore is found acceptable.

An acceptable post-approval stability testing protocol has been provided.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and Pharmaceutical development

Description and composition of the finished product

The finished product is a single-dose pre-filled syringe (PFS) presentation for subcutaneous administration and includes is a sterile, clear, colourless to pale yellow solution for injection. It is presented at a concentration of 60 mg/mL of denosumab in a 1 mL type I glass, single use, pre-filled syringe with a needle safety guard. The finished product (FP) is available in a single strength of 60 mg/mL, containing 60 mg/1.0 mL denosumab, i.e. 60 mg denosumab in a 1.0 mL nominal fill volume. There is no overfill.

The proposed finished product is a biosimilar candidate to the EU-approved reference product Prolia (RMP) and has the same quantitative and qualitative composition as the RMP.

The pre-filled syringe and plunger stopper are compliant with appropriate Ph. Eur. monographs for primary containers and closure and is an integral drug device combination product. A Notified Body Opinion (NBOp) confirming full compliance with the relevant GSPRs was requested during the procedure and was provided.

The formulation contains denosumab (as the active pharmaceutical ingredient) sorbitol, glacial acetic acid, polysorbate-20, sodium hydroxide and water for injection.

Pharmaceutical development

Formulation development

The proposed finished product INTP23.1 is a biosimilar candidate to the EU-approved reference product Prolia (RMP) and is formulated to have the same quantitative and qualitative formulation composition as that of the RMP.

The formulation development section describes and justifies the chosen formulation and is found sufficiently comprehensive and well described.

There is no formula overage in the FP PFS presentation and the information given on physicochemical and biological properties is found sufficient.

Manufacturing process development

The section on manufacturing process development for the FP PFS presentation has been sufficiently described and justifies the commercial manufacturing process.

Process development studies have been performed on filter adsorption, tubing compatibility, various mixing studies and studies on process hold times as well AS freeze-thaw cycle studies.

The manufacturing process development activities consisted of process characterisation studies for all the manufacturing steps of the FP PFS presentation. Process characterisation details have been provided. Based on the knowledge obtained from the process characterisation, criticality of the parameters and the potential risks in the FP manufacturing process were evaluated including an FMEA analysis to justify the proposed categorisation and classification of process parameters, their set points, ranges and control strategy.

Control strategy

The development of the control strategy for the finished product has been sufficiently described. The FP PFS process control strategy has been developed on the assessment of all the process parameters for the different manufacturing steps that could potentially impact the FP quality via FMEA and characterisation studies. The classification and definition of terms used for in-process controls and process parameters as well as all the CPPs, IPCs, set-points, NORs and PARs for the commercial manufacturing process are provided in the dossier. The establishment of a QTPP as well as the identification of relevant CQAs has been described. The data provided confirm the overall process control strategy and the commercial manufacturing process of the FP vial is consequently found appropriately validated. This is found acceptable.

Comparability

Based on the process comparability data submitted it can be concluded that the FP PFS batches manufactured at 5.0 L and 20.0 L scale exerted similar operational and performance parameters.

Nitrosamine risk assessment and elemental impurities

An acceptable risk assessment of N-nitrosamine contamination has been performed and a report has been provided in module 1. It is agreed that there is no risk of formation and entry of N-nitrosamine impurities in the DP.

A risk assessment of elemental impurities in the FP has been performed and a report of the study results has been provided in section P.5.5. The analysis of three batches of FP PFS for elemental impurities showed no inorganic elements of concern above the limits specified ICH guideline Q3D and it is agreed to the conclusion by the applicant that the overall risk of exposure to elemental impurities to the patient is anticipated to be negligible and no further control/testing is required.

The information provided on manufacturing process development for the FP PFS presentation is found sufficient and acceptable.

<u>Container closure system</u>

The development of the container closure system is found sufficiently presented. The primary packaging material for the FP PFS presentation consists of a 1 mL type 1 glass non-graduated syringe barrel with needle and rigid needle shield along with FluroTec coated plunger stopper and plunger rod.

Each pre-filled syringe contains 1.0 mL of finished product solution with a concentration of 60 mg/mL with respect to denosumab.

The pre-fillable glass syringe and plunger stopper are compliant with appropriate Ph. Eur. monographs for primary containers and closures and are further addressed in section P.7.

The pre-filled syringe is assembled with an UltraSafe Plus passive needle guard system. Further details on this device are provided.

The suitability of the container closure system was demonstrated and confirmed by the results provided on compatibility testing of the PFS, stability testing (results in section P.8), agitation and thermal cycling studies, extractables and leachables testing as well as a plunger movement study. The report on the extractable study is provided in section 3.2.R and the report on leachables testing in section P.2.4.

The leachables study is ongoing on 3 batches of FP PFS. Results are obtained up to 6 months and the study will be continued up to 36 months. No issues are raised at this point and this is found acceptable.

The suitability of the container closure system to protect the content in the FP PFS from microbial contamination during storage, transportation and use has also been demonstrated during long-term stability and shipping validation studies, results have been provided in sections P.2.5, P.3.5 and P.8.1.

The information on elemental impurities is found in section P.5.5.

Microbiological attributes

The information given on microbiological attributes is found sufficient and acceptable.

Compatibility

Compatibility of the FP PFS with the container closure system has been studied by a combination of agitation stress studies and thermal cycling studies and stability data. Furthermore, as part of the qualification of the container closure system, container closure integrity testing has been performed with a validated dye ingress method and it is agreed to the conclusion by the applicant that the integrity as well as the compatibility have been successfully demonstrated for the FP PFS and the product contact components.

No reconstitution diluents are being used to administer the FP PFS.

The information provided on container closure system, microbiological attributes and compatibility is found acceptable at large although some issues are raised that should be appropriately solved during the procedure.

2.4.3.2. Manufacture of the product and process controls

Manufacturers

The details of sites involved in manufacturing, testing, packaging/labelling and release of INTP23.1 (denosumab) solution for Injection in pre-filled syringe are included in the following table.

The information provided on manufacturers and batch formula is found acceptable and conforming with GMP requirements

The finished product PFS is manufactured at a batch size of 20.0 L. The quality standards for each component of the FP vial are provided.

The review of the manufacturer information in module 1 is within the remit of the EMA Inspection Sector.

No further issues that would trigger a GMP inspection have been identified.

Description of manufacturing process and process controls and controls of critical steps and intermediates

The manufacturing process for the FP PFS consists of preparation of formulation buffer, thawing of frozen AS, mixing of AS with formulation buffer to formulated bulk solution, bioburden reduction and sterile filtration of formulated bulk solution, aseptic filling, visual inspection, assembly of plunger rod and needle safety device, labelling, packaging and storage.

The FP vial is manufactured by aseptic technique and the solution is passed through a series of two 0.2 µm PVDF-filters at the bioburden reduction and the sterile filtration steps. Filter integrity testing is performed both pre- and post-use for the second 0.2 µm filter during the sterile filtration before the aseptic filling step.

All the critical process operational parameters and their control strategy have been defined and are provided. Further assessor´s comments on the control strategy is given above in section P.2.3. In addition, the applicant has proposed a maximum filling duration of NMT 24 hr for the filling of Osvyrti. This filling time is supported by the media fill simulation studies provided and is considered acceptable.

Furthermore, as a general comment, it should be noted that a change to a process parameter and/or an in-process control will generate a variation application.

The manufacturing process of the FP PFS includes thawing of AS, preparation of formulation buffer, preparation of formulated bulk solution, sterile filtration, aseptic filling in PFS, assembly of plunger rod and safety device and labelling and packaging.

Process development studies have been performed on filter adsorption, tubing compatibility, various mixing studies and studies on process hold times as well AS freeze-thaw cycle studies.

It is described that the 70 mg/mL FP vial presentation has been used for the major part of the process development studies as it includes the higher protein concentration and it will be applicable to both the protein concentrations. Only the filter adsorption study has been performed for both the FP vial presentation (70 mg/mL) and the FP PFS presentation (60 mg/mL), since protein adsorption to the filter might be impacted by protein concentration. This is found reasonable and agreed to.

The manufacturing process development activities consisted of process characterisation studies for all the manufacturing steps of the FP PFS presentation. Process characterisation details have been provided. Based on the knowledge obtained from the process characterisation, criticality of the parameters and the potential risks in the FP manufacturing process were evaluated including an FMEA analysis to justify the proposed categorisation and classification of process parameters, their set points, ranges and control strategy.

Reprocessing

The manufacturing process of the FP PFS does not contain any reprocessing and is consequently not allowed for the steps up to labelling and packaging. However, the labelling and packaging process permits reprocessing to correct labelling when required. This is found acceptable.

Assembly

The pre-filled syringes are assembled with the needle safety guard, along with fixation of the plunger rod. An operating temperature of NMT 25°C is maintained during needle safety guard assembly and labelling.

Hold times

Process steps durations and hold times in the manufacturing process of the FP vial have been summarised and defined together with their respective storage temperature (NMT 25°C). The parameters mentioned have been confirmed in the process validation study and via media fill validation.

In general, the information provided is found sufficiently detailed and acceptable.

The applicant has also confirmed that the number of AS batches included in a single FP PFS batch is up to two batches.

As previously requested, the duration of the needle safety guard assembly with the pre-filled syringes has been defined and the corresponding hold time justified.

Process validation and/or evaluation

In conclusion, the PPQ validation study for the FP PFS 60 mg/mL presentation has been successfully performed. Further, the FP PFS manufacturing process will be continuously monitored in the future in a continued process verification programme. As previously requested, the applicant has also provided an acceptable justification for the process parameters used in the mixing of the formulation buffer as well as provided a sufficient justification for the maximum hold time of NMT 48 hours for AS thaw.

Furthermore, validation support studies have been performed including hold times (buffer and filtered formulated bulk), filter validation, media fills, shipping validation and sterilisation process, component compatibility and equipment validation.

Comparability

It can be noted that comparability has been sufficiently demonstrated for all the attributes tested and evaluated in the comparison of 5.0 L to 20.0 L manufacturing process and the quality of the corresponding FP PFS 60 mg/mL presentation. The process is considered comparable, scalable from 5 to 20 L and consistent quality has been demonstrated for the FP PFS batches manufactured. See section P.2.3 for further assessor´s comments.

Hold times

A hold time study has been performed for all the four PPQ batches and hold time validation data have been provided. Furthermore, a hold time study has also been performed for the filtered and unfiltered formulation buffer and formulated bulk solution in 20 L vessels. The proposed hold times are all found acceptable and justified by the provided validation data.

Filter validation

Successful filter validation reports have been provided for the filter used for the final filtration of the formulated bulk solution. All study results met the predetermined acceptance criteria with respect to microbial retention and chemical compatibility and show that the 0.2 µm filter is fit for the purpose and justifies the use in commercial manufacturing.

Transport validation

Shipping validation studies has been performed for the FP PFS presentation and includes a shipping simulation study, the results from this study are provided. This shipping simulation study has been performed to simulate worst-case conditions with respect to shaking, vibration, shock, pressure and temperature excursions. The result of the test samples was comparable with the results of control samples and it is agreed to the conclusion by the applicant that the shipping simulation conditions employed on FP PFS presentation did not impact finished product quality.

Shipping validation reports including real time shipping validation data have been provided. The provided results in the reports are found acceptable and the transport of the product can be considered suitably validated.

Validation of the aseptic filling process (media fills)

Media fills were used to validate the aseptic filling process and the results are provided. Several media fill runs have been performed for the media fill qualification with a design to simulate the filling process and include worst-case conditions that provide a challenge to the aseptic operations in full commercial scale. Media fills have been run at various filling speeds. Satisfactory results are provided without any contaminated units. In conclusion, the provided media fill results demonstrate that the vial filling line of the FP manufacturer Intas Pharmaceuticals Ltd, at the PFS combo filling line, is capable to produce sterile finished product in pre-filled syringe.

In conclusion, the process validation activities demonstrate that the process is robust and performs as intended, giving a product which meets the quality requirements when run within the defined operating ranges.

2.4.3.3. Product specification

Product specification

The release and stability specifications for INTP23.1 Finished product (FP) have been presented and include tests for appearance, assay, purity. physicochemical and microbiological properties.

FP specification and justification of specifications

A large and broad set of relevant tests is included in the finished product specifications document in section P.5.1 for the FP PFS presentation. The acceptance criteria in the specifications document applies for both release and stability testing (end-of-shelf-life (EOSL)). The release and EOSL specifications are identical for the relative potency (binding assay) and all purity/impurities tests; i.e.SE-HPLC, icIEF, reducing CE-SDS and non-reducing CE-SDS.

The proposed release and stability specifications for the FP PFS presentation have been based upon guidance in ICH Q6B and batch release and stability data from batches used in clinical studies as well as commercial scale PPQ/validation batches.

As previously requested, the applicant has revised the limits for HMW species as measured by SE-HPLC and the LMW species as measured by non-reducing CE-SDS as well as provided a sufficient justification for maintaining the proposed acceptance criteria for the total charge variants and purity as measured by icIEF. These proposals are found sufficient and acceptable, and the AS and FP specifications have been aligned.

The proposed acceptance criteria for the surfactant polysorbate 20 is found acceptable and is set to ensure sufficient amounts of polysorbate 20 and thus adequate product quality at release and throughout the finished product shelf-life. The acceptance criteria have been sufficiently justified.

Device functionality testing/functional suitability is included in a specifications. Testing is performed at both release and upon stability and the specifications are identical. The proposed acceptance criteria for device functionality testing of the FP PFS presentation (break loose force, glide force and needle

safety activation force) are all found acceptable. Additionally, identification test by icIEF is performed for the secondary packaged batch. This test is identical with the test performed on the FP PFS presentation upon release and this is found acceptable.

As previously requested, the applicant has clarified the calculation for the endotoxin limit and the relevant sections of the dossier have been appropriately updated.

In addition, the proposed acceptance criteria for the general test (physical appearance, pH, subvisible particles, extractable volume, gross content, osmolality), safety tests (sterility, CCIT) and identification test (pI by icIEF, relative potency) are found acceptable as well.

Analytical procedures

Test method number are detailed for all analytical procedures used in the finished product specifications document; the method descriptions and the method validation documents are satisfactory.

As previously requested, the applicant has provided an updated LER study demonstrating that the formulation does not cause endotoxin masking.

Furthermore, as previously requested, the applicant has provided an acceptable and tabulated summary of the transfer of methods from Intas to Kymos for biological methods.

Batch analyses

Batch analysis data has been provided for all the FP PFS batches manufactured during development, used in the clinical trials (Phase I and III) and stability as well as for the PPQ-batches manufactured at full commercial scale. It can be noted that all the manufactured FP PFS batches are included in the biosimilarity exercise. Information for all the manufactured FP PFS batches include information with respect to FP batch size, manufacturing date, AS batch size, AS batch(es) used and use of the FP PFS batch. The batch analysis data complies with the limits in the proposed FP PFS release specification in place at the time of manufacture and confirm process and product batch-to-batch consistency. In conclusion, the provided batch data demonstrate a reproducible manufacturing of the FP PFS presentation.

Impurities of the finished product

No new impurities have been identified in the FP PFS presentation compared to the ones identified for the AS. The potential process- and product-related impurities have been sufficiently addressed.

A risk assessment report on elemental impurities in line with ICH Q3D has been provided. Three FP PFS batches have been analysed and no elemental impurities were found above the limit of 30 % of Permissible Daily Exposure (PDE) limits as per ICH guideline Q3D. The conclusion by the applicant is that the overall risk of exposure to elemental impurities to the patient is anticipated to be negligible and no further control/testing is required. This is accepted.

Furthermore, a N-nitrosamine contamination report on AS and FP has been provided and appropriately updated with relevant information as provided in this N-nitrosamine contamination report.

<u>Container closure system</u>

The development of the container closure system for the FP PFS presentation has been sufficiently described.

The primary packaging material for the FP PFS presentation consists of a 1 mL type 1 glass non-graduated syringe barrel with needle and rigid needle shield along with FluroTec coated plunger

stopper and plunger rod. The syringe barrel and plunger stopper are provided as sterile and ready to use.

Acceptable dimensional drawing and specifications are provided the glass syringe barrel and rigid needle shield and the rubber plunger stopper.

Each pre-filled syringe contains 1.0 mL of finished product solution (60 mg/mL).

The pre-fillable glass syringe and plunger stopper are compliant with appropriate Ph. Eur. monographs for primary containers and closures, Ph Eur 3.2.1 and Ph Eur 3.2.9, respectively. Information with respect to name and address of the supplier of the primary packaging material and the secondary packaging material is provided as well.

The manufacturing process for the FP PFS presentation is acceptably describe. The pre-filled syringe is further assembled with the UltraSafe Plus™ passive needle guard system. The pre-filled syringe is a combination product and integral medicinal device, intended to deliver the finished product solution subcutaneously in a fixed dose format. The pre-filled syringe has no graduation marks.

The pre-filled syringe is assembled with an UltraSafe Plus passive needle guard system.

The sterilisation of the glass syringe barrel and the rubber plunger stopper is performed at standard conditions by ethylene oxide for the glass syringe and by gamma irradiation for the rubber plunger stopper using validated methods in accordance with ISO 11135 and ISO 11137, respectively. The specifications for both the glass syringe barrel and the rubber plunger stopper include testing for sterility (Ph Eur 2.6.19) and bacterial endotoxins (Ph Eur 2.6.19). Test for residual ethylene oxide and ethylene chlorohydrin with acceptance criteria according to the guideline EMA/CHMP/CVMP/QWP/850374/2015 is included in the CoA from the manufacturer for the glass syringe barrel. This is found acceptable. The suitability of the container closure system to protect the solution from microbial contamination during storage, transportation and use of the FP PFS presentation has been demonstrated during long-term stability testing and shipping validation studies, results are provided. Furthermore, the suitability of the container closure system has also been acceptably demonstrated by the extractables and leachables testings.

2.4.3.4. Stability of the product

The proposed shelf-life for the FP PFS presentation (60 mg/mL) is 24 months when stored at the recommended storage condition of 2 to 8°C.

Sufficient stability data has been submitted for studies conducted under real time, accelerated and stress conditions. Photostability testing has been performed according to ICH Q1B and showed that the FP PFS presentation is photosensitive and, in addition, that the intended commercial pack with secondary packaging material is able to protect the FP PFS from photodegradation, in-line with the wording in section 6.4 in the SmPC.

Compatibility of the FP PFS presentation with the container closure system has been studied by a combination of agitation stress studies and thermal cycling studies and stability data. Furthermore, as part of the qualification of the container closure system, container closure integrity testing has been performed with a validated dye ingress method and it is agreed that the integrity has been successfully demonstrated.

The suitability of the container closure system to protect the content in the FP PFS from microbial contamination during storage, transportation and use has been demonstrated during long-term stability and shipping validation studies, results have been provided.

Shipping validation studies for the FP PFS presentation has been performed via a shipping simulation study and the results are provided. This shipping simulation study has been performed to simulate worst-case conditions with respect to shaking, vibration, shock, pressure and temperature excursions. The result of the test samples was comparable with the results of control samples and it is agreed to the conclusion by the applicant that shipping simulation conditions employed on FP PFS did not impact finished product quality.

Post-approval stability protocol and stability commitment

The applicant commits to continue all the ongoing stability studies at long-term conditions (2 to 8 °C) through the proposed shelf-life. In addition, at least one commercial batch of FP PFS presentation will be placed annually on stability studies at long-term conditions (5 ± 3 °C). The real-time stability schedule for post-approval studies have been provided and found acceptable although the design of this protocol is part of GMP and therefore not formally assessed in this report.

Proposed shelf-life and storage conditions

The proposed shelf-life for the FP PFS presentation (60 mg/mL) is 24 months when stored at the recommended storage condition of 2 to 8°C.

Furthermore, it can be noted that the issues raised on clinical qualification of limits of HMWs by SEC, LMWs by NR CE-SDS and charged variants by icIEF have been resolved. Therefore, since comparability has already been concluded between the FP vial presentation manufactured at the 5 L and the 20 L commercial scale, the proposed shelf-life of 24 months at 2 to 8°C for the FP PFS is agreed to.

However, functionality testing needs to be performed for the PPQ batches of the FP PFS already at the 18 months-point and the applicant should confirm that these data will be submitted for assessment as soon as they are available. **(REC**Biosimilarity

INTP23.1 60 mg/mL pre-filled syringe (PFS) is developed as a proposed biosimilar product to EU approved Prolia. In parallel, INTP23.1 120 mg/1.7 mL vial is developed as a proposed biosimilar product to EU approved Xgeva. The analytical similarity exercise was designed to integrate the characterisation of both formulations of INTP23.1 to demonstrate overall biosimilarity of INTP23.1 to the RMPs. This is found acceptable and in line with a previous CHMP scientific advice (EMEA/H/SA/4311/1/2019/III).

Table 1. Summary of analytical biosimilarity exercise

Attribute category	Quality attribute	Analytical test
Primary structure	Amino acid sequence	Amino acid sequence
		N terminal sequencing
	Molecular mass determination	Intact mass by LC-MS
		Reduced mass by LC-MS
	Amino acid sequence	Amino acid sequencing by LC-MS and MS/MS
		Peptide mapping by UV-UPLC
	Isoelectric point	icIEF
Higher order structure analysis	Secondary structure	Far UV circular dichroism
	Tertiary structure	Near UV circular dichroism
	Secondary structure	Thermal stability by differential scanning calorimetry
	Tertiary structure	Intrinsic Fluorescence Spectroscopy
	Disulphide bridge assessment	Disulphide bridge assessment by LC-MS
	Free cysteine estimation	Ellman's test
Functional characteristic analysis	Potency	sRANKL binding by ELISA
		U2OS cell based assay

		RAW264.7 cell based assay
	Target binding	RANKL binding by SPR
		mRANKL binding assay
	Fc receptor binding	FcRn receptor binding by SPR
		FcγRIIa receptor binding by SPR
		FcγRI receptor binding by SPR
		FcγRIIIa receptor binding by SPR
	C1q binding	C1q binding assay
	ADCC binding	ADCC assay
	CDC binding	CDC assay
Particulate and aggregates	High molecular weight variants/ Oligomeric species	SEC-MALS
	Sub-visible particle count	Light obscuration test
	High molecular weight variants/ Oligomeric species	Analytical ultra centrifugation
Product variants	Disulphide isoforms	RP-UHPLC
	High molecular weight variants/ Aggregates	SE-HPLC
	Low molecular weight variants	CE-SDS (Reducing and non-reducing)
	N-Glycosylation	HILIC
	Sialic acid estimation	RP-HPLC with DMB labelling
	Charge variants analysis	icIEF
	Oxidised variants	RP-UPLC
Pharmaceutical properties	Protein concentration	UV by A280
	Formulation and other characteristics	pH
		Physical appearance
		Extractable volume
		Osmolality

In summary, the presented analytical data show similarity of the proposed biosimilar Osvyrti and the reference medicinal product Prolia. Quality attributes related to the mechanism of action of Osvyrti were similar. The analytical differences observed for several quality attributes have been appropriately addressed by the applicant and justified with regard to their potential impact on clinical performance of the product.

Pharmaceutical properties

Biosimilarity with respect to pharmaceutical properties, i.e., protein concentration, pH, physical appearance, extractable volume and osmolality was evaluated. The protein concentration was adequately demonstrated to be comparable for INTP23.1 PFS with the RMP Prolia, and for INTP23.1 vial with the RMP Xgeva. Furthermore, the pH, physical appearance and osmolality was sufficiently demonstrated to be similar to the RMP.

The extractable volume was demonstrated to be 1.0-1.1 mL for INTP23.1 PFS and 1.7 – 2.0 mL INTP23.1 vial. This complies with the FP specification limits for INTP23.1 DP. Also, the results are comparable to those obtained for few batches of the RMP.

Forced degradation study

Comparative forced degradation studies included thermal, oxidative, high pH, low pH and photo stress conditions. The applicant has used four INTP23.1 (two PFS and two vial) batches compared to one EU Prolia and two EU Xgeva batches. The study was performed by a head-on-head comparison. Similar rates of degradation were seen under all the degradation studies between the biosimilar and the RMPs. Sub-visible particle testing was not carried out during the forced degradation studies. Although, a physical appearance test was performed through visual inspection and no presence of any visible

particulate matter was detected. Protein concentration was analysed during the photo and thermal stress conditions as pH had not showed any change during the pilot studies. Protein concentration and pH were analysed during the first and last time points of the high pH and low pH conditions. Neither were studied during the oxidative stress study. Results have been provided for each and the results show the INTP23.1 and EU batches are similar.

2.4.3.5. Adventitious agents

The expression host is CHO-S adapted to serum free growth. The applicant states that the materials used with INTP23.1 active substance during the manufacturing process, are not of human or animal origin and thus not considered to carry a TSE or BSE risk. The information is found sufficient and it is concluded that the risk of BSE/TSE is negligible.

The cell banks have been tested for sterility, mycoplasma and fungi and shown to be free of contamination. Bioburden is measured as an in-process test during AS manufacture. The unprocessed bulk is tested for bioburden and mycoplasma, as part of in-process testing, and release of the AS is tested for bioburden. Bioburden is an in-process control test on the formulated finished product prior to 0.2 µm sterilizing filtration. Finished product lots are tested for endotoxin and sterility. The safety for non-viral adventitious agents has been satisfactorily addressed.

Information on virus testing of cell banks is presented in section 3.2.S.2.3 and also in section 3.2.A.2. The results from virus testing are as expected for CHO-cells with the presence of A- and C-type retrovirus like particles. Certificates of analysis are provided for the MCB and WCB. Summary descriptions of the tests performed are provided. The original reports for the testing of adventitious virus on the MCB, WCB and EoPC have been provided.

Testing and results for viral adventitious agents in unprocessed bulk harvests are presented. The updated information provided by the applicant on UBH testing is found acceptable.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of active substance and finished product has been presented in a satisfactory way. The presented documentation shows that the active substance and finished product is manufactured in a well-controlled and validated process.

INTP23.1 60 mg/mL pre-filled syringe (Osvytri) is developed as a proposed biosimilar product to EU approved Prolia. In parallel, INTP23.1 120 mg/1.7 mL vial is developed as a proposed biosimilar product to EU approved Xgeva. The analytical similarity exercise was designed to integrate the characterisation of both formulations of INTP23.1 to demonstrate overall biosimilarity of INTP23.1 to the RMPs. The overall approach is found acceptable. INTP23.1 is considered to be biosimilar to the EU approved Prolia at the quality level. Some minor differences are noted but the applicant justifies these differences as being not clinically meaningful, which is accepted.

From the quality perspective, no questions remain and the MAA for Osvyrti is approvable.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical

performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

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

Functionality testing needs to be performed for the PPQ batches of the pre-filled syringe finished product at the 18 months-point and the applicant is recommended to submit these data for assessment as soon as they are available.

2.5. Non-clinical aspects

2.5.1. Introduction

The active substance of INTP23.1 and Prolia and Xgeva is denosumab, a fully human monoclonal antibody of the IgG2 subclass, directed to receptor activator of nuclear factor kappa-B ligand (RANKL) and is produced in Chinese Hamster Ovary cells. When denosumab binds to RANKL it prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and resulting in net increase in bone mass and strength in both cortical and trabecular bone.

The demonstration of biosimilarity of INTP23.1 and Prolia and Xgeva is based on the totality of evidence data of analytical, nonclinical, and clinical comparative studies to demonstrate structural and functional similarity.

The non-clinical programme was focused on primary pharmacodynamics (PD). A series of in vitro PD studies was performed to assess any potential differences in biological activity between INTP23.1 and the EU (and US) reference medicinal products Prolia and Xgeva. Given that INTP23.1 is developed as a proposed biosimilar, secondary PD, safety pharmacology and PD drug interaction, PK/toxicokinetic (TK), or relevant toxicology studies were not deemed necessary. This is in line with EMA guideline [EMA/CHMP/BMWP/403543/2010] and the scientific advice given by EMA in December 2019 (EMA/CHMP/SAWP/653442/2019).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

For the non-clinical evaluation of INTP23.1, a series of comparative in vitro studies to evaluate similarity between INTP23.1 and reference medicinal products Prolia and Xgeva (EU and US).

The in vitro pharmacological properties of INTP23.1 were investigated using binding and functional assays. The in vitro PD activity of INTP23.1 was compared with multiple batches of the reference products. In total 12 lots of INTP23.1 with PFS presentation and 11 lots of INTP23.1 with vial, 11 and

10 lots of EU-approved Prolia and Xgeva, and 10 and 8 lots of US-licensed Prolia and Xgeva, were used for analytical/functional similarity assessment.

The in vitro assessment of binding and function included in vitro pharmacodynamics assays regarding Fab-dependent biological activities, Fc binding activities, Fc effector function characterisation as summarised in the table below.

Table 2 Functional characteristics analysis

Attribute	**Analytical technique**
Potency and target binding	sRANKL binding by ELISA
	U2OS cell based assay
	RAW264.7 cell based assay
	RANKL binding by SPR
	mRANKL binding assay
Fc binding	FcRn binding by SPR
	FcγRI binding by SPR
	FcγRII binding by SPR
	FcγRIIIa binding by SPR
C1q binding	C1q binding assay
ADCC binding	ADCC assay
CDC binding	CDC assay

In general, the functional data indicate that the INTP23.1 and EU-approved (and US-sourced) Prolia and Xgeva are similar. However, differences in FcRn binding was observed in that INTP23.1 showed higher potency compared to the RMPs.

Overall, the functional *in vitro* data package is deemed adequate for demonstrating the similar biological activity of INTP23.1 and EU-approved Prolia and Xgeva and reflects the principal mode of action of denosumab.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed in alignment with regulatory guidance for biosimilar development.

2.5.2.3. Safety pharmacology programme

No safety pharmacology studies were conducted given that omission of these studies is in line with regulatory guidance for biosimilar development.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted given that omission of these studies is in line with regulatory guidance for biosimilar development.

2.5.3. Pharmacokinetics

No pharmacokinetic studies were conducted and are not generally required for a biosimilar for the approval of the marketing authorisation within EU, and in line with EMA guidance documents for biosimilar development.

2.5.4. Toxicology

No non-clinical toxicological studies with INTP23.1 were performed in alignment with regulatory guidance for biosimilar development and biotechnology-derived pharmaceutical development.

2.5.5. Ecotoxicity/environmental risk assessment

The active substance of INTP23.1 (denosumab) is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, INTP23.1 is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

The non-clinical data package was focused on comprehensive *in vitro* functional activity analyses. The in vitro assessment of binding and function included in vitro pharmacodynamics assays regarding Fab-dependent biological activities, Fc binding activities, Fc effector function characterisation. The functional in vitro data package is deemed adequate for demonstrating the similar biological activity of INTP23.1 and the EU-approved (and US-sourced) Prolia and Xgeva and reflects the principal mode of actions of denosumab. In general, the functional data indicate that the INTP23.1 and EU-approved (and US-sourced) Prolia and Xgeva are similar. However, INTP23.1 showed higher potency in FcRn binding compared to the reference medicinal products (RMPs). This is explained by that the Fc region of INTP23.1 is slightly less oxidised. This difference is considered not clinically relevant as there was no clinical effect on clearance nor bioequivalence. These in vitro functional studies were included under Module 3 and are presented in more detailed and reviewed under Quality/Biosimilarity section.

No additional in vivo pharmacology studies were conducted and are not generally required for a biosimilar for the approval of the marketing authorisation within EU, and in line with EMA guidance documents for biosimilar development. This approach was also agreed by CHMP Scientific Advice (given during 2019, Procedure No. EMA/CHMP/SAWP/653442/2019).

Comparative *in vivo* pharmacokinetic/toxicokinetic studies with INTP23.1 and the EU (and US) approved RMPs Prolia and Xgeva were not conducted and are not required for biosimilars.

Neither single- or repeat dose toxicity, genotoxicity, carcinogenicity, developmental and reproductive toxicology, local tolerance nor other toxicity studies were performed withINTP23.1. According to the EMA guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1, Dec 2014), a stepwise approach is recommended for evaluation of the similarity of the biosimilar and the reference product, since *in vitro* assays may often be more specific and sensitive to detect differences between the biosimilar and the reference product than studies in animals, and therefore these assays can be considered as paramount for the non-clinical biosimilar comparability exercise. Studies regarding safety pharmacology, reproduction toxicology, and carcinogenicity are not required for non-clinical testing of biosimilars, which usually applies for studies on local tolerance as well. This approach was endorsed by the EMA within the scope of a previous scientific advice provided in December 2019

[EMA/CHMP/SAWP/653442/2019], supporting the proposed strategy of the applicant to not conduct any *in vivo* animal studies with INTP23.1 and its RMPs.

The proposed text for section 4.6 and 5.3 of the SmPC is in line with that of the reference product.

Adequate justification for absence of ERA has been provided. Monoclonal antibodies are unlikely to pose a significant risk to the environment. Environmental risk assessment studies are therefore not required in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

2.5.7. Conclusion on the non-clinical aspects

The non-clinical *in vitro* functional activity data support the biosimilarity between INTP23.1 and the EU (and US) reference medicinal products Prolia and Xgeva.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

- **Tabular overview of clinical studies**

An overview of the submitted clinical studies is presented in the table below.

Table 3 Overview of the clinical studies

Study Type, Identifier and Status	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy subjects or Diagnosis of patients	Duration of Treatment
PK/PD Project No. 0568-19 Completed	Clinical Study Report & PK Report and Adverse Event Listing 5.3.3.1 Bio-Analytical Report & Method validation Report 5.3.1.4 Literature References 5.4	**Primary objective:** To compare the pharmacokinetic parameters of Intas Denosumab against US-Xgeva and EU-Xgeva. **Secondary objective:** To compare pharmacodynamic, immunogenicity and safety of Intas Denosumab against US-Xgeva and EU-Xgeva. To compare the pharmacokinetic and pharmacodynamic parameters of US-Xgeva and EU-Xgeva.	**Study Design:** Randomized, double-blind, three-arm, balanced, single-dose, parallel-group, comparative pharmacokinetic and pharmacodynamic study. **Type of Control:** Active control	**Test Product-T** Intas Denosumab 120 mg/1.7 mL, Intas, India **Reference Product-R1** Xgeva 120 mg/1.7 mL, Amgen Inc., USA. **Reference Product-R2** Xgeva 120 mg/1.7 mL, Amgen Europe B.V., The Netherlands **Dosage Regimen** 35 mg (0.5 mL) SC for three tst products	Planned-234 (78 subjects per arm) Dosed-234 Analyzed-234 Completed-220 Discontinued/ Withdrawn-14	Healthy subjects	Single dose

Study Type, Identifier and Status	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy subjects or Diagnosis of patients	Duration of Treatment
Efficacy/PK/PD Lambda Project No. 0774-19, Novum/ Cromos Project No. 72189811/CP1352 Study Complete	Clinical Study Report & PK Report and Adverse Event Listing, Individual Subject Listings & CRFs 5.3.5.1 Bio-Analytical Report & Method validation Report 5.3.1.4 Literature References 5.4	**Primary Objective:** To compare PK and efficacy/PD (LS BMD and bone resorption marker) with reference product, Prolia in postmenopausal women with osteoporosis. **Secondary Objective:** To compare the secondary efficacy endpoints, PD, immunogenicity and safety with reference product, Prolia To evaluate the safety and immunogenicity of after single transition from reference product, Prolia	**Study Design:** Randomized, double-blind, active-controlled, parallel-arm, multicenter study of Intas Denosumab (60 mg/ml) with Prolia in postmenopausal women with osteoporosis **Type of Control:** Active control	**Test Product-T** Denosumab 60 mg/mL Solution for injection in single-use prefilled syringe **Reference Product-R** EU Prolia® 60 mg/mL Solution for injection in single-use prefilled syringe **Route of administration:** Subcutaneous	**Treatment Period:** Planned- 552 Dosed- 552 Completed (clinical phase)-464 Drop-out: 88 Analyzed: Immunogenicity- 552 PK- 261 PD- 258 **Transition-Extension Period:** Planned- 136 Dosed- 123 Completed (clinical phase)- 121 Drop-out: 2	Postmenopausal women with osteoporosis between the ages of 55 to 90 years	Single dose repeated at 6 months for all patients and again at 12 months for patients entering the Transition-Extension Period

2.6.2. Clinical pharmacology

The overall clinical development programme included 2 pivotal studies to demonstrate PK and PD similarity between Intas Denosumab and Amgen's denosumab.

- Study 0568-19: The purpose of this study was to demonstrate PK and PD similarity in healthy male subjects between Intas Denosumab, Xgeva (US) and Xgeva (EU) after a single SC dose of 35 mg denosumab.
- Study 0774-19: The purpose of this study was to demonstrate similarity in PK, PD, efficacy and safety between Intas Denosumab and Prolia in postmenopausal women with osteoporosis.

A total of 29 blood samples (each of 3.5 mL) for pharmacokinetics evaluation, 19 blood samples (each of 3.5 mL) for pharmacodynamics evaluation and 7 blood samples (each of 6.0 mL) were collected for immunogenicity evaluation during the study from each subject except for the discontinued / withdrawn subjects and missing samples to analyse the pharmacokinetic, pharmacodynamic and immunogenicity profiles of the test and reference products.

2.6.2.1. Pharmacokinetics

Study 0568-19

The study was a randomised, double-blind, three-arm, balanced, single-dose, parallel-group, comparative pharmacokinetic and pharmacodynamic study of Intas Denosumab, Xgeva (US) and Xgeva (EU) after a single SC infusion in healthy adult male subjects.

A total of 234 healthy male subjects who met the required entry criteria were planned to be randomly assigned to one of 3 treatment groups in a 1:1:1 ratio to receive a single SC injection of Intas Denosumab, Xgeva (US) or Xgeva (EU) to the outer area of the right upper arm.

All the randomised subjects in the study were provided with calcium and vitamin D supplements. The recommended administration of these supplements was at least 600 mg calcium (daily) and at least 400 IU vitamin D but <1000 IU daily for the duration of the study.

Subjects were administered single dose of 35 mg (0.5 ml of 1.7 ml vial) of either test or reference (US or EU) product.

PK blood samples were collected at pre-dose (within a period of 60 minutes before dosing) and at different timepoints post-dose.

All the subjects enrolled in the study were Asian male. The mean age of study subjects was 40.1 years and ranged from 28 to 49 years.

A summary of key PK parameters for all 3 products (Intas Denosumab, Xgeva (US) and Xgeva (EU)) is presented in the below Table.

Table 4 Summary of the key PK parameters for Intas Denosumab, Xgeva (US) and Xgeva (EU)

Parameter	Statistics	Intas Denosumab	Xgeva (US)	Xgeva (EU)
C_{max} (ng/mL)	N	73	74	73
	Mean	3575.800	3575.620	3692.786
	SD	792.2290	744.4719	859.4908
	CV%	22.2	20.8	23.3
	Min	1719.236	1943.919	1568.017
	Median	3424.359	3443.716	3654.356
	Max	6648.997	6171.668	5766.326
$AUC_{0-\infty}$ (ng.h/mL)	N	73	74	70
	Mean	3302965.279	3317962.602	3289815.104
	SD	907985.0184	880723.8626	905931.9716
	CV%	27.5	26.5	27.5
	Min	1390984.778	1579809.150	1787959.342
	Median	3061653.308	3257312.420	3140131.119
	Max	6969004.458	5857917.026	6190663.531
AUC_{0-t} (ng.h/mL)	N	73	74	70
	Mean	3256406.946	3267471.220	3233569.867
	SD	903850.3421	883452.2669	890319.2897
	CV%	27.8	27.0	27.5
	Min	1314061.006	1479608.738	1751945.682
	Median	3024642.644	3215453.319	3085811.269
	Max	6892055.747	5819399.842	6151919.648
AUC_{0-CT} (ng.h/mL)	N	73	74	70
	Mean	2529094.139	2545943.908	2471443.513
	SD	841961.5525	819767.8569	907344.4784
	CV%	33.3	32.2	36.7
	Min	930935.873	1057444.698	911147.129
	Median	2323587.161	2377263.657	2343769.731
	Max	5967816.144	4831001.462	5508188.424
AUC_{CT-t} (ng.h/mL)	N	73	74	70
	Mean	727312.806	721527.313	762126.354
	SD	244620.3130	171950.2471	280053.9549
	CV%	33.6	23.8	36.7
	Min	383125.133	362525.545	284186.768
	Median	670169.846	732066.115	688025.516
	Max	1670868.854	1162642.887	2146259.156

Table 5. Summary of statistical comparisons of pharmacokinetic parameters [Intas Denosumab vs Xgeva (EU)] (N=146)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Inter Subject CV (%)	Power (%)
	Intas Denosumab (T) (N=73)	Xgeva (EU) (R2) (N=73)	Ratio (T/R2) %			
lnC_{max}	3499.035	3560.109	98.3	92.06 – 104.93	23.9	100.0
$lnAUC_{0-t}$	3170257.368	3127048.723^	101.4	94.36 – 108.93	26.0	100.0
$lnAUC_{0-\infty}$	3219974.340	3185980.706^	101.1	94.12 – 108.52	25.8	100.0
$lnAUC_{0-CT}$	2425495.195	2320182.281^	104.5	95.41 – 114.54	33.5	99.1
$lnAUC_{CT-t}$	696883.771	729183.993^	95.6	87.71 – 104.14	31.3	99.5

Table 6. Summary of statistical comparisons of pharmacokinetic parameters [Intas Denosumab vs Xgeva (US)] (N=147)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Inter Subject CV (%)	Power (%)
	Intas Denosumab (T) (N=73)	Xgeva (US) (R1) (N=74)	Ratio (T/R1) %			
lnC_{max}	3509.370	3481.316	100.8	94.94 – 107.04	21.9	100.0
$lnAUC_{0-t}$	3167878.487	3138660.443	100.9	93.78 – 108.63	26.9	100.0
$lnAUC_{0-\infty}$	3215254.757	3194284.285	100.7	93.65 – 108.19	26.4	100.0
$lnAUC_{0-CT}$	2420174.785	2400043.604	100.8	92.20 – 110.29	33.1	99.3
$lnAUC_{CT-t}$	698769.907	704004.157	99.3	91.98 – 107.11	27.9	99.9

Table 7. Summary of statistical comparisons of pharmacokinetic parameters [Xgeva (EU) vs Xgeva (US)] (N=147)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Inter Subject CV (%)	Power (%)
	Xgeva (EU) (R2) (N=73)	Xgeva (US) (R1) (N=74)	Ratio (R2/R1) %			
lnC_{max}	3559.827	3484.752	102.2	96.04 – 108.66	22.6	100.0
$lnAUC_{0-t}$	3112874.843^	3145127.253	99.0	92.11 – 106.35	26.2	100.0
$lnAUC_{0-\infty}$	3169816.567^	3200894.995	99.0	92.26 – 106.30	25.8	100.0
$lnAUC_{0-CT}$	2313362.981^	2410707.397	96.0	87.61 – 105.11	33.5	99.1
$lnAUC_{CT-t}$	719949.550^	698903.965	103.0	95.45 – 111.17	27.8	99.9

Study 0774-19

A total of 552 patients were randomised in a 1:1 ratio to receive denosumab or denosumab-ref. Among these, 296 patients (148 patients per arm) were to be enrolled for the PK assessment. Of 296 enrolled and dosed patients, 261 patients were qualified for PK set and were included in the PK set.

The pharmacokinetic results are presented below.

Table 8. Pharmacokinetic parameters of denosumab after first dose (N=261)

Parameters (Units)	Mean ± SD (untransformed data)	
	Denosumab (T) (N=131)	Prolia (R) (N=130)
T_{max} (h)[#]	213.717 (44.917 - 624.833)	213.659 (24.000 - 960.217)
C_{max} (ng/mL)	7325.545 ± 2363.1326	6639.595 ± 2345.6058
AUC_{0-t} (ng.h/mL)	6547550.472 ± 2429206.1024[^]	5865078.843 ± 2474605.0787
$AUC_{0-\infty}$ (ng.h/mL)	6687930.416 ± 2663193.4027[^]	6018503.210 ± 2726540.6961
λ_z (1/h)	0.002 ± 0.0007[^]	0.002 ± 0.0007
$t_{½}$ (h)	340.587 ± 140.8047[^]	337.030 ± 275.6144
AUC_%Extrap_obs (%)	1.431 ± 4.8445[^]	1.644 ± 5.7915
Cl/F (L/h)	10.683 ± 5.5845[^]	12.136 ± 6.5422
Vd/F (L)	4898.494 ± 2608.9967[^]	5286.826 ± 2405.2623

[#]T_{max} is represented as median (min-max) value. [^]N=129

Note: Two patients in test arm (Randomization no. R144 and R153) had three consecutive missing (M) samples in elimination phase and hence AUC_{0-t} and other elimination phase dependent parameters of the same were not considered for the computation of descriptive statistics.

Table 9. Pharmacokinetic parameters of denosumab after second dose (N=261)

Parameters (Units)	Mean ± SD (untransformed data)	
	Denosumab (T) (N=131)	Prolia (R) (N=130)
T_{max} (h)[#]	5039.833 (4967.950 - 7127.167)	5039.842 (4965.717 - 8687.417)
C_{max} (ng/mL)	3966.928 ± 1795.4954	3531.820 ± 1658.0300
AUC_{0-t} (ng.h/mL)	4623179.223 ± 2553063.7731[^]	3931375.688 ± 2311613.5088[@]
$AUC_{0-\infty}$ (ng.h/mL)	6490865.206 ± 2218281.5990[*]	6410932.132 ± 2253196.8254[$]
λ_z (1/h)	0.002 ± 0.0004[*]	0.002 ± 0.0004[$]
$t_{½}$ (h)	480.136 ± 243.9164[*]	463.123 ± 228.8392[$]
AUC_%Extrap_obs (%)	2.788 ± 5.4830[*]	2.482 ± 5.2805[$]
Cl/F (L/h)	10.200 ± 3.1212[*]	10.619 ± 4.1218[$]
Vd/F (L)	6869.952 ± 3998.7844[*]	7006.283 ± 4848.8129[$]

Table 10. Summary statistics of pharmacokinetic parameters for denosumab after first dose (N=261)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Inter Patients CV (%)	Power (%)
	Denosumab (T)	Prolia (R)	Ratio (T/R)%			
lnC_{max}	6856.356	6251.419	109.7	101.85 - 118.11	37.1	99.9
$lnAUC_{0-t}$	6052572.354	5378094.961	112.5	103.12 - 122.82	44.2	99.5
$lnAUC_{0-\infty}$	6156141.837	5501141.954	111.9	102.39 - 122.31	45.0	99.3

Immunogenicity

Study 0568-19

Of 234 subjects included in the safety set; 233 subjects were included in the immunogenicity analyses. In the safety set, post-dose incidence of the subjects with ADAs to denosumab was reported as 10 (12.82%), 14 (17.95%), and 7 (8.97%) in Intas Denosumab (biosimilar), US-Xgeva and EU-Xgeva group, respectively. No subject in any treatment group was positive for NAbs.

Table 1. Analyses of ADA attributes

	EU approved Xgeva®	US licenced Xgeva®	INTP23.1
Total subjects	78	78	78
Number of ADA positive	7	14	10
Percentage	8.97	17.95	12.82
Median titer	2	1	1
Mean titer	3	3	2
Highest titer	1:8	1:16	1:4
Transient Positive	5	10	7
Persistent Positive	2	4	3
Neutralizing Positive	0	0	0

Study 0774-19

All 552 patients that were included in the safety set of main phase, were included in the immunogenicity analyses of main phase. Of 552 patients, 291 patients (145 in Intas Denosumab (biosimilar) and 146 in Prolia) were potential positive in screening. Of these 291 patients, 50 patients (29 in Intas Denosumab (biosimilar) and 21 in Prolia) were confirmatory positive. Amongst confirmatory positive patients, 9 patients (5 in Intas Denosumab (biosimilar) and 4 in Prolia) were neutralising positive in treatment (main) phase of the study, i.e. <2% patients found NAb positive in the study.

Table 11. Analyses of ADA attributes (main phase)

	EU Approved Prolia®	INTP23.1
Total subject enrolled	276	276
Number of positive	21	29
Percentage	7.61	10.51
Median titer	4	8
Mean titer	120	96
Highest titer	1:2048	1:4096
Transient Positive	12	13
Persistent Positive	9	16
Neutralizing Positive	5	4

All 123 patients included in the safety set of transition-extension phase were included in the immunogenicity analyses of transition-extension phase. Immunogenicity was low with little difference between Intas Denosumab (biosimilar) and Prolia, with only one patient (<1%) in the Intas Denosumab (biosimilar) arm exhibiting neutralizing antibodies.

Table 12. Analyses of ADA attributes (extension phase)

	EU approved Prolia®	INTP23.1
Total subject enrolled	**62**	**61**
Number of positive	**2**	**4**
Percentage	**3.23**	**6.56**
Highest titer	**1:1**	**1:2048**
Neutralizing Positive	**0**	**1**

Impact of ADA/NAb on PK

Study 0568-19

Summary of serum denosumab PK parameters for ADA positive and ADA negative following a single dose of Intas Denosumab (biosimilar), US-Xgeva and EU-Xgeva is presented below.

Table 13. Summary of the influence of ADAs on primary PK parameters

Parameter	Statistics	INTP23.1		Xgeva (US)		Xgeva (EU)	
		ADA Positive	ADA Negative	ADA Positive	ADA Negative	ADA Positive	ADA Negative
C_{max} (ng/mL)	N	10	63	14	60	6	67
	Mean	3683.928	3558.636	3637.502	3561.181	3179.86	3738.72
	SD	996.7143	763.1926	667.2023	765.8629	520.8759	871.3598
	CV%	27.1	21.4	18.3	21.5	16.4	23.3
AUC_{0-t} (ng.h/mL)	N	10	63	14	60	6	64
	Mean	3114015.49	3279008.76	3169794.12	3290262.55	2966268.3	3258629.39
	SD	1329305.28	829707.125	771247.272	912049.179	502080.464	916903.058
	CV%	42.7	25.3	24.3	27.7	16.9	28.1
$AUC_{0-\infty}$ (ng.h/mL)	N	10	63	14	60	6	64
	Mean	3171584.36	3323819.39	3220729.68	3340650.28	3018468.78	3315253.82
	SD	1338032.93	833245.231	762667.703	910386.308	482968.712	934180.702
	CV%	42.2	25.1	23.7	27.3	16	28.2

Study 0774-19

Impact of ADAs on the primary PK parameters was assessed by comparing the descriptive statistics of parameters between pool of patients having positive and negative immune response for each dose of each treatment. Results are presented below.

Table 14. Comparison of primary PK parameters of denosumab with immunogenicity response

Treatment	PK Parameter	Dose	IM Response	N	Mean	SD	Minimum	Maximum
T (Denosumab)	C_{max} (ng/mL)	First	Negative	114	7245.349	2295.2139	2016.917	15552.312
			Positive	17	7863.334	2795.4967	4039.563	15664.265
		Second	Negative	114	3995.371	1808.8301	0.000	11357.470
			Positive	17	3776.192	1743.9700	954.307	7773.469
		Third	Positive	12	3959.314	2439.0352	0.000	9049.717
	AUC_{0-t} (ng.h/mL)	First	Negative	114	6490495.115	2418671.1825	1254446.145	14562102.236
			Positive	15	6981171.187	2550843.8460	3386132.026	12938041.964
		Second	Negative	113	4725010.717	2571515.4213	102879.935	16265766.005
			Positive	17	3946299.297	2388217.3274	635952.864	9746282.206
		Third	Positive	11	4655208.809	2649041.4391	1795900.199	11180104.129
	$AUC_{0-\infty}$ (ng.h/mL)	First	Negative	114	6642251.611	2682301.1084	1316589.206	18817767.216
			Positive	15	7035089.338	2574621.9460	3408131.211	13036217.730
		Second	Negative	63	6481704.976	2273862.1462	3403901.396	16378563.732
			Positive	6	6587047.630	1672360.4140	5398731.527	9804054.916
		Third	Positive	6	5726808.850	3187723.6973	2731256.767	11281452.494
R (Prolia)	C_{max} (ng/mL)	First	Negative	113	6674.369	2301.6189	930.978	12383.807
			Positive	17	6408.451	2685.3947	2759.760	12368.521
		Second	Negative	113	3473.434	1601.9193	0.000	7949.469
			Positive	17	3919.921	2004.2938	1001.094	7501.417
		Third	Positive	5	4163.334	998.3873	2576.711	5083.393
	AUC_{0-t} (ng.h/mL)	First	Negative	113	5879402.399	2479633.6504	1021664.397	14224356.406
			Positive	17	5769869.327	2514145.9982	2439773.103	12154246.690
		Second	Negative	112	3864430.126	2284659.4237	216899.711	11662029.876
			Positive	17	4372428.803	2509770.2744	359309.655	9465768.018
		Third	Positive	5	5441422.014	1979320.8993	2464924.765	7858767.321
	$AUC_{0-\infty}$ (ng.h/mL)	First	Negative	113	6048585.195	2765252.9537	1041259.174	18921577.752
			Positive	17	5818546.486	2522217.2621	2478775.764	12235824.340
		Second	Negative	36	6357977.145	2380576.9301	2359605.371	11684217.331
			Positive	8	6649229.574	1664810.5545	3668464.909	9607181.591
		Third	Positive	4	6333671.315	1279271.7503	5278478.063	8054788.636

Abbreviations: $AUC_{0-\infty}$ = area under the concentration versus time curve from time zero to infinity; AUC_{0-t} = area under the concentration versus time curve from time zero to the last measurable concentration; C_{max} = maximum measured concentration; R = reference; T = test.

2.6.2.2. Pharmacodynamics

Mechanism of action

Denosumab is a genetically engineered fully human monoclonal antibody (IgG2) produced in a mammalian cell line (Chinese hamster ovary cells). It targets and binds with high affinity and specificity to RANKL, a transmembrane protein that plays a significant role in osteoclast mediated bone resorption. By binding to RANKL, denosumab prevents activation of RANKL's receptor, RANK. Denosumab thus inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and cancer-induced bone destruction.

Primary and Secondary pharmacology

Study 0568-19

The PD set included all subjects who complete the study with available concentration (% serum CTX and PINP reduction) and for whom the PD profile can be adequately characterised.

PD parameters were calculated by measuring serum CTX and P1NP and using a non-compartmental model and are defined in Table 20.

Table 15 Non-compartmental pharmacodynamic parameters

E_{max} (%)	Maximum % reduction from baseline
$AUEC_{0-t}$ (h.%)	Area under the % reduction from baseline versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method
T_{max} (h)	Time of the maximum % reduction from baseline.

Actual time-points were used for the calculation of the PD parameters. All concentration values below the lower limit of quantification were set to zero for the PD calculations. Pharmacodynamic effect for serum CTX and serum P1NP were assessed as % reduction from baseline.

Of the 234 subjects enrolled and dosed, 220 subjects were included in the PD set. Intas Denosumab (N=73), US-Xgeva (N=74), EU-Xgeva (N = 73).

The statistical comparison of CTX (for % reduction from baseline serum) PD parameters for Intas Denosumab vs. EU-Xgeva is summarised in table below.

Table 16. Summary of statistical comparisons of CTX (for % reduction from baseline serum) parameters [Intas Denosumab vs. EU-Xgeva] (N = 146)

Parameters	Geometric Least Squares Means			90% Confidence Interval	95% Confidence Interval	Inter Subject CV (%)	Power (%)
	Intas Denosumab (T) (N=73)	Xgeva (US) (R1) (N=74)	Ratio (T/R1) %				
lnE_{max}	92.408	95.442	96.8	95.10 - 98.57	94.77-98.92	6.2	100.0
$lnAUEC_{0-t}$	462716.370	464618.250	99.6	96.43 - 102.85	95.83-103.50	11.7	100.0

Source: Table 14.2.2.1.

Abbreviations: $AUEC_{0-t}$ = Area under the % reduction from baseline versus time curve from time zero to the last measurable concentration; E_{max} = Maximum % reduction from baseline .^N = 71

Note: Although ln transformation was used in the statistical analysis, the results shown in the table above have been back transformed to the original scale.

Figure 1 shows the mean CTX (for % reduction from baseline serum)-time profile following Intas Denosumab, Xgeva (US), or Xgeva (EU) on linear scale.

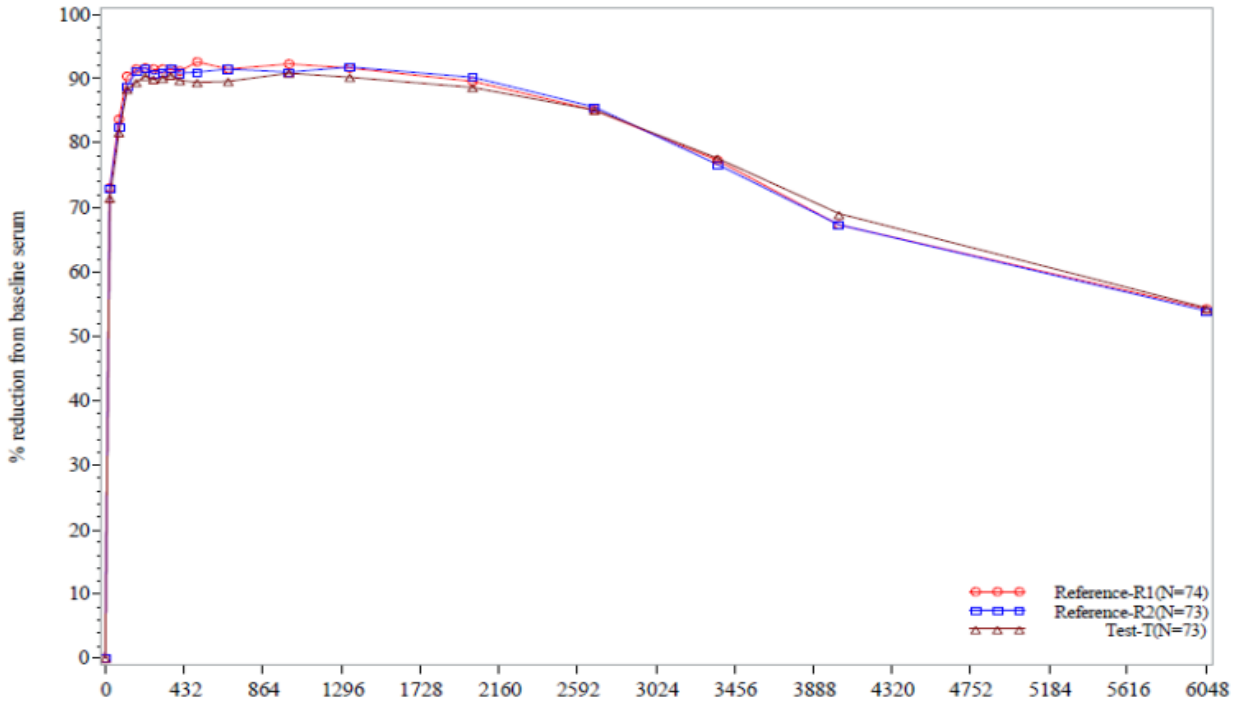

Figure 1. Mean CTX (for % reduction from baseline serum)-time profile following Intas Denosumab, Xgeva (US), or Xgeva (EU) on linear scale

Table 17. Summary of CTX (for % reduction from baseline serum)

Parameter	Statistics	Intas Denosumab	Xgeva (US)	Xgeva (EU)
E_{max} (%)	N	73	74	73
	Mean	93.277	95.367	94.241
	SD	7.164	5.510	6.376
	CV%	7.7	5.8	6.8
	Min	77.241	78.161	78.571
	Median	92.952	100.000	95.203
	Max	100.000	100.000	100.000
$AUEC_{0-t}$ (h.%)	N	73	74	71
	Mean	465097.040	466671.915	463693.287
	SD	51359.015	48789.203	53351.404
	CV%	11.0	10.5	11.5
	Min	309919.321	328533.592	311520.361
	Median	466727.174	466759.571	463812.835
	Max	558442.357	568697.538	551563.436
T_{max} (h)	N	73	74	73
	Mean	533.492	606.781	502.577
	SD	649.014	672.070	538.205
	CV%	121.7	110.8	107.1
	Min	72.000	72.000	72.000
	Median	312.483	288.325	264.000
	Max	3360.017	2688.250	2688.333

Table 18. Summary of statistical comparisons of P1NP (for % reduction from baseline serum) parameters [Intas denosumab vs. Xgeva (EU)] (N=146)

Parameters	Geometric Least Squares Means			90% Confidence Interval	95% Confidence Interval	Inter Subject CV (%)	Power (%)
	Intas Denosumab (T) (N=73)	Xgeva (EU) (R2) (N=73)	Ratio (T/R2) %				
lnE_{max}	74.60	74.78	99.8	97.12 - 102.46	96.62 - 103.00	9.6	100.0
$lnAUEC_{0-t}$	330191.71	317851.87^	103.9	98.52 - 109.54	97.51 - 110.67	19.1	100.0

Source: Table 14.2.3.3.

^N=71

Note: Subject Nos. 1163 and 1183 had three consecutive missing sample in late phase. Hence, same was not considered for the computation of descriptive statistics for pharmacodynamic parameters $AUEC_{0-t}$.

Regarding Ln transformation, the issue is similar to CTX. However, as P1NP was only a supportive PD parameter, no additional analyses using geometric mean ratios Intas Denosumab/ EU-Xgeva (no ln transformation) were requested for P1NP parameter.

Figure 2 shows the mean P1NP (for % reduction from baseline serum)-time profiles following administration of Intas Denosumab, Xgeva (US), or Xgeva (EU) (linear scale)

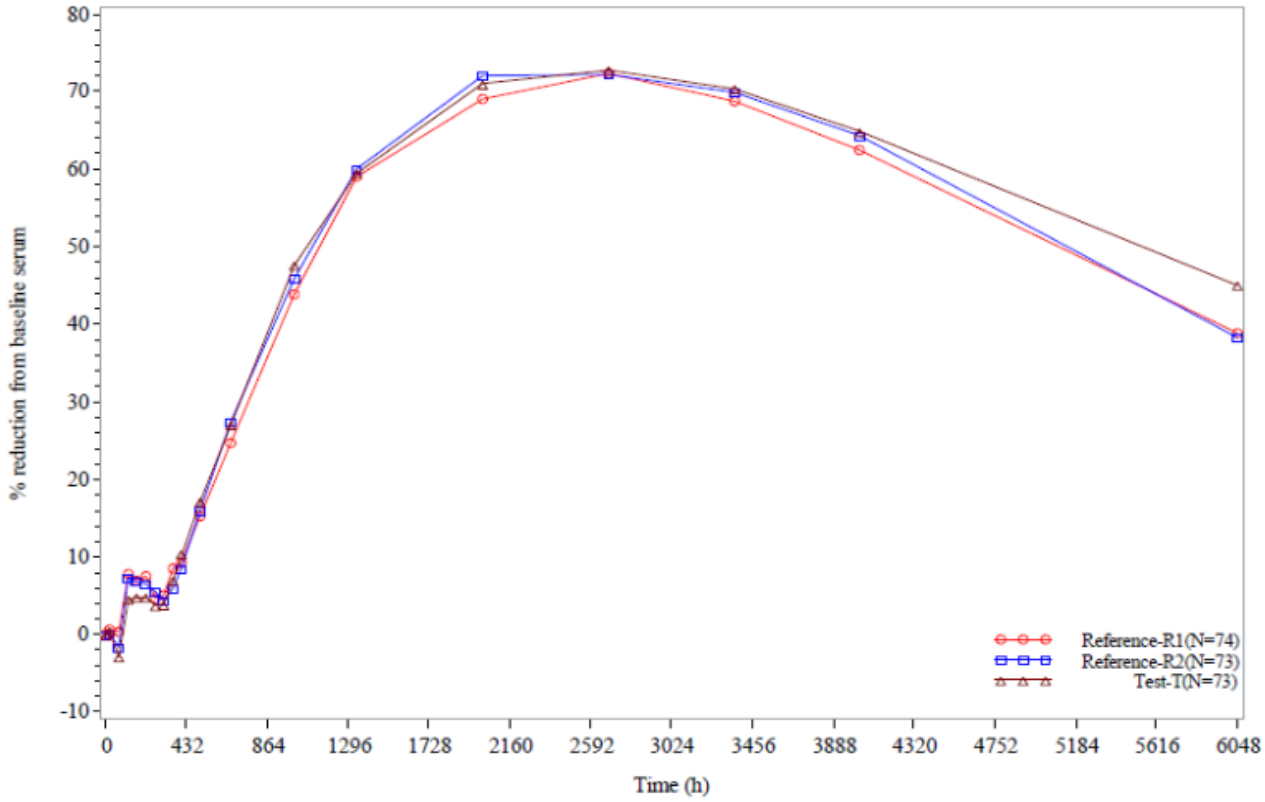

Figure 2. Mean P1NP (for % reduction from baseline serum)-time profiles following administration of Intas Denosumab, Xgeva (US), or Xgeva (EU) (linear scale)

Table 19. Summary of P1NP (for % reduction from baseline serum)

Parameter	Statistics	Intas Denosumab	Xgeva (US)	Xgeva (EU)
E_{max} (%)	N	73	74	73
	Mean	74.78	74.91	74.95
	SD	7.107	8.181	7.030
	CV%	9.5	10.9	9.4
	Min	53.38	53.44	50.83
	Median	75.19	76.65	75.45
	Max	85.80	86.97	89.29
$AUEC_{0-t}$ (h.%)	N	73	74	71
	Mean	333621.18	318536.03	324002.23
	SD	48133.005	66574.350	59678.151
	CV%	14.4	20.9	18.4
	Min	202057.81	131164.52	100160.62
	Median	340013.28	337284.67	336337.03
	Max	437176.49	408100.43	437937.54
T_{max} (h)	N	73	74	73
	Mean	2617.489	2779.355	2716.487
	SD	643.4272	622.5645	586.6385
	CV%	24.6	22.4	21.6
	Min	504.150	1344.133	2016.000
	Median	2688.233	2688.425	2688.300
	Max	4033.317	4034.017	4033.100

Study 0774-19

Of the 296 enrolled and dosed patients, 258 patients were included in the PD set. 3 patients had major protocol deviation affecting pharmacodynamic assessment for first dose only. Hence, these patients are included for the statistical analysis of second dose, accordingly total count in PD analysis for second dose are 261 patients. PD data from the excluded patients are listed in the tables but not included in the main summary statistics or statistical comparisons.

Study 0774-19 used the same PD parameters and methodology as study 0568-19.

Table 20. Pharmacodynamic parameters

Pharmacodynamic Parameters:		
E_{max}	:	Maximum % reduction from baseline.
$AUEC_{0-t}$	:	Area under the % reduction from baseline versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method
T_{max}	:	Time of the maximum % reduction from baseline.

Summary statistics for serum CTX (for % reduction from baseline) after first dose (i.e. geometric least squares means, ratio, 90% confidence interval, 95% confidence interval, inter patients CV and power) of Intas Denosumab vs. EU-Prolia are summarised in the table below.

Table 21. Summary statistics of pharmacodynamic parameters for serum CTX (for % reduction from baseline) after first dose (N=258)

Parameters	Geometric Least Squares Means			90% Confidence Interval	95% Confidence Interval	Inter Patients CV (%)	Power (%)
	Denosumab (T) (N=131)	Prolia (R) (N=127)	Ratio (T/R)%				
lnE_{max}	97.032	95.936	101.1	99.55 - 102.76	99.24 - 103.08	7.7	100.0
$lnAUEC_{0-t}$	336815.658^	328601.779	102.5	96.72 - 108.63	95.64 - 109.85	28.4	100.0

(Refer Table No. 14.2.2.2), ^N=129

Note: Although ln transformation was used in the statistical analysis, the results shown in the table above have been back transformed to the original scale.

There were no negative values for Emax and one negative value for $AUEC_{0-t}$. Since log-transformation is not possible for negative values, the patient with the negative $AUEC_{0-t}$ value was excluded from the analysis.

Summary statistics of pharmacodynamic parameters for serum P1NP (for % reduction from baseline) after first dose (i.e., geometric least squares means, ratio, 90% confidence interval, 95% confidence interval, inter patients CV and power) of Intas Denosumab vs. EU-Prolia are summarised in the table below.

Table 22. Summary statistics of pharmacodynamic parameters for serum P1NP (for % reduction from baseline) after first dose (N = 258)

Parameters	Geometric Least Squares Means			90% Confidence Interval	95% Confidence Interval	Inter Patients CV (%)	Power (%)
	Denosumab (T) (N=131)	Prolia (R) (N=127)	Ratio (T/R)%				
lnE_{max}	76.59	75.99	100.8	96.28 -105.50	95.44 - 106.43	22.4	100.0
$lnAUEC_{0-t}$	209034.01^	208048.31	100.5	93.06 - 108.47	91.70 -110.09	38.1	99.9

(Refer Table No. 14.2.3.1)

Regarding Ln transformation, the issue is similar to CTX. However, as P1NP was only a supportive PD parameter, no additional analyses using geometric mean ratios Intas Denosumab/ EU-Xgeva (no ln transformation) were requested for P1NP parameter.

In study 0774-19, impact of immune response on the primary pharmacokinetic and pharmacodynamic parameters were assessed by comparing the descriptive statistics of parameters between pool of patients having positive and negative immune response for each dose of each treatment. Patients having at least one positive confirmatory response over entire duration of the study is considered as positive immune (IM) response. Patients with no confirmatory positive response during entire study are considered as negative immune (IM) response.

Data on the comparison of primary pharmacodynamic parameters of serum CTx (for % reduction from baseline) are presented in Table 28.

Table 23. Comparison of primary pharmacodynamic parameters of serum CTx (for % reduction from baseline)

Treat-ment	PD Parameter	Dose	IM Response	N	Mean	SD	Minimum	Maximum
T	E_{max} (%)	First	Negative	114	98.201	5.4146	71.678	100.000
			Positive	17	96.973	7.4022	73.106	100.000
		Second	Negative	114	92.692	10.8691	57.979	100.000
			Positive	17	91.264	16.1278	41.975	100.000
		Third	Positive	12	91.825	13.5707	59.686	100.000
	$AUEC_{0-t}$ (h.%)	First	Negative	114	342182.869	65270.1026	166291.851	436851.860
			Positive	15	321025.160	74754.6305	159427.449	400269.840
		Second	Negative	114	293685.697	75489.6235	69628.001	398477.136
			Positive	17	260305.904	84332.3162	80968.573	362900.573
		Third	Positive	12	263061.927	76405.4346	134050.210	373383.979
R	E_{max} (%)	First	Negative	110	97.231	7.6625	53.892	100.000
			Positive	17	95.942	7.8574	77.701	100.000
		Second	Negative	113	87.309	25.1960	-131.532	100.000
			Positive	17	93.270	11.4380	59.659	100.000
		Third	Positive	5	80.343	18.5315	59.727	100.000
	$AUEC_{0-t}$ (h.%)	First	Negative	110	331633.986	81264.0306	-164362.233	433930.524
			Positive	17	340703.916	54980.5782	214913.103	411214.304
		Second	Negative	112	278536.708	86808.1104	-200550.083	394473.786
			Positive	17	283586.474	70746.1915	117351.819	372474.345
		Third	Positive	5	268940.404	102224.6837	175618.176	398925.731

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetic data were obtained from study 0568-19 in healthy male subjects and study 0774-19 in postmenopausal women with osteoporosis.

Study 0568-19

For the purpose of investigating the pharmacokinetics properties of Intas Denosumab in comparison to the reference products Xgeva (US) and Xgeva (EU), the study design of the Phase I study is acceptable.

A single dose, parallel-group design is acceptable for denosumab, that has a long mean half-life of 28 days (range 14 to 55 days).

The chosen dose for the study in healthy volunteers was 35 mg and is therefore lower than the recommended dose from the Xgeva SmPC. This dose is however in accordance with the scientific advice given by the CHMP 2019. The dose of 35 mg is considered sensitive to detect differences regarding PK among the treatment arms and is therefore considered appropriate for this study. Comparability of the non-specific elimination pathway may not be adequately captured in the PK study using a subtherapeutic dose. Nonetheless, this has been adequately characterised in study 0774-19 conducted with the 60 mg dose in the postmenopausal osteoporosis (PMO) patient population.

The use of healthy volunteers is agreed and is in line with the Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). Supportive PK data in patients are also available in line with guideline recommendation.

For AUC0-inf, AUC0-t and Cmax the 90% confidence interval for the ratio of the test and reference products fell within the conventional bioequivalence acceptance range of 80.00-125.00% when comparing Intas Denosumab to the reference product from EU as well as from US, and also when comparing the EU versus the US reference products. Thus, the 90% confidence interval (CI) for the ratios of the geometric means of the primary (AUC0-inf and Cmax) met the predefined acceptance criteria (80.00% to 125.00%) for PK equivalence for all 3 pairwise comparisons.

PK similarity is considered to be adequately demonstrated for Intas Denosumab and the reference products (Xgeva (US) and Xgeva (EU)) following administration of a single 35 mg SC dose to healthy subjects.

Study 0774-19

For $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional bioequivalence acceptance range of 80.00-125.00%.

Immunogenicity

Study 0568-19

The incidence of ADAs was comparable between the three treatment groups (Intas Denosumab (biosimilar): 12.82%, EU-Xgeva: 8.97% and US-Xgeva: 17.95%). The majority of subjects were found negative for ADA at all timepoints. Where subjects found positive for ADA, the majority of positive results exhibited low titre values. No subject had a positive result for NAb.

Study 0774-19

In the safety set, the incidence of subjects with ADAs was reported as 10.51% and 7.61% in Intas Denosumab (biosimilar) and EU-Prolia treatment group, respectively. Among the confirmed positive patients, 9 patients (5 in Intas Denosumab (biosimilar) and 4 in EU-Prolia) were found to be NAb positive during the treatment main phase. The mean and median titres were comparable between both groups in the main phase. From the 123 patients in transition-extension phase, only one patient in the Intas Denosumab (biosimilar) group was found NAb positive.

In accordance with the above data, the final wording in section 5.1 on Immunogenicity reflects that antibodies to denosumab may develop during denosumab treatment without referring to a specific incidence.

Impact of ADA/NAb on PK

Study 0568-19

The PK parameters C_{max}, AUC_{0-t} and AUC_{inf} in the ADA negative subgroup were comparable between the Intas Denosumab (biosimilar), US-Xgeva and EU-Xgeva treatment groups, and these results were also consistent with the results on the whole PK population. The results indicate that there is no impact of ADAs on the PK of Intas Denosumab (biosimilar) or EU-Xgeva.

Study 0774-19

Based on the comparison of descriptive statistics of PK parameters of denosumab on treatment group level, there seems to be no differences in PK behaviour of denosumab in ADA-positive and ADA-negative patients, at the respective doses, for both the treatment groups.

In accordance with the above data, the final wording in section 5.1 on Immunogenicity includes the following statement:
"Anti-denosumab antibodies may develop during denosumab treatment. No apparent correlation of antibody development with pharmacokinetics, clinical response or adverse event has been observed.".

Pharmacodynamics

PD endpoint CTX is considered co-primary in the evaluation for denosumab biosimilars in the EU.

Tmax, Emax and AUEC0-t% of bone biomarker serum CTX were secondary efficacy evaluation parameters of the phase I study and Co-primary parameters in phase III study.

In the phase I study in heathy volunteers, the 95% CIs of the geometric LSM ratios, derived from the analysis on the ln transformed serum CTX Emax (99% to 103%) and serum CTX AUEC0-t (96% to 104%) of Intas Denosumab relative to US-Xgeva and EU-Xgeva were well within the acceptance range of 80.00% to 125.00%.

Similarly, in the phase III study in osteoporosis patients, the 95% CIs of the geometric LSM ratios, derived from the analysis on the ln transformed serum CTX Emax (95% to 99%) and serum CTX AUEC0-t (96% to 104%) of Intas Denosumab relative to US-Xgeva and EU-Xgeva were well within the acceptance range of 80.00% to 125.00%.

In the phase I study, 95% Confidence Interval for the PD P1NP parameters lnEmax and lnAUEC0-t seem to be well within the acceptance range of 80.00 - 125.00% that is commonly used to conclude PK bioequivalence. Same conclusions could be made in the phase III study. Regarding Ln transformation, P1NP was only a supportive PD parameter, no additional analyses using geometric mean ratios Intas Denosumab/ EU-Xgeva (no ln transformation) were thus requested for P1NP parameter.

Impact of immune response on the primary pharmacodynamic parameters was not found in the phase I study report. Impact on PK parameters has been described. This issue is, however, not further pursued as data is presented from the phase III study. Based on comparison of descriptive statistics of pharmacodynamic parameters of serum CTx (for % reduction from baseline), there seems to be no difference in pharmacodynamic behaviour of serum CTx (for % reduction from baseline) in patients with positive and negative immune responses at respective doses for both the treatment arm.

Based on comparison of descriptive statistics of pharmacodynamic parameters of serum CTx (for % reduction from baseline), there seems to be no difference in pharmacodynamic behaviour of serum CTx (for % reduction from baseline) in patients with positive and negative immune responses at respective doses for both the treatment arm.

Similar comparison of descriptive statistics was presented for P1NP parameter (for % reduction from baseline), the data was assessed (although not presented in this report) and no major differences in were observed.

During the procedure the CHMP noted the GCP non-compliance, identified in four sites (see section 2.3), as described in the clinical trial report. However the CHMP noted that the concerned sites were not included in the PD analysis set for co-primary endpoint CTX or P1NP in phase III study (0774-19). Therefore, new analyses were not required and the PD data were considered acceptable by the CHMP.

2.6.4. Conclusions on clinical pharmacology

Overall, comparable PK and PD of the test and reference products could be demonstrated in the two clinical studies, which support the biosimilarity of Osvyrti to the reference products.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

No dose response studies were performed and this is considered acceptable by the CHMP.

2.6.5.2. Main study(ies)

Study 0774-19

Study 0774-19 was a phase III, randomised, double-blind, active-controlled, parallel arm, multicentre study comparing pharmacokinetics, pharmacodynamics, and immunogenicity of denosumab of Intas Pharmaceutical Limited(60mg/mL) with Prolia in Postmenopausal Women with Osteoporosis.

An overview of the study design is presented in the figure below.

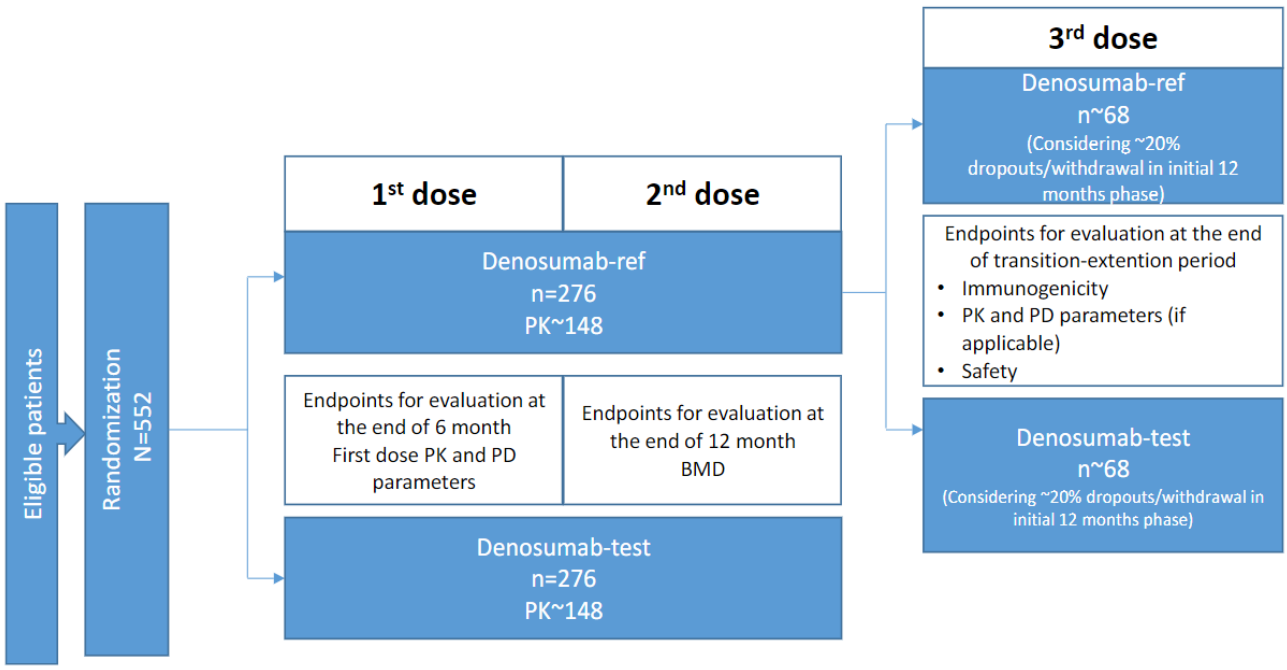

Figure 1. Study design

Methods

- **Study Participants**

Main inclusion criteria were as follows:

- 55 to 90 years of age, medically/clinically stable, body weight between 50 kg and 90 kg at screening.

- Absolute bone mineral density T-score is ≤ -2.5 and ≥ -4.0 at the lumbar spine as measured by DXA (dual-energy x-ray absorptiometry), confirmed by the independent central imaging team.

- At least two vertebrae in the L1-L4 region and at least one hip joint are evaluable by DXA, confirmed by the independent central imaging team.

- Postmenopausal ambulatory female and who are not considered to be of child-bearing potential

Main exclusion criteria were as follows:

- clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances ; known allergies, hypersensitivity, or intolerance to denosumab or its excipients (refer to the IB).

- History of any prior use of denosumab.

- Metabolic or bone disease (except osteoporosis) that may interfere with the interpretation of the results, such as Paget's disease, osteomalacia, osteogenesis imperfecta, osteopetrosis, rheumatoid arthritis, ankylosing spondylitis or any other joint disease limiting mobility, Cushing's disease, hyperprolactinemia, malabsorption syndrome.

- Latex or dry natural rubber allergy.

- Contraindications to the use of denosumab or Vitamin D and Calcium as per IB/local prescribing information at screening and/or baseline.

- Any of the following oral/dental conditions: prior history or current evidence of osteomyelitis or osteonecrosis of the jaw ; active dental or jaw condition which requires oral surgery, planned invasive dental procedure expected during study period ; non-healed dental or oral surgery ; poor oral hygiene ; ill-fitting denture.

-Hyper- or hypocalcaemia, defined as albumin-adjusted serum calcium outside the normal range at screening. Serum calcium levels may be retested once in case of an elevated/low serum calcium level as assessed by the clinical laboratory. Final decision to include the patient based on the risk of hypocalcaemia to be taken by the Investigator.

- History of frequent occurrence of hypocalcaemia, history of severe hypocalcaemia or presence of diseases that can precipitate hypocalcaemia frequently and severe renal impairment.

-Uncontrolled hyper- or hypoparathyroidism and history of hypoparathyroidism, as per protocol definitions

- 25 (OH) Vitamin D lower than 20 ng/mL

- History of external beam or implant radiation therapy involving the skeleton.

- History and /or presence of 1 severe fracture or 2 moderate vertebral fractures.

- Patients with bone metastases or a history of malignancies affecting bones.

- Smokers or who have smoked within last 6 months prior to start of the study.

- major surgery, (e.g. requiring general anaesthesia) within 12 weeks before screening, or will not

have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study.

- Hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening.

- human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening.

- Medical history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-V) criteria within 1 year before Screening.

- Lymphoma, leukaemia, or any malignancy (current or suspected) within the past 5 years as per protocol definitions

- QTc interval >470 msec or QT interval >480 msec in participants with bundle branch block.

- Administration of bisphosphonate as per protocol definitions

- Teriparatide or any PTH analogues treatment received within 12 months prior to randomisation.

- Systemic oral or transdermal oestrogen, SERMs, or calcitonin treatment of more than 1 month of cumulative use within 6 months prior to randomisation.

- Androgen deprivation or hormonal ablation therapy of more than 1 month of cumulative use within 6 months prior to randomisation.

- Tibolone or cinacalcet treatment received within 3 months prior to randomisation.

- Systemic glucocorticoids: ≥ 5 mg prednisone equivalent per day for more than 10 days within 3 months prior to randomisation.

- Abnormal laboratory values as per protocol definitions

- Taken any prohibited therapies, Concomitant Therapy before the planned first dose of study IMP.

- Received any investigational IMP 30 days or 5 half-lives (whichever is longer) before the signing the consent or is currently enrolled in an investigational study.

- Unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis. This includes but is not limited to hepatitis virus infections, drug- or alcohol-related liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, or any other liver disease considered clinically significant by the investigator.

- Any other clinical/social/ psychiatric condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

- **Treatments**

The Test Product-T (denosumab 60 mg/mL) or Reference Product-R (Prolia® 60 mg/mL) was administered twice during the treatment (main) phase of this study as subcutaneous injection on Visit-2 (Day 1 ± 3) and on Visit-9 (Day 181 ± 14) to the patients in treatment period as per randomisation schedule based on an algorithm implemented in the interactive web response system (IWRS).

Further, Test Product-T or Reference Product-R was administered as subcutaneous injection on Visit-16 (Any day within 21 days after EOS visit ± 5)(in transition-extension period) to the patients who (a)

were randomised in reference arm AND (b) had completed PK assessments during 12-month treatment period.

All other protocol-required drugs (i.e., vitamin D and calcium supplements), that were commercially available, were provided by the Sponsor. From screening to end of study, participants received daily calcium and vitamin D supplementation that at a minimum were in the range of at least 1000 mg calcium and at least 400 IU vitamin D.

- **Objectives**

Primary

- To compare the pharmacokinetic parameters of denosumab and denosumab-ref in postmenopausal women with osteoporosis.

-To compare the pharmacodynamic c effect of treatment with denosumab and denosumab-ref on bone mineral density (BMD) and bone resorption marker in postmenopausal women with osteoporosis.

Secondary

- To compare the efficacy of treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis.

- To compare the pharmacodynamic effects of the treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis.

- To compare the immunogenicity of denosumab and denosumab-ref in postmenopausal women with osteoporosis.

- To compare the safety of treatment with denosumab and denosumab-ref in postmenopausal women with osteoporosis.

- To evaluate the safety and immunogenicity of denosumab and denosumab-ref after single transition from denosumab-ref to denosumab and denosumab-ref in postmenopausal women with osteoporosis.

Outcomes/endpoints

Primary

- Pharmacokinetics: Cmax , AUC0-t , and AUC0-∞ after first dose of denosumab and denosumab-reference(s).

- Mean percentage change in BMD at lumbar spine from baseline to 12 months between Intas Denosumab and EU-Prolia.

- Pharmacodynamics: Emax and AUEC0-t of % reduction from baseline serum C-terminal telopeptide (CTX) after first dose of denosumab and denosumab-references.

Secondary

- Mean percentage change in bone mineral density (BMD) of lumbar spine from baseline to 06 months between denosumab and denosumab- reference(s).

- Mean percentage change in BMD of femoral neck and total hip from baseline to 06 and 12 months between denosumab and denosumab- reference(s).

- Pharmacodynamics: Tmax of % reduction from baseline serum C-terminal telopeptide (CTX) after first dose of denosumab and denosumab- reference(s).

- Pharmacodynamics: Emax, AUEC0-t , Tmax of % reduction from baseline serum N-terminal propeptide of type 1 collagen (P1NP) after first dose of denosumab and denosumab- reference(s).

- Mean percentage reduction in serum N-terminal propeptide of type 1 collagen (P1NP) concentrations from baseline to 06 and 12 months between denosumab and denosumab- reference(s).

- Mean percentage reduction in CTX serum concentrations from baseline to 06 and 12 months between denosumab and denosumab- reference(s).

- Incidence of clinical fracture between denosumab and denosumab- reference(s). over 12 months.

- Incidence of anti-denosumab antibody in denosumab and denosumab- reference(s). arm over 12 months.

- Monitoring of adverse events and lab parameters in denosumab and denosumab- reference(s) arm.

- Incidence of anti-denosumab antibody in denosumab and denosumab-ref arms after single transition from denosumab- reference(s).

- Assessment for difference in PK or PD in patients who are found to be immunogenic.

- Monitoring of adverse events and lab parameters in denosumab and denosumab-ref arms after single transition from denosumab- reference(s).

- **Sample size**

Lumbar spine BMD

An equivalence test of means using two one-sided equal-variance t-tests with sample sizes of 220 completers in each treatment group achieves 90% power at a 2.5% significance level when the equivalence limits are -1.45 and 1.45, the actual difference between the means is 0.0, and the standard deviation assumed as 4.20 for each group. With 1:1 treatment allocation, in total 440 completers (220 in each treatment group) are required to meet these conditions. Considering ~20% dropouts/withdrawals, 552 patients (276 patients per arm) were to be enrolled for BMD assessment.

Serum CTX

Based on the literature, back calculated inter subject CV was found to be ~13% for AUEC0-t in healthy volunteers for reduction from baseline for serum CTX. Hence, the sample size has been calculated considering the same using SAS with following estimates : T/R ratio = 95.0-105.0%; CV% = 13% (AUEC0-t); alpha = 2.5%; Power = 90% and 95% CI = 80.00-125.00%. Based on above estimates, 26 completers (13 completers per arm) will be required. Considering ~20% dropouts/withdrawals and 1:1 treatment allocation ratio, 34 patients (17 patients per arm) was required.

- **Randomisation and Blinding (masking)**

At the randomisation visit after ensuring that a patient meets all eligibility criteria, participants were assigned to 1 of 2 IMP groups (Intas Denosumab or Prolia) based on an algorithm implemented in the interactive web response system (IWRS) before the study.

Dynamic central randomisation was implemented in conducting this study. Dynamic central randomisation minimises the imbalance in the distribution of the number of participants across IMP groups within the levels of each individual stratification factor: age (≥65, <65) and prior osteoporosis

treatment status (present, absent). Based on the algorithm, the IWRS was assigned a unique IMP code, which dictated the IMP assignment and matching study IMP kit for the participant.

After completion of 1-year study participants (who were randomised for Reference arm and involved in PK analysis) were re-randomised on either Test or Reference arm using IWRS for further six-month immunogenicity and safety evaluation.

Central randomisation schedule was generated by the vendor who was not involved in the conduct of the study.

Blinding

The study was a double-blind study.

The blinding was broken when the trial database was declared clean and locked, which was on 27 November 2023.

- **Statistical methods**

The study analysis sets were to be defined as follows:

Intent-To-Treat (ITT) set: The ITT set was defined as all randomised patients who received at least one dose of study medication.

Modified intent-to-treat (mITT) set: The mITT set was defined as all randomised patients who received at least one dose of study medication and had undergone at least one post-dose efficacy evaluation.

Per protocol (PP) set: The PP set was defined as all randomised patients who completed the study with no major protocol deviations.

Pharmacodynamic (PD) set: The PD set was to be included for all patients for whom concentration data (% serum CTX and PINP reduction) was available and for whom the PD profile (for first dose only) can be adequately characterised (specific criteria are listed below). Patients who completed the study with no major protocol deviations which influence the PD, were to be included in the PD set.

Criteria for exclusion of the pharmacodynamic parameters are as below:

- Three consecutive missing or non-reportable samples before actual Tmax may significantly influence all pharmacodynamic parameter estimations. Hence, all pharmacodynamic parameters were to be excluded.

- Three consecutive missing or non-reportable samples in terminal phase (i.e. after Tmax) may significantly influence the AUEC0-t. Hence, AUEC0-t were to be excluded.

Safety set: The safety set was defined as all randomised patients who received at least one dose of study medication.

The confidence level for efficacy was 95%. The study conclusion was to be based on the primary endpoint (PK & BMD/PD). Hence, multiplicity adjustment was not applicable. No interim analysis was conducted.

The original statistical analysis plan is dated 28 November 2022, which was during the study period (10 November 2021 [first patient's first visit] to 03 November 2023 [last patient's last visit]). An

amendment of the immunogenicity analysis was issued on 08 December 2023 (after unblinding on 27 November 2023).

Efficacy analyses

All primary and secondary efficacy analysis was to be done on ITT, mITT and PP set.

The primary efficacy analysis was an analysis of covariance (ANCOVA) model in the PP set. This model estimated the difference in mean percent change in lumbar spine BMD between the treatment groups, with baseline BMD as a covariate. Therapeutic equivalence was concluded if the 95% confidence interval fell within ±1.45% (this equivalence margin is discussed in *Sample size determination* below). Similar models were used for the secondary BMD endpoints.

The equivalence margin of ±1.45% was selected based on the results of a pooled analysis of three denosumab trials (Bone 2008, McClung 2006, Cummings 2009). According to this analysis, a margin of ±1.45% would preserve 70% of the treatment effect (0.3*4.83%), as estimated by the lower bound of the 95% confidence interval for the pooled effect.

The mITT set was analysed using two different methods: an ANCOVA model, with missing data imputed using last observation carried forward (LOCF) and a Mixed Model for Repeated Measures (MMRM) model, in which missing data were assumed to be Missing At Random (MAR).

The ITT set was analysed in a predefined sensitivity analysis, originally proposed by FDA . In this ANCOVA-based analysis, missing BMD values were imputed as 'baseline value - 0.73' for test and 'baseline value + 0.73' for reference product, ± 0.73 being half of the predefined equivalence limit. Additionally, imputation with the reverse adjustment, i.e., 'baseline value + 0.73' for test and 'baseline value - 0.73' for reference product was performed.

A tipping point analysis was to be provided for participants in the mITT set who missed efficacy data for a particular visit. Missing value was to be imputed with median of available values of remaining patients at that particular visit.

Results from the BMD were presented in subgroups for age <65 year and >=65 year as well as for patients with prior osteoporosis therapy yes/no.

Pharmacodynamic analyses

The ln-transformed pharmacodynamic parameters Emax and AUEC0-t of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose were to be subjected to Analysis of Variance (ANOVA).

ANOVA model was to be included the term Centre and Formulation as fixed effect. Each ANOVA were

to include calculation of LSMs, the difference between adjusted formulation means and the standard error associated with this difference. This statistical analysis was to be performed using PROC GLM of SAS procedure.

An F-test were to be performed to determine the statistical significance of the effects involved in the model at a significance level of 5 % (alpha = 0.05).

In case there were a centre with less than five patients, then that data was to be pooled with the subsequent centre.

90% and 95% confidence intervals were to be calculated and reported for ln-transformed pharmacodynamic parameters Emax and AUEC0-t of % reduction from baseline serum Cterminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose.

Ratio of geometric least square means of test and reference formulations were to be computed and reported for ln-transformed pharmacodynamic parameters Emax and AUEC0-t of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose.

Inter-patient variability was to be computed and reported for ln-transformed pharmacodynamic parameters Emax and AUEC0-t of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) and % reduction from baseline Serum N-terminal propeptide of type 1 collagen (P1NP) after first dose.

Any missing samples (M) or not reportable concentration values (NR) were not to be included in the pharmacodynamic analysis.

Bioequivalence of Test Product-T vs. Reference Product-R was concluded, if the 95% confidence interval for the ratio of geometric least squares means fell within the acceptance range of 80.00-125.00% for ln-transformed pharmacodynamic parameter Emax and AUEC0-t of % reduction from baseline Serum C-terminal telopeptide (Serum CTX) after first dose.

Data quality assurance

According to the applicant, monitoring procedures developed by Lambda was followed to comply with GCP guidelines and to ensure acceptability of the study data for international registration purposes. Quality Assurance assessed compliance to the study requirements as per Good Clinical Practices, principles of Good Laboratory practices, Internal Standard Operating Procedures, Protocol, and applicable regulatory requirement.

Quality Assurance assessed compliance to the study requirements as per Good Clinical Practices, principles of Good Laboratory practices, Internal Standard Operating Procedures, Protocol, and applicable regulatory requirements. As a part of quality assurance audit programme, various activities involved during conduct of the study and documents /data /CRFs generated (Clinical, Statistical,

Clinical Data Management phases and final report writing) were audited In-process / retrospectively to ensure compliance to the study requirements. Quality Assurance statement of the audits conducted assuring compliance to the above requirements was issued by Head-QA.

Results

- **Participant flow**

A total of 552 patients [Test Arm = 276 patients; Reference Arm = 276 patients] were randomised and dosed treatment period in the study.

Out of 552 enrolled patients, a total of464 patients [Test Arm = 236 patients; Reference Arm = 228 patients] completed the main phase (12-months of treatment duration) of the study.

Table 24. Disposition of patients.

Sr. No.	**Reason**	**Number of Patients**
1.	Death	1
2.	Lost to follow-up	7
3.	Physician decision	1
4.	Protocol violation	2
5.	Withdrawal by subject	50
6.	*Site was terminated due to non-compliance and the subjects were withdrawn from the study.	27
Total		**88**
*Due to non-compliance of study eligibility criteria and falsified submission of DXA Scans to Lambda's DiaSoft-D platform by Site No. 121, 122, 123 and 124; all ongoing study patients were withdrawn as per sponsor discretion and further recruitment at these sites were stopped with immediate effect. Refer Appendix No. 16.3.2 for further details.		

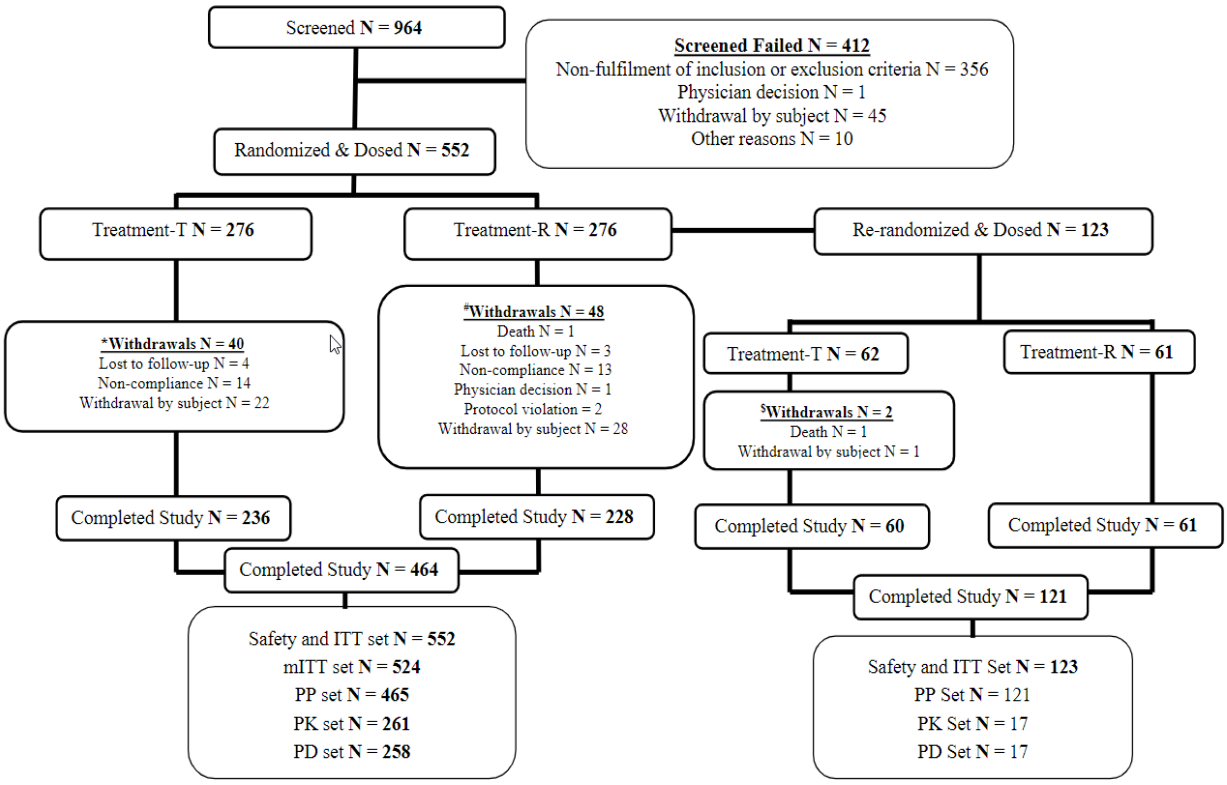

Figure 4. Participant flow

A total of 123 patients [Test Arm = 62 patients; Reference Arm = 61 patients] were re- randomised and dosed in Transition-extension Period of the study.

Out of 123 enrolled patients, a total of 121 patients [Test Arm = 62 patients; Reference Arm = 61 patients] completed Transition-extension Period of the study. There was one death and one withdrawal by subject.

All patients who complied with all the inclusion and none of the exclusion criteria were dosed in the trial. Number of the patients enrolled and included in respective analysis sets for treatment phase (main phase) and transition phase (extension phase) of the study are in Figure 5.

- **Recruitment**

The first patient first visit was on 10 November and the last patient last visit was on 3 November 2023.

- **Conduct of the study**

The following major protocol deviations were identified: patients with no DXA assessment ; patients excluded from PP set of treatment period due to withdrawal from the study, missing visit, missing PD samples collected under fasting conditions for multiple consecutive visits.

There were no changes in the conduct of the study or planned analysis. However, three major incidences were reported during the conduct of the study: sites GCP non-compliance in India, Deep freezer Malfunction (Sample lost), Sample Non-Reportable.

Further discussion on GCP aspects can be found in section 2.6.6.

- **Baseline data**

The mean age for the 552 patients was 63 ± 6.3 years. Of total 552 patients, 522 (94.6%) patients were Indian and 30 (5.4%) patients were Georgian. The age of 359 (65.0%) patients was <65 and the age of 193 (35.0%) patients was ≥ 65. The mean weight was 60.9 ± 8.10 kg. The mean BMI was 26.80 ± 3.433 kg/m 2. (Safety Set, ITT Set)

- **Numbers analysed**

A total 552 patients were enrolled in treatment phase (main phase) of the study. All 552 patients were qualified for Safety set and ITT set, 524 patients were qualified for mITT set, 465 patients were qualified for PP set, 261 patients were qualified for PK set and 258 for PD set in treatment phase (main phase) of study.

A total 123 patients were enrolled in transition-extension phase of the study. All 123 patients were qualified for Safety set and ITT set; 121 patients were qualified for PP set. 17 patients were included for PK and PD analysis in transition-extension phase of study.

- **Outcomes and estimation**

Primary Endpoint

Data are presented in Table 30, Table 31,Table 32, Table 33, Table 34, Table 35 and *Table 36*.

Table 25. Summary statistics for %CFB in BMD of lumbar spine (main phase, PP set, N=465)

Visit (Months)	Statistics	Denosumab (T) (N=235)	Prolia (R) (N=230)	Mean Difference	95% CI	Acceptance Criteria (T vs R)	Conclusion (For EMA)
6 months	n	235	229	-0.92	-2.47 to 0.64	Not Applicable	Not Applicable
	Mean	5.11	5.86				
	SD	10.209	6.383				
12 months	n	235	230	-0.20	-1.42 to 1.03	-1.45 to 1.45	Therapeutic equivalent
	Mean	6.25	6.36				
	SD	6.819	6.609				

(Refer Table No. 14.2.6.1)

Note 1: N=Number of Patient in respective analysis set, n= Available observation in respective group.

Note 2: %Change from baseline (%CFB) = ((post-baseline visit – baseline)/ baseline) X 100

Note 3: 95% CI has been calculated using ANCOVA considering baseline as a covariate.

Table 26. Summary statistics for %CFB in BMD of lumbar spine (main phase, mITT set with LOCF, N = 524)

Visit (Months)	Statistics	Denosumab (T) (N = 265)	Prolia (R) (N = 259)	Mean Difference	95% CI
12 months	n	265	259	-0.53	-1.74 to -0.68
	Mean	5.72	6.19		
	SD	6.677	7.349		
(Refer Table No. 14.2.6.5) Note 1: N = Number of patients in respective analysis set, n = Available observation in respective group.					

Note 2: %Change from baseline (%CFB) = ((post-baseline visit – baseline)/ baseline) x 100
Note 3: 95% CI has been calculated using ANCOVA considering baseline as a covariate.
Note 4: Missing data has been imputed using last observation carried forward (LOCF) for the patients in mITT set who receive at least one dose of study medication and undergone at least one post-dose efficacy evaluation.

Table 27. Summary statistics for %CFB in BMD of lumbar spine (main phase, mITT set with MMRM, N = 524)

Visit (Months)	Statistics	Denosumab (T) (N = 265)	Prolia (R) (N = 259)	Mean Difference	95% CI
12 months	n	235	230	-0.14	-1.36 to 1.08
	Mean	6.25	6.36		
	SD	6.82	6.61		

(Refer Table No. 14.2.6.6)
Note 1: N = Number of patients in respective analysis set, n = Available observation in respective group.
Note 2: %Change from baseline (%CFB) = ((post-baseline visit – baseline)/ baseline) x 100
Note 3: 95% CI has been calculated using ANCOVA considering baseline as a covariate.
Note 4: Participants in the mITT set who missed efficacy data for a particular visit has been imputed using Mixed Model for Repeated Measures (MMRM) method. This analysis assumes that the missing data mechanism is Missing At Random (MAR).

At the CHMP request, a reanalysis of the primary endpoint in (1) all randomised patients and (2) all randomised patients except patients from sites which had falsified DXA data. The results of these reanalyses are presented in the tables below.

Table 28. Summary statistics for %CFB in BMD of lumbar spine at 12 months (main phase, all randomised patients with LOCF, N=552) [including all sites]

Denosumab (N=276)			Prolia (N=276)			Denosumab vs. Prolia	
n	Mean	SD	N	Mean	SD	Mean Difference	95% CI
276 [observed: 248, imputed: 28]	5.50	6.638	276 [observed: 244, imputed: 32]	5.80	7.273	-0.36 LSM (T) = 5.47 LSM (R) = 5.83	-1.53 to 0.80

The 95% confidence interval for the percentage change in BMD from baseline to 12 month is outside the acceptance range [-1.45 to 1.45] after including all randomized patients in the analysis of covariance model with all missing data imputed using LOCF. (Refer Attachment #83.1A)

Table 29. Summary statistics for %CFB in BMD of lumbar spine at 12 months (main phase, all randomised patients with MMRM, N=552) [including all sites]

Denosumab (N=276)			Prolia (N=276)			Denosumab vs. Prolia	
n	Mean	SD	n	Mean	SD	Mean Difference	95% CI
276 [observed: 248, estimated: 28]	6.12	6.73	276 [observed: 244, estimated: 32]	6.57	7.41	-0.46 LSM (T) = 6.22 LSM (R) = 6.68	-1.71 to 0.79

The 95% confidence interval for the percentage change in BMD from baseline to 12 month is outside the acceptance range [-1.45 to 1.45] after including all randomized patients using MMRM, in which data were assumed to be missing at random. (Refer Attachment #83.1B).

Table 30. Summary statistics for %CFB in BMD of lumbar spine at 12 months (main phase, LOCF, N=522) [excluding randomised patients from sites which had DXA falsified data]

Denosumab (N=261)			Prolia (N=261)			Denosumab vs. Prolia	
n	Mean	SD	n	Mean	SD	Mean Difference	95% CI
261 [observed: 235, imputed: 26]	5.62	6.735	261 [observed: 233, imputed: 28]	5.69	6.511	-0.13 LSM (T) = 5.59 LSM (R) = 5.72	-1.27 to 1.01

The 95% confidence interval for the percentage change in BMD from baseline to 12 month is within the acceptance range [-1.45 to 1.45] after excluding 30 patient data pertaining to site #121 to #124 patients and imputation of missing data using LOCF. (Refer Attachment #83.2A).

Table 31. Summary statistics for %CFB in BMD of lumbar spine at 12 months (main phase, MMRM, N=522) [excluding randomised patients from sites which had DXA falsified data]

Denosumab (N=261)			Prolia (N=261)			Denosumab vs. Prolia	
n	Mean	SD	n	Mean	SD	Mean Difference	95% CI
261 [observed: 235, estimated: 26]	6.25	6.82	261 [observed: 233, estimated: 28]	6.37	6.57	-0.15 LSM (T) = 6.34 LSM (R) = 6.49	-1.37 to 1.06

The 95% confidence interval for the percentage change in BMD from baseline to 12 month is within the acceptance range [-1.45 to 1.45] excluding data of site 121 to 124 patients using MMRM. (Refer Attachment #83.2B).

Secondary Endpoint (main phase)

Data are presented in Table 37 and Table 38.

Table 32. Summary statistics for %CFB in BMD of femoral neck and total hip

Parameter	Visit (Months)	Statistics	Denosumab (T) (N = 276)	Prolia (R) (N = 276)	Mean Difference	95% CI
Femoral neck (n = 552)	6 months	n	252	244	-0.44	-1.85 to 0.96
		Mean	1.94	2.27		
		SD	7.600	8.809		
	12 months	n	235	230	-1.10	-2.54 to 0.34
		Mean	2.24	3.34		
		SD	7.567	9.064		
	6 months	n	252	244	0.29	-1.82 to 2.40

Parameter	Visit (Months)	Statistics	Denosumab (T) (N = 276)	Prolia (R) (N = 276)	Mean Difference	95% CI
Total hip (n = 552)		Mean	2.86	2.59		
		SD	6.646	16.754		
	12 months	n	235	230	-0.48	-2.76 to 1.79
		Mean	3.44	3.85		
		SD	6.199	17.754		
(Refer Table No. 14.2.7.2) Note 1: N = Number of patients in respective analysis set, n = Available observation in respective group. Note 2: %Change from baseline (%CFB) = ((post-baseline visit – baseline)/ baseline) x 100 Note 3: 95% CI has been calculated using ANCOVA considering baseline as a covariate.						

According to the applicant, the above presentation of secondary endpoints is using ITT population. This seems not as the correct description. This is PP analysis using available data at time points 6 months and 12 months.

Table 33. Incidence of clinical fracture over 12 months (main phase, safety set)

System Organ Class	Preferred Term	Denosumab (N = 276) n (%) e	Prolia (N = 276) n (%) e	Total (N = 552) n (%) e
Injury, poisoning and procedural complications	Upper limb fracture	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
(**Refer Table No. 14.3.12)**				

During the treatment phase of 12 months, one patient had upper limb fracture in Intas Denosumab arm. The study was not powered for equivalence for clinical fracture.

Thoracic- and lumbar x-rays were performed at baseline and end of study as efficacy parameters. During the study, thoracic and lumbar spine x-ray assessment was scheduled at screening, end of the study visit (visit 15; Day 361) and end of the treatment visit. X-rays were evaluated by central imaging vendor (Independent reviewer) who was remaining blinded to treatment. One patient (0.4%) in denosumab group and 2 patients (0.7%) in Prolia group suffered an incidental (new) fracture, an incidence that was numerically comparable and statistically not significant.

- **Ancillary analyses**

Data on the primary endpoint during the transition-extension phase are presented in Table *39* and Table 40.

Table 34. Descriptive statistics for %CFB in BMD score of lumbar spine (extension phase, PP set, N = 121)

Visit (Months)	Statistics	Denosumab (N = 60)	Prolia (N = 61)
At 18 months	n	58	58
	Mean	6.33	7.50
	SD	5.206	5.331
	Median	6.13	7.70
	Min, Max	-6.73, 18.84	-1.76, 32.35
	95% CI	4.96 to 7.70	6.09 to 8.90
	p-value (between)	0.2371	-

Visit (Months)	Statistics	Denosumab (N = 60)	Prolia (N = 61)
(Refer Table No. 14.2.6.20) Note 1: N = Number of patients in respective analysis set, n = Available observation in respective group. Note 2: %Change from baseline (%CFB) = ((post-baseline visit – baseline)/ baseline) x 100 Note 3: p-value (between) calculated in treatment Intas Denosumab and Prolia using independent t-test. Note 4: p-value < 0.05 is statistically significant.			

Table 35. Descriptive statistics for BMD score of lumbar spine (extension phase, PP set, N = 121)

Visit (Months)	Statistics	Denosumab (N = 60)	Prolia (N = 61)
Baseline	n	60	61
	Mean	0.80	0.79
	SD	0.054	0.057
	Median	0.80	0.80
	Min, Max	0.70, 0.89	0.69, 0.89
	95% CI	0.79 to 0.82	0.78 to 0.81
	p-value (between)	0.4228	-
18 months	n	58	58
	Mean	0.85	0.85
	SD	0.068	0.065
	Median	0.85	0.84
	Min, Max	0.69, 1.00	0.73, 1.00
	95% CI	0.84 to 0.87	0.83 to 0.87
	p-value (between)	0.8483	-
(Refer Table No. 14.2.6.22) Note 1: N = Number of Patient in respective analysis set, n = Available observation in respective group. Note 2: %Change from baseline (%CFB) = ((post-baseline visit – baseline)/ baseline) x 100 Note 3: p-value (between) calculated in treatment Denosumab and Prolia using independent t-test. Note 4: p-value < 0.05 is statistically significant.			

The primary endpoint (lumbar spine BMD) was also analysed in the transition-extension phase. This analysis was supposed to be performed in the per-protocol set, but only 116 out of 121 patients in this set have been included in the analysis. The applicant has explained that 5 additional patients were excluded from the per-protocol set because of missing endpoint data. This explanation is satisfactory.

- **Summary of main efficacy results**

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

Table 36. Summary of efficacy for trial 0774-19

Title: A randomized, double-blind, active-controlled, parallel arm, multicenter study comparing pharmacokinetics, pharmacodynamics, and immunogenicity of denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in postmenopausal women with osteoporosis	
Study identifier	Lambda Project No. 0774-19 Novum/Cromos Project No. 72189811/CP1352
Design	Randomised Double-blind Active-controlled Parallel arm

Title: A randomized, double-blind, active-controlled, parallel arm, multicenter study comparing pharmacokinetics, pharmacodynamics, and immunogenicity of denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in postmenopausal women with osteoporosis			
Study identifier	Lambda Project No. 0774-19 Novum/Cromos Project No. 72189811/CP1352		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable 6 months
Hypothesis	Equivalence		
Treatments groups	Denosumab Intas		276 randomised
	Prolia		276 randomised
Endpoints and definitions	Co-primary endpoint	LS BMD	Percent change in BMD of lumbar spine from baseline to 12 months.
	Co-primary endpoint	CTX Emax	Emax of % reduction from baseline serum C-terminal telopeptide (CTX) after first dose
	Co-primary endpoint	CTX $AUEC_{0-t}$	$AUEC_{0-t}$ of % reduction from baseline serum C-terminal telopeptide (CTX) after first dose
Database lock	27 November 2023		

Results and Analysis

LS BMD	**Per protocol set (this analysis was pre-specified)**		
Descriptive statistics and estimate variability	Treatment group	Denosumab Intas	Prolia
	Number of subjects	235	230
	% change in LS BMD, mean (SD)	6.25 (6.819)	6.36 (6.609)
Effect estimate per comparison	Least squares mean difference (95% CI)	-0.20 (-1.42 to 1.03)	
	Acceptance range	-1.45 to 1.45	
LS BMD	**Modified intent-to-treat set, imputation with LOCF (this analysis was pre-specified)**		
Descriptive statistics and estimate variability	Treatment group	Denosumab Intas	Prolia
	Number of subjects	265	259
	% change in LS BMD, mean (SD)	5.72 (6.677)	6.19 (7.349)
Effect estimate per comparison	Least squares mean difference (95% CI)	-0.53 (-1.74 to -0.68)	
	Acceptance range	-1.45 to 1.45	
LS BMD	**Modified intent-to-treat set, imputation with MMRM (this analysis was pre-specified)**		
Descriptive statistics and estimate variability	Treatment group	Denosumab Intas	Prolia
	Number of subjects	265	259
	% change in LS BMD, mean (SD)	6.25 (6.82)	6.36 (6.61)
Effect estimate per comparison	Least squares mean difference (95% CI)	-0.14 (-1.36 to 1.08)	
	Acceptance range	-1.45 to 1.45	
LS BMD	**All randomised set, imputation with LOCF (this analysis was requested by CHMP)**		
Descriptive statistics and estimate variability	Treatment group	Denosumab Intas	Prolia

Title: A randomized, double-blind, active-controlled, parallel arm, multicenter study comparing pharmacokinetics, pharmacodynamics, and immunogenicity of denosumab of Intas Pharmaceutical Limited (60 mg/mL) with Prolia® in postmenopausal women with osteoporosis			
Study identifier	Lambda Project No. 0774-19 Novum/Cromos Project No. 72189811/CP1352		
	Number of subjects	276	276
	% change in LS BMD, mean (SD)	5.50 (6.638)	5.80 (7.273)
Effect estimate per comparison	Least squares mean difference (95% CI)	-0.36 (1.53 to 0.80)	
	Acceptance range	-1.45 to 1.45	
LS BMD	**All randomised set, imputation with MMRM (this analysis was requested by CHMP)**		
Descriptive statistics and estimate variability	Treatment group	Denosumab Intas	Prolia
	Number of subjects	276	276
Effect estimate per comparison	% change in LS BMD, mean (SD)	6.12 (6.73)	6.57 (7.41)
	Least squares mean difference (95% CI)	-0.46 (-1.71 to 0.79)	
	Acceptance range	-1.45 to 1.45	
LS BMD	**All randomised set excluding the patients from sites with falsified data, imputation with LOCF (this analysis was requested by CHMP)**		
Descriptive statistics and estimate variability	Treatment group	Denosumab Intas	Prolia
	Number of subjects	261	261
	% change in LS BMD, mean (SD)	5.62 (6.735)	5.69 (6.511)
Effect estimate per comparison	Least squares mean difference (95% CI)	-0.13 (-1.27 to 1.01)	
	Acceptance range	-1.45 to 1.45	
LS BMD	**All randomised set excluding the patients from sites with falsified data, imputation with MMRM (this analysis was requested by CHMP)**		
Descriptive statistics and estimate variability	Treatment group	Denosumab Intas	Prolia
	Number of subjects	261	261
	% change in LS BMD, mean (SD)	6.25 (6.82)	6.37 (6.57)
Effect estimate per comparison	Least squares mean difference (95% CI)	-0.15 (-1.37 to 1.06)	
	Acceptance range	-1.45 to 1.45	
CTX Emax	**Pharmacodynamic set**		
Descriptive statistics and estimate variability	Treatment group	Denosumab Intas	Prolia
	Number of subjects	131	127
	Geometric least squares means	97.032	95.936
Effect estimate per comparison	Ratio of geometric least squares means (95% CI)	101.1 (99.24 to 103.08)	
	Acceptance range	80.00 to 125.00	
CTX $AUEC_{0-t}$	**Pharmacodynamic set**		
Descriptive statistics and estimate variability	Treatment group	Denosumab Intas	Prolia
	Number of subjects	131	127
	Geometric least squares means	336815.658^	328601.779
Effect estimate per comparison	Ratio of geometric least squares means (95% CI)	102.5 (95.64 to 109.85)	
	Acceptance range	80.00 to 125.00	

2.6.5.3. Clinical studies in special populations

Not applicable.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Study 0774-19 was a phase III, randomised, double-blind, active-controlled, parallel arm, multicentre study comparing pharmacokinetics, pharmacodynamics, and immunogenicity of denosumab of Intas Pharmaceutical Limited (60mg/mL) with Prolia in postmenopausal women with osteoporosis.

The overall study design, including study population and primary/secondary endpoints was discussed and agreed and the EMA via Scientific Advice. The study population of women with osteoporosis patients has been considered adequate for pivotal trials of biosimilars of Prolia. The inclusion and exclusion criteria as detailed in the study report were acceptable. The trial was double blinded. The baseline characteristics were balanced between treatment groups.

The primary clinical endpoint was mean percentage change in BMD at lumbar spine from baseline to 12 months between Intas Denosumab and EU-Prolia. The equivalence margin of ±1.45% is acceptable for EMA.

The statistical analyses followed the protocol and the statistical analysis plan. Although the statistical analysis plan was amended once after unblinding, this amendment was minor and concerned only the descriptive immunogenicity analysis.

The protocol stated that dynamic randomisation had been used, but during the CHMP assessment, it became clear that a pre-generated randomisation list had been used instead. CHMP considered this acceptable.

A relatively large number of patients did not complete the main phase of the trial (n=88/552, 16%). An important contributing factor to this was the sponsor's decision to terminate 4 sites due to non-compliance with the eligibility criteria and falsification of DXA scans. These sites had recruited a total of 30 patients (15 in each arm). With these patients excluded, 11% (n=60/522) of the remaining patients did not complete the main phase of the trial. It is noted that in this subset of 522 patients, more patients in the reference arm than in the test arm did not complete the main phase (14% vs. 10%, n=35 vs. 25). However, the difference could be due to chance.

The applicant used a per-protocol (PP) set in the primary efficacy analysis and a modified intention-to-treat (mITT) set in supportive analyses. Both analysis sets are equally important for establishing biosimilarity, but the mITT set was not appropriately defined. First, the missing data of patients who completely lacked follow-up visits should be imputed rather than excluded from the analysis. Second, all 30 patients who were recruited at the 4 sites that falsified DXA scans should be excluded, as none of these data are trustworthy. A reanalysis was requested by the CHMP and considered satisfactory (see below).

In the mITT set, two different analyses were conducted with different ways of handling missing data: (1) an analysis of covariance model, with imputation of missing data using the last-observation-carried-forward method, and (2) a mixed model for repeated measure, which assumes that data were missing at random. Both methods have advantages and disadvantages and are therefore considered informative.

Regarding GCP aspects, the applicant reported that 4 sites were terminated because DXA scans had been falsified and patient eligibility criteria had been violated. These 4 sites had randomised a total of 30 patients.

The applicant was asked to provide more information about the falsified DXA scans**,** as falsifying data is a serious violation of good clinical practice and constitutes scientific misconduct, but the applicant initially provided limited information about this problem. The applicant's response was a detailed account of how the falsification of data was discovered and handled, including the measures taken to ensure that no GCP issues occurred at other sites. The applicant also submitted monitoring reports for the sites in question.

In addition to the applicant's information, CHMP triggered a GCP inspection to verify the corrective and preventive measures taken and the conduct of the trial in other sites. The inspectors found some departures from GCP, but concluded that the trial was ethically conducted, and that the data were of sufficient quality to be evaluated in a Marketing Authorisation Application Therefore, CHMP considered the issue resolved.

Efficacy data and additional analyses

The primary efficacy endpoint was mean percentage change in BMD of lumbar spine from baseline to 12 months. The % change from baseline in BMD of lumbar spine at 12 months in PP set was 6.25 for test and 6.36 for reference. The mean difference is -0.20 and the 95% confidence interval for the percentage change in BMD from baseline to 12 months [-1.42 to 1.03] is within the acceptance range of [-1.45 to 1.45].

The % change from baseline in BMD of lumbar spine at 12 months in mITT set with LOCF was 5.72 for test and 6.19 for reference. The mean difference is -0.53 for percentage CFB in BMD of lumbar spine and its 95% CI is [-1.74 to -0.68].

For mITT set with MMRM, the % change from baseline in BMD of lumbar spine at 12 months in was 6.25 for test and 6.36 for reference. The mean difference is -0.14 for percentage CFB in BMD of lumbar spine and its 95% CI is -1.36 to 1.08. This is within acceptance range of [-1.45 to 1.45].

These supportive analyses conducted in the mITT set were considered inappropriate because patients who lacked follow-up data were excluded but patients from sites that falsified data were included. Therefore, the CHMP requested additional analyses including all randomised patients, except for patients from sites that falsified data.

The reanalyses failed to show significant therapeutic equivalence in all randomised patients, regardless of whether LOCF or MMRM was used. In contrast, significant therapeutic equivalence was found with both methods after exclusion of the 30 patients from sites that falsified DXA data. Overall based on these latter analyses, the CHMP concluded that the phase III study demonstrated the therapeutical equivalence between Intas Denosumab and Prolia, acknowledging the multiplicity issue arising from the various analyses performed.

The % change from baseline in BMD at femoral neck at 12 months in PP set was 2.24 for test and 3.34 for reference. The % change from baseline in BMD at total hip at 12 months in PP set was 3.44 for test and 3.85 for reference. The mean difference for percentage CFB in BMD at 12 months of femoral neck

and total hip are -1.10 and -0.48 respectively and their 95% CIs are [-2.54 to 0.34] and [-2.76 to 1.79].

These point estimates for femoral hip and total hip are numerically lower for the test compared to the reference. An acceptance range was not pre-defined for the secondary endpoints. The 95% CIs are wider than for lumbar spine.

In pre-defined subgroup analyses, the mean difference for percentage CFB in BMD of lumbar spine for age group <65 years and >=65 years at 12 months is -0.65 and 0.74 respectively, and their 95% CIs are -2.13 to 0.84 and -1.40 to 2.89, respectively. The results do not indicate that the biosimilar would have different efficacy in different age groups; however, the study was not powered to show formal equivalence in these subgroups.

The primary endpoint (lumbar spine BMD) was also analysed in the transition-extension phase. This analysis was supposed to be performed in the PP set, but only 116 out of 121 patients in this set were included in the analysis. The applicant was asked to explain why 5 additional patients were excluded, and the reason was that endpoint data were missing for these patients, which was considered to be a satisfactory answer.

2.6.7. Conclusions on the clinical efficacy

Overall, based on the reanalysis of the data taking into account an appropriate definition of mITT and the exclusion of the randomised patients who had falsified DXA scans, the CHMP concluded that the phase III study data can be considered acceptable to support therapeutical equivalence between Intas Denosumab and Prolia.

2.6.8. Clinical safety

The safety of Intas Denosumab was evaluated in healthy male subjects (Phase-I) and in postmenopausal women with osteoporosis (Phase-III).

- Phase I (0568-19): Comparative pharmacokinetic and pharmacodynamic study
- Phase-III (0774-19): Comparative pharmacokinetic, pharmacodynamic, safety, immunogenicity and clinical efficacy study

In Study 0568-19, safety assessments after the single dose of 35 mg s.c. study drug consisted of AEs and SAEs, injection site assessment, physical examination, vital signs (blood pressure, pulse rate, respiratory rate and body temperature), ECG, and clinical laboratory tests (haematology, biochemistry including calcium, urine analysis). Furthermore, ADA formation against Intas denosumab, EU-Xgeva, and US-Xgeva was also evaluated.

In Study 0774-19, safety assessments after dosing consisted of AEs and SAEs, injection site assessment, physical examination, vital signs (blood pressure, pulse rate, and body temperature), ECG, and clinical laboratory tests (haematology, biochemistry e.g. calcium, and urine analysis). Periodontal examination and thoracic- and lumbar spine x-ray were performed at screening, by end of study visit and when clinically required. Study participants were instructed to take daily vitamin D and calcium supplements.

2.6.8.1. Patient exposure

Data are presented in Table 42 and Table 43.

Table 37. Extent of exposure (Study 0568-19)

Product Type	Number of subjects (N)	Exposure
Intas Denosumab	78	Single dose 35 mg
US-Xgeva	78	Single dose 35 mg
EU-Xgeva	78	Single dose 35 mg

Table 38. Extent of exposure (Study 0774-19)

Product Type	Period	Number of subjects (N)	Exposure
Denosumab Solution for Injection in Single use Prefilled syringe (60 mg/mL)	Main	85	Single dose of 60 mg
		253	Two doses of 60 mg ~ 6 months apart
Prolia® Solution for injection in single-use prefilled syringe (60 mg/mL)	Main	32	Single dose of 60 mg
		183	Two doses of 60 mg ~ 6 months apart
	Extension	62	Three doses (2x Prolia® + 1x Intas Denosumab) 60 mg ~ 6 months apart
		61	Three doses of Prolia® 60 mg ~ 6 months apart

2.6.8.2. Adverse events

Summary of adverse events

Data are presented in Table 44, Table 45 and Table 46.

Table 39. Overall summary of adverse events in Study 0568-19

	Intas Denosumab (N=78) n (%) e	**US-Xgeva (N=78) n (%) e**	**EU-Xgeva (N=78) n (%) e**	**Total (N=234) n (%) e**
At least one Post dose AE	33 (42.3) 46	25 (32.1) 48	29 (37.2) 38	87 (37.2) 132
At least one AE leading to discontinuation	5 (6.4) 5	4 (5.1) 5	4 (5.1) 5	13 (5.6) 15
At least one related AE	6 (7.7) 6	4 (5.1) 6	7 (9.0) 7	17 (7.3) 19
AE Severity				
At least one mild AE	30 (38.5) 42	25 (32.1) 46	28 (35.9) 36	83 (35.5) 124
At least one moderate AE	3 (3.8) 3	2 (2.6) 2	2 (2.6) 2	7 (3.0) 7
At least one severe AE	1 (1.3) 1	0 (0.0) 0	0 (0.0) 0	1 (0.4) 1
AE Toxicity Grading				
At least one Grade 1 AE	18 (23.1) 23	16 (20.5) 28	20 (25.6) 25	54 (23.1) 76
At least one Grade 2 AE	18 (23.1) 20	14 (17.9) 19	8 (10.3) 9	40 (17.1) 48
At least one Grade 3 AE	3 (3.8) 3	1 (1.3) 1	4 (5.1) 4	8 (3.4) 8

	Intas Denosumab (N=78) n (%) e	US-Xgeva (N=78) n (%) e	EU-Xgeva (N=78) n (%) e	Total (N=234) n (%) e
At least one Grade 4 AE	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
At least one Grade 5 AE	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
At least one SAE	3 (3.8) 3	1 (1.3) 1	2 (2.6) 2	6 (2.6) 6

N = Number of subjects in respective treatment.
n = Number of subjects in respective categories; e = Number of events.
Percentages are calculated based on total number of subjects in each category.
Each subject is counted at the most once within each PT.
Adverse Events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1

Table 40. Overall summary of adverse events in study 0774-19 (treatment period, safety set)

	Intas Denosumab (N=276) n (%) e	Prolia® (N=276) n (%) e	Total (N=234) n (%) e	p-value
At least one TEAE	180 (65.2) 369	184 (66.7) 461	364 (65.9) 830	07194
At least one TEAE leading to discontinuation	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
At least one TESAE	2 (0.7) 2	2 (0.7) 2	4 (0.7) 4	1.0000
At least one AESI	152 (55.1) 235	160 (58.0) 285	312 (56.5) 520	0.4922
Severity grade				
Mild	176 (63.8) 358	182 (65.9) 450	358 (64.9) 808	
Moderate	9 (3.3) 9	7 (2.5) 9	16 (2.9) 18	
Severe	2 (0.7) 2	2 (0.7) 2	4 (0.7) 4	
Relationship to study treatment				
Unlikely	59 (21.4) 118	50 (18.1) 146	109 (19.7) 264	
Possible	8 (2.9) 8	7 (2.5) 8	15 (2.7) 16	
Probable/Likely	145 (52.5) 243	160 (58.0) 306	305 (55.3) 549	
Certain	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1	
Conditional/Unclassified	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Unassessable/Unclassifiable	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Action taken with study treatment				
Dose increased	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Dose not changed	133 (48.2) 255	165 (59.8) 384	298 (54.0) 609	
Not applicable	105 (38.0) 144	51 (18.5) 77	156 (28.3) 221	
Dose reduced	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Drug interrupted	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Drug withdrawn	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Unknown	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Outcome				
Unknown	9 (3.3) 10	10 (3.6) 10	19 (3.4) 20	
Converted to SAE	1 (0.4) 2	0 (0.0) 0	1 (0.2) 2	
Recovered with sequelae	0 (0.0) 0	1 (0.4) 2	1 (0.2) 2	

	Intas Denosumab (N=276) n (%) e	Prolia® (N=276) n (%) e	Total (N=234) n (%) e	p-value
Recovered without sequelae	175 (63.4) 341	181 (65.6) 435	356 (64.5) 775	
Death	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1	
Not yet recovered	8 (2.9) 8	6 (2.2) 6	14 (2.5) 14	
Stable	7 (2.5) 8	6 (2.2) 7	13 (2.4) 15	
Serious Adverse Event (SAE)				
Relationship to Study Treatment				
Certain	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Unlikely	2 (0.7) 2	2 (0.7) 2	4 (0.7) 4	
Conditional/Unclassified	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Possible	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Unassessable/Unclassifiable	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Seriousness Criteria				
Result in persistent or Significant Disability/incapacity	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Death	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1	
Hospitalisation or prolongation of existing hospitalisation	2 (0.7) 2	1 (0.4) 1	3 (0.5) 3	
Life Threatening	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Other Medically Important Event	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Outcome				
Change in Severity	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Death	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1	
Recovered with sequelae	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1	
Recovered without sequelae	2 (0.7) 2	0 (0.0) 0	2 (0.4) 2	
Not yet recovered	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Stable	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Unknown	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	

N = Number of patients in respective treatments.
n = Number of patients in respective categories; e = Number of events.
Percentages are based on total number of patients in each treatment.
p-value is calculated based on a chi-square test. If any cell has counts less than 5, then the Fisher's exact test is used.
Source: Listing 16.2.7.1 and Table 14.3.1.1 of CSR.

Table 41. Overall summary of adverse events in study 774-19 (extension period, safety set)

	Intas Denosumab (N=62) n (%) e	Prolia® (N=61) n (%) e	Total (N=123) n (%) e	p-value
At least one TEAE	25 (40.3) 25	25 (41.0) 54	50 (40.7) 99	0.9405
At least one TEAE leading to discontinuation	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
At least one TESAE	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1	
At least one AESI	18 (29.0) 19	20 (32.8) 22	38 (30.9) 41	0.7414
Severity grade				
Mild	24 (38.7) 44	25 (41.0) 54	49 (39.8) 98	
Moderate	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Severe	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1	
Relationship to study treatment				
Certain	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Possible	1 (1.6) 1	1 (1.6) 1	2 (1.6) 2	
Probable/Likely	17 (27.4) 19	19 (31.1) 21	36 (29.3) 40	
Unlikely	9 (14.5) 25	8 (13.1) 32	17 (13.8) 57	
Conditional/Unclassified	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Unassessable/Unclassifiable	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Seriousness Criteria				
Death	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1	
Action taken with study treatment				
Dose increased	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Dose not changed	2 (3.2) 2	3 (4.9) 3	5 (4.1) 5	
Not applicable	24 (38.7) 43	23 (37.7) 51	47 (38.2) 94	
Dose reduced	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Drug interrupted	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Drug withdrawn	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Unknown	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Outcome				
Recovered with sequelae	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Death	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1	
Recovered without sequelae	22 (35.5) 38	24 (39.3) 51	46 (37.4) 89	
Stable	2 (3.2) 3	1 (1.6) 2	3 (2.4) 5	
Change in severity	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	
Unknown	3 (4.8) 8	1 (1.6) 1	4 (3.3) 4	
Serious Adverse Event (SAE)				
Relationship to Study Treatment				
Unlikely	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1	
Outcome				
Death	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1	

N = Number of patients in respective treatments.
n = Number of patients in respective categories; e = Number of events.
Percentages are based on total number of patients in each treatment.
p-value is calculated based on a chi-square test. If any cell has counts less than 5, then the Fisher's exact test is used.
Source: Listing 16.2.7.1 and Table 14.3.1.2 of CSR.

Adverse events by system organ class and preferred term

Data are presented in Table 47, Table 48 and Table 49.

Table 42. Summary of adverse events by system organ class and preferred term (safety set) (0568-19)

System Organ Class Preferred Term	Intas Denosumab (N=78) n (%) e	US-Xgeva (N=78) n (%) e	EU-Xgeva (N=78) n (%) e
Cardiac disorders			
Coronary artery disease	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Gastrointestinal disorders			
Abdominal pain	1 (1.3%) 1	0 (0.0%) 0	1 (1.3%) 1
Constipation	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
Diarrhoea	0 (0.0%) 0	0 (0.0%) 0	1 (1.3%) 1
Mesenteric artery thrombosis	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
Nausea	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
Vomiting	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
General disorders and administration site conditions			
Pyrexia	0 (0.0%) 0	1 (1.3%) 1	1 (1.3%) 1
Hepatobiliary disorders			
Hepatic cirrhosis	0 (0.0%) 0	0 (0.0%) 0	1 (1.3%) 1
Infections and infestations			
Coronavirus infection	1 (1.3%) 1	0 (0.0%) 0	1 (1.3%) 1
Eczema infected	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Fungal skin infection	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Injury, poisoning and procedural complications			
Animal bite	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Injury	1 (1.3%) 1	0 (0.0%) 0	1 (1.3%) 1
Limb injury	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
Investigations			
Alanine aminotransferase increased	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
Amylase increased	1 (1.3%) 1	1 (1.3%) 1	1 (1.3%) 1
Blood bilirubin increased	0 (0.0%) 0	2 (2.6%) 3	1 (1.3%) 1
Blood calcium increased	6 (7.7%) 7	6 (7.7%) 7	7 (9.0%) 8
Blood creatinine increased	2 (2.6%) 2	1 (1.3%) 3	1 (1.3%) 1
Blood glucose increased	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
Blood phosphorus decreased	2 (2.6%) 2	1 (1.3%) 1	3 (3.8%) 3
Eosinophil count increased	0 (0.0%) 0	1 (1.3%) 2	0 (0.0%) 0
Glucose urine present	1 (1.3%) 1	1 (1.3%) 1	0 (0.0%) 0
Haemoglobin decreased	2 (2.6%) 2	0 (0.0%) 0	0 (0.0%) 0
Lipase increased	1 (1.3%) 1	0 (0.0%) 0	2 (2.6%) 2
Platelet count decreased	2 (2.6%) 2	3 (3.8%) 5	4 (5.1%) 6
Transaminases increased	1 (1.3%) 2	1 (1.3%) 2	4 (5.1%) 4
Vitamin D decreased	10 (12.8%) 11	8 (10.3%) 9	1 (1.3%) 1
White blood cell count decreased	1 (1.3%) 1	1 (1.3%) 1	1 (1.3%) 1
Metabolism and nutrition disorders			
Hypophosphatemia	0 (0.0%) 0	0 (0.0%) 0	1 (1.3%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Back pain	0 (0.0%) 0	0 (0.0%) 0	1 (1.3%) 1
Foot fracture	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
Musculoskeletal chest pain	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
Nervous system disorders			
Headache	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Vertigo	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0

System Organ Class Preferred Term	Intas Denosumab (N=78) n (%) e	US-Xgeva (N=78) n (%) e	EU-Xgeva (N=78) n (%) e
Renal and urinary disorders			
Pollakiuria	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	0 (0.0%) 0	0 (0.0%) 0	1 (1.3%) 1
Skin and subcutaneous tissue disorders			
Furuncle	1 (1.3%) 1	1 (1.3%) 1	1 (1.3%) 1
Pruritus	0 (0.0%) 0	1 (1.3%) 1	0 (0.0%) 0
Tinea infection	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Vascular disorders			
Heat stroke	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Ischemic cerebral infarction	1 (1.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Subjects with At least one post-dose AE	33 (42.3%) 46	25 (32.1%) 48	29 (37.2%) 38

N = Number of subjects in respective treatment.
n = Number of subjects in respective categories; e = Number of events.
Percentages are calculated based on total number of subjects in each category.
Each subject is counted at the most once within each PT.
Adverse Events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1

Table 43. Adverse events grouped by preferred term (treatment period) (0774-19)

System Organ Class	MedDRA (PT) (Version 24.1)	Test Arm (T) (N=276) n (%) e	Reference Arm (R) (N=276) n (%) e	Total (N=552) n (%) e
Blood and lymphatic system disorders	Anaemia	11 (4.0) 12	7 (2.5) 7	18 (3.3) 19
	Leukocytosis	2 (0.7) 2	0 (0.0) 0	2 (0.4) 2
	Leukopenia	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Neutropenia	3 (1.1) 3	1 (0.4) 1	4 (0.7) 4
Cardiac disorders	Angina unstable	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Aortic valve stenosis	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Coronary artery disease	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Ear and labyrinth disorders	Ear pain	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Vertigo positional	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Endocrine disorders	Hypothyroidism	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
Gastrointestinal disorders	Abdominal discomfort	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Abdominal pain	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
	Abdominal pain upper	0 (0.0) 0	2 (0.7) 2	2 (0.4) 2
	Anorectal discomfort	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Constipation	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Diarrhoea	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Dyspepsia	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Gastritis	1 (0.4) 1	3 (1.1) 4	4 (0.7) 5
	Haemorrhoids	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
	Hyperchlorhydria	2 (0.7) 2	4 (1.4) 4	6 (1.1) 6

System Organ Class	MedDRA (PT) (Version 24.1)	Test Arm (T) (N=276) n (%) e	Reference Arm (R) (N=276) n (%) e	Total (N=552) n (%) e
	Mouth ulceration	0 (0.0) 0	2 (0.7) 7	2 (0.4) 7
	Nausea	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Stomatitis	1 (0.4) 1	1 (0.4) 2	2 (0.4) 3
	Toothache	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Gastrointestinal disorders	Vomiting	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
General disorders and administration site conditions	Asthenia	6 (2.2) 6	4 (1.4) 5	10 (1.8) 11
	Chest discomfort	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Chest pain	2 (0.7) 3	1 (0.4) 2	3 (0.5) 5
	Localised oedema	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Pain	0 (0.0) 0	3 (1.1) 3	3 (0.5) 3
	Peripheral swelling	0 (0.0) 0	2 (0.7) 2	2 (0.4) 2
	Pyrexia	3 (1.1) 4	6 (2.2) 7	9 (1.6) 11
	Vessel puncture site erythema	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Hepatobiliary disorders	Hyperbilirubinemia	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Infections and infestations	Bronchitis	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Cystitis	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Gastroenteritis	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Gastrointestinal infection	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Gingivitis	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Lower respiratory tract infection	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Nasopharyngitis	6 (2.2) 6	1 (0.4) 1	7 (1.3) 7
	Paronychia	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Sepsis	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Tinea versicolor	1 (0.4) 2	0 (0.0) 0	1 (0.2) 2
	Upper respiratory tract infection	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Urinary tract infection	8 (2.9) 9	9 (3.3) 9	17 (3.1) 18
	Viral infection	3 (1.1) 3	3 (1.1) 4	6 (1.1) 7
Injury, poisoning and procedural complications	Upper limb fracture	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
Investigations	Haemoglobin decreased	5 (1.8) 6	2 (0.7) 2	7 (1.3) 8
	Vitamin D decreased	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Metabolism and nutrition disorders	Decreased appetite	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
	Hypercalcemia	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Hyperglycaemia	0 (0.0) 0	3 (1.1) 3	3 (0.5) 3
	Hyperkalaemia	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Hyperuricemia	2 (0.7) 2	0 (0.0) 0	2 (0.4) 2
	Hypocalcaemia	152 (55.1) 233	160 (58.0) 285	312 (56.5) 518
	Hypovitaminosis	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Type 2 diabetes mellitus	3 (1.1) 3	4 (1.4) 4	7 (1.3) 7

System Organ Class	MedDRA (PT) (Version 24.1)	Test Arm (T) (N=276) n (%) e	Reference Arm (R) (N=276) n (%) e	Total (N=552) n (%) e
	Vitamin D deficiency	17 (6.2) 18	22 (8.0) 25	39 (7.1) 43
Musculoskeletal and connective tissue disorders	Arthralgia	3 (1.1) 4	10 (3.6) 15	13 (2.4) 19
	Back pain	3 (1.1) 6	4 (1.4) 5	7 (1.3) 11
	Bone pain	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Intervertebral disc protrusion	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Musculoskeletal chest pain	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Musculoskeletal stiffness	0 (0.0) 0	2 (0.7) 2	2 (0.4) 2
	Pain in extremity	2 (0.7) 2	3 (1.1) 6	5 (0.9) 8
	Periarthritis	1 (0.4) 2	0 (0.0) 0	1 (0.2) 2
Nervous system disorders	Burning sensation	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Dizziness	2 (0.7) 2	2 (0.7) 2	4 (0.7) 4
	Embolic stroke	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Headache	6 (2.2) 7	6 (2.2) 8	12 (2.2) 15
	Paraesthesia	0 (0.0) 0	2 (0.7) 2	2 (0.4) 2
Psychiatric disorders	Insomnia	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
Renal and urinary disorders	Acute kidney injury	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
	Dysuria	0 (0.0) 0	1 (0.4) 2	1 (0.2) 2
	Haematuria	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Pollakiuria	0 (0.0) 0	1 (0.4) 2	1 (0.2) 2
	Renal colic	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Respiratory, thoracic and mediastinal disorders	Cough	5 (1.8) 6	2 (0.7) 2	7 (1.3) 8
	Dyspnoea exertional	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
	Epistaxis	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Vascular disorders	Hypertension	5 (1.8) 5	4 (1.4) 4	9 (1.6) 9

N = Number of patients in respective treatments
n = Number of patients in respective categories; e = Number of events
Note: Percentages are based on total number of patients in each treatment.
Treatment Specification:
Test Arm (T): Denosumab Solution for Injection in single use prefilled syringe (60 mg/mL);
Reference Arm (R): Prolia® Solution for injection in single-use prefilled syringe (60 mg/mL)
Summary of adverse events by system organ class and preferred term is presented in Table No. 14.3.2.1 [Summary of adverse events by SOC and PT (Main Phase, Safety set)].

Table 44. Adverse events grouped by preferred term (transition-extension period) (0774-19)

System Organ Class	MedDRA (PT) (Version 24.1)	Test Arm (T) (N=62) n (%) e	Reference Arm (R) (N=61) n (%) e	Total (N=123) n (%) e
Blood and lymphatic system disorders	Anaemia	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
Cardiac disorders	Myocardial ischemia	0 (0.0) 0	1 (1.6) 1	1 (0.8) 1
Gastrointestinal disorders	Diarrhoea	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
	Gastritis	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
	Hyperchlorhydria	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
	Mouth ulceration	0 (0.0) 0	1 (1.6) 1	1 (0.8) 1

System Organ Class	MedDRA (PT) (Version 24.1)	Test Arm (T) (N=62) n (%) e	Reference Arm (R) (N=61) n (%) e	Total (N=123) n (%) e
General disorders and administration site conditions	Asthenia	1 (1.6) 1	4 (6.6) 5	5 (4.1) 6
	Chest discomfort	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
	Death	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
	Pain	2 (3.2) 2	0 (0.0) 0	2 (1.6) 2
Infections and infestations	Infection parasitic	0 (0.0) 0	1 (1.6) 1	1 (0.8) 1
	Paronychia	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
	Viral infection	1 (1.6) 1	1 (1.6) 1	2 (1.6) 2
Injury, poisoning and procedural complications	Hand fracture	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
Investigations	Haemoglobin decreased	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
Metabolism and nutrition disorders	Hypocalcaemia	18 (29.0) 19	20 (32.8) 22	38 (30.9) 41
	Type 2 diabetes mellitus	1 (1.6) 1	1 (1.6) 1	2 (1.6) 2
	Vitamin D deficiency	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
Musculoskeletal and connective tissue disorders	Arthralgia	2 (3.2) 3	4 (6.6) 8	6 (4.9) 11
	Back pain	1 (1.6) 2	3 (4.9) 4	4 (3.3) 6
	Neck pain	0 (0.0) 0	1 (1.6) 1	1 (0.8) 1
	Pain in extremity	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
Nervous system disorders	Dizziness	1 (1.6) 1	3 (4.9) 3	4 (3.3) 4
	Headache	0 (0.0) 0	1 (1.6) 1	1 (0.8) 1
Psychiatric disorders	Anxiety disorder	0 (0.0) 0	1 (1.6) 1	1 (0.8) 1
Respiratory, thoracic and mediastinal disorders	Cough	2 (3.2) 2	2 (3.3) 2	4 (3.3) 4
	Rhinorrhoea	0 (0.0) 0	1 (1.6) 1	1 (0.8) 1
Skin and subcutaneous tissue disorders	Pruritus	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
Vascular disorders	Hypertension	1 (1.6) 1	0 (0.0) 0	1 (0.8) 1
	Peripheral coldness	0 (0.0) 0	1 (1.6) 1	1 (0.8) 1

N = Number of patients in respective treatments
n = Number of patients in respective categories; e = Number of events
Note: Percentages are based on total number of patients in each treatment.
Treatment Specification:
Test Arm (T): Denosumab Solution for Injection in single use prefilled syringe (60 mg/mL);
Reference Arm (R): Prolia® Solution for injection in single-use prefilled syringe (60 mg/mL)
Summary of adverse events by system organ class and preferred term is presented in Table No. 14.3.2.2 [Summary of adverse events by SOC and PT (Extension Phase, Safety set)].

Adverse drug reactions

In healthy adult males (study 0568-19), the number of adverse events considered related to treatment were few in all treatment arms (Intas denosumab=6, US Xgeva=6, EU-Xgeva=7). The adverse events considered related to treatment in the Intas denosumab treatment arm comprised arthralgia (n=1), headache (n=1), decrease in phosphorus (n=2), increase in calcium (n=1), vertigo (n=1). Such adverse events could be expected with denosumab treatment even though decreased calcium is listed as very common in the SmPC of Xgeva and not hypercalcaemia (listed as uncommon following treatment discontinuation in patients with giant cell tumour of the bone).

In healthy adult males (study 0568-19), the number of adverse events considered related to treatment were few in all treatment arms (Intas denosumab=6, US Xgeva=6, EU-Xgeva=7). The adverse events considered related to treatment in the Intas denosumab treatment arm comprised arthralgia (n=1), headache (n=1), decrease in phosphorus (n=2), increase in calcium (n=1), vertigo (n=1). Such adverse events could be expected with denosumab treatment even though decreased calcium is listed as very common in the SmPC of Xgeva and not hypercalcaemia (listed as uncommon following treatment discontinuation in patients with giant cell tumour of the bone).

In the extension period 29% of subjects experienced at least one TEAE considered related to treatment in the test arm compared with 32.8% in the reference arm. The most common adverse drug reaction considered related to treatment was by far hypocalcaemia regardless of treatment arm. In the treatment arm 27.4% of subjects experienced the adverse drug reaction hypocalcaemia vs. 32.8% in the reference arm. In the test arm 1.6% of subjects experienced anaemia considered related to the test drug vs no subjects in the reference arm.

In summary, no significant differences were observed between treatment arms with regards to adverse drug reactions during the extension period.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events

In healthy adult males (study 0568-19, three SAEs occurred in patients receiving test drug and three SAEs occurred in subjects receiving reference drugs. The SAEs in the test arm consisted of ischemic cerebral infarct, heat stroke and coronary artery disease. The SAEs in the reference arms consisted of coronavirus infection, hepatic cirrhosis, and mesenteric artery thrombosis. All SAEs were considered unlikely related to study drug.

In post-menopausal women with osteoporosis (study 0774-19, main part), there were two SAEs in the test arm and two SAEs in the reference arm. The SAEs in the test arm consisted of gastroenteritis and lower respiratory tract infection. The SAEs in the reference arm consisted of coronary artery disease and embolic stroke.

In the extension period, the incidence of fractures (1 fracture in the main treatment period and 1 fracture in the extension period) was overall quite low for a study population of postmenopausal women at risk of osteoporotic fractures. The overall fracture incidence in the Prolia SmPC was 7.2% in clinical trials but over 3 years. The incidence of vertebral fractures according to the Prolia SmPC was 1.4% over 0-2 years in clinical studies.

Deaths

There was one death in the transition-extension period of the main study 0774-19.

Other significant adverse events

There were two other significant AEs in the test arm (coronavirus infection and animal bite), but none was considered related to the study drug.

There were 8 other significant AEs in the reference arms. One was considered possibly related to the study drug (platelet count decreased), but two other cases of platelet count decrease were considered unlikely related to the study drugs. The number of haematologic adverse events were overall few.

Overall, none of the SAE, death, other significant AEs were considered causally related to the test product.

2.6.8.4. Laboratory and other findings

Laboratory findings

Data are presented in Table 50, Table 51 and Table 52.

Table 45. Summary of clinically significant abnormalities (0568-19)

Clinically Significant Abnormality	Number of patients with clinically significant abnormality	Outcome		Treatment		
		Recovered	Unknown	T	R1	R2
Blood calcium increased	22	20	2	7	7	8
Hypophosphatemia	1	1	0	0	0	1
Blood phosphorus decreased	6	6	0	2	1	3
Transaminases increased	7	7	0	2	2	3
Blood creatinine increased	6	6	0	2	3	1
Platelet count decreased	13	13	0	2	5	6

Table 46: Medical history/AEs due to abnormal clinically significant laboratory parameters (treatment period) (0774-19)

Treatment	Visit	Medical history	Outcome
-	Visit-1 (Day-21 to -1)	Low Haemoglobin	Resolved/ Recovered
-	Visit-1 (Day-21 to -1)	Anaemia	Resolved/ Recovered
Treatment	**Visit**	**Adverse event term**	**Outcome**
R	Visit-6 (Day 91)	Anaemia	Not yet recovered
R	Visit-15 EOS (Day 361)	Anaemia	Recovered without sequelae
T	Visit-15 EOS (Day 361)	Anaemia	Not yet recovered
T	Visit-15 EOS (Day 361)	Anaemia	Recovered without sequelae
T	Visit-12 (Day 271)	Anaemia	Recovered without sequelae
T	Visit-9 (Day 181)	Anaemia	Recovered without sequelae
T	Visit-12 (Day 271)	Anaemia	Recovered without sequelae
T	Visit-9 (Day 181)	Anaemia	Recovered without sequelae
T	Visit-12 (Day 271)	Anaemia	Recovered without sequelae
T	Visit-9 (Day 181)	Anaemia	Recovered without sequelae
T	Visit-12 (Day 271)	Anaemia	Stable

R	Visit-6 (Day 91)	Leukopenia	Recovered without sequelae
R	Visit-12 (Day 271)	Anaemia	Recovered without sequelae
T	Visit-12 (Day 271)	Leukocytosis	Recovered without sequelae
T	Visit-9 (Day 181)	Anaemia	Recovered without sequelae
T	Visit-15 EOS (Day 361)	Leukocytosis	Recovered without sequelae
R	Visit-6 (Day 91)	Anaemia	Recovered without sequelae
T	Visit-12 (Day 271)	Anaemia	Recovered without sequelae
R	Visit-12 (Day 271)	Anaemia	Recovered without sequelae
R	Visit-15 EOS (Day 361)	Urinary Tract Infection	Recovered without sequelae
T	Visit-6 (Day 91)	Anaemia	Not yet recovered
R	Visit-12 (Day 271)	Neutropenia	Recovered without sequelae
T	Visit-9 (Day 181)	Neutropenia	Recovered without sequelae
R	Visit-12 (Day 271)	Microhaematuria	Recovered without sequelae

Table 47. AEs due to abnormal clinically significant laboratory parameters (transition-extension period) (0774-19)

Treatment	Visit	Adverse event term	Outcome
T	Visit-20 ET (Transition-Extension Period- Day 181 after last visit)	Anaemia	Recovered without sequelae

Vital signs and physical findings

No clinically significant abnormalities were observed with regards to vital signs and physical examinations. For example, no clinically significant injection site reactions were reported. No ECG changes were observed when taken routinely but might occur in cases of severe hypocalcaemia.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Not applicable

2.6.8.7. Immunological events

Immunogenicity is discussed under section 2.6.2 Clinical Pharmacology. No ADA associated hypersensitivity reactions were reported in Both studies 0568-19 and 0774-19.

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

Not applicable

2.6.8.9. Discontinuation due to adverse events

In healthy adult males (study 0568-19), a total of 14 subjects were withdrawn from the study; 6 subjects were withdrawn due to SAE and the other 8 subjects were withdrawn due to AE(s).

The subjects with SAEs were withdrawn from the study on medical grounds and followed up until resolution of their AEs. The causality assessment was judged as unlikely for all the serious AEs. Three subjects had received the test product and three subjects had received the reference product.

There were 10 other significant AEs reported during the conduct of the study. The subjects were withdrawn from the study on medical grounds. They were followed up until resolution of their AEs. The causality assessment was judged as unlikely for nine significant AEs and as possible one significant AE.

In post-menopausal women with osteoporosis (study 0744-19, main part), , none of the patients were withdrawn due to AEs. However, 3 patients were withdrawn from the study due to SAEs and 1 patient was withdrawn from the study due to death. Two SAEs were reported by 0.7% (n=2) of 276 patients after receipt of Test Product-T and 1 SAE was reported by 0.4% (n=1) of 276 patients after receipt of Reference Product-R during Treatment Period of the study. The relationship all SAEs was unlikely to study treatment. The patients were followed up until resolution of their SAEs. The outcome of 1 SAE was "Recovered with Sequelae" and of 2 SAEs was "Recovered without Sequelae".

During Transition-Extension Period of the study, none of the patients were withdrawn due to AE. However, 1 patient was withdrawn from the study due to death.

There were no dose reductions or dose interruptions.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The safety of Intas Denosumab was evaluated in a PK and PD study in healthy adult male subjects (Study 0568-19) and in an integrated PK, PD, confirmatory efficacy, safety, and immunogenicity study in female subjects with postmenopausal osteoporosis (Study 0774-19). The comparator drugs in Study 0568-19 were EU-Xgeva and US-Xgeva. The comparator drug in Study 0774-19 was EU-Prolia. In study 0568-19 the subjects were administered one single dose of 35 mg Intas denosumab, US-Xgeva or EU-Xgeva. In study 0774-19 the subjects received 60 mg of the test drug or Prolia at baseline and after 6 months in the main treatment phase. A subset of patients also received a third dose of the test drug or Prolia by month 12 in the transition-extension phase after receiving Prolia during the main

treatment period. The safety set was defined as all randomised patients who received at least one dose of study medication.

A total of 293 subjects were exposed to at least one dose of the applicant´s denosumab-biosimilars. Seventy-eight subjects were exposed to the test drug in study 0568-19. End of trial was by day 253. Thirty-two subjects were exposed to a single dose of the test drug in study 0774-19 and 183 subjects received two doses. In the extension phase, 62 subjects were switched from Prolia to the test drug by the time of the third dose. Treatment period was from Day 1 to Day 361 (EOS) in study 0774-19. Transition- extension period was from any day within 21 days after EOS visit to Day 181 after last visit.

Overall, the design of the clinical studies is considered adequate for a safety and immunogenicity assessment of Intas denosumab. The safety assessments performed during Studies 0568-19 and 0774-19 were designed to capture the known safety issues listed in the Prolia and Xgeva labels, which is appropriate. The extent of exposure is also considered sufficient to assess the safety of Intas denosumab vs. Amgen's denosumab. The applicant has provided information regarding baseline medical history and concomitant medications of subjects in both studies as requested. No significant imbalances were noted between treatment arms in either study.

In the phase I study 0568-19, 42% of subjects receiving Intas denosumab experienced at least one post dose AE compared with 32% in the US-Xgeva treatment arm and 37% in the EU-Xgeva arm. These differences depending on treatment regarding number of subjects experiencing TEAEs are considered acceptable. There were no significant differences in subjects with moderate AEs (Intas denosumab 3.8%, US-Xgeva 2.6%, EU-Xgeva 2.6%). There was only one subject experiencing a severe AE in the Intas denosumab arm and none in the reference arms. In summary, the AEs were in general mild (grade 1 and 2) and without significant differences in frequency depending on drug given.

Adverse events occurring in more than one subject in the Intas denosumab treatment arm were blood calcium increased (7.7%), blood creatinine increased (2.6%), blood phosphorus decreased (2.6%), haemoglobin decreased (2.6%), platelet count decreased (2.6%) and vitamin D decreased (12.8%). These AEs were also observed in the reference arms with similar frequencies. No adverse events of hypo- or hypercalcaemia were reported.

The applicant has confirmed that no injections site reactions were reported at all during the study in healthy subjects or in the study in postmenopausal women. This could be considered an unexpected finding, but it is also acknowledged that injection site reactions are not described in the SmPC of Xgeva or Prolia. Furthermore, there were only a few injection site reactions in the pivotal study with Prolia.

Out of the total reported 132 AEs the causality assessment was judged as unlikely for 113 AEs and as possible for 19 AEs. In the Intas denosumab arm 6 AEs were considered possibly or probably related to the drug. These ADRs concerned blood calcium increased, blood phosphorus decreased, platelet decreased, arthralgia and headache. The character and number of ADRs in the reference arms did not differ significantly from the ADRs in the Intas denosumab arm. There were no deaths during the study but 6 serious adverse events of which 3 occurred in subjects receiving the test product. These serious adverse events in the test arm concerned ischemic cerebral infarction, heat stroke and coronary artery disease. The applicant has provided case narratives supporting that it is unlikely that these SAEs were related to the test drug. The conclusions by the applicant that causality between the SAEs and the test drug has not been established are agreed.

In the main treatment period of the phase III study 0774-19 more than half of subjects experienced at least one TEAE (Intas denosumab: 65%; Prolia: 66.7%). No TEAE led to study discontinuation. There were no significant differences in the number of subjects experiencing moderate TEAEs (Intas denosumab: 3.3%; Prolia 2.5%). Neither were there any differences in the number of subjects

experiencing severe TEAEs (0.7% in both treatment arms). A high proportion of subjects experienced TEAEs considered by the investigator to be related to the study drug (Intas denosumab: 54.7%; Prolia: 59.8%).

Hypocalcaemia was by far the most common adverse event in both treatment arms. The number of subjects experiencing hypocalcaemia was similar between treatment arms (test arm n=152; reference arm= 160) and the number of hypocalcaemia events was also similar (test arm: n=233; reference arm n=285). Hypocalcaemia is a well-known adverse drug reaction with denosumab, but the reported frequency in this study (55.1% of subjects experienced hypocalcaemia in the test arm, 58.0% in the reference arm) could be considered unexpectedly high since hypocalcaemia is listed as a rare adverse drug reaction in the SmPC section 4.8 of Prolia. The applicant has described that all calcium values below the lower limit of normal were reported as AEs regardless of symptoms. The CTCAE version 5.0 was used to identify and grade hypocalcaemia events. There were no reports of medical conditions predisposing subjects to hypocalcaemia, for example pre-existing hypocalcaemia, vitamin D-deficiency, renal impairment or concomitant calcium lowering medication. Study participants were instructed to take calcium- and vitamin D supplements throughout the duration of the study and only one subject did not follow this instruction. The majority of subjects with hypocalcaemia experienced mild events. In the test arm 41.7% of study participants had hypocalcaemia grade 1 versus 45.3% in the reference arm in the main treatment phase of the study. These patients were asymptomatic, and no intervention was required. In the test arm 7.6% of study participants experienced hypocalcaemia grade 2 versus 10.5% in the reference arm and 1.1% (n= 3) of study participants in the test arm had hypocalcaemia grade 3 versus 0.4% (n=1) in the reference arm. Hypocalcaemia grade 4 was reported in 0.4% of subjects (n=1) receiving test drug and 0.4% (n=1) of subjects receiving reference drug. None of the hypocalcaemia events led to change in study drug administration. In the main treatment phase, 54.3% of study participants recovered without sequelae in the test arm and 56.9% in the reference arm. In the test arm 1.4% was recorded as not yet recovered vs 0.4% in the reference arm. One patient (0.4%) was recorded as stable in the test arm.

In the extension phase, 29% (n=18) of study participants in the test arm experienced hypocalcaemia grade 1 versus 23.0% (n=14) in the reference arm. Regarding grade 2, hypocalcaemia was reported in 6.5% (n=4) and 4.9% (n=3) of study participants in the test arm and reference arm respectively. No grade 3 or 4 events were reported during the extension phase. One patient was subject to change in calcium and vitamin D supplementation as a result of hypocalcaemia. All participants with hypocalcaemia in the extension phase recovered without sequelae except one subject with unknown status.

In summary, approximately 50% of subjects experienced hypocalcaemia in the main treatment phase of study 0774-19 whereas hypocalcaemia is listed as rare in Prolia´s SmPC section 4.8. No risk factors for hypocalcaemia have been identified among study participants explaining the seemingly high reported frequency of hypocalcaemia. However, there were no differences between treatment arms in the frequency of hypocalcaemia and the majority of hypocalcaemia events were mild and most subjects were asymptomatic.

More patients experienced anaemia and neutropenia in the test arm compared with the reference arm (anaemia: n=11 vs. n=7; neutropenia n=3 vs. n=1). Two subjects experienced a decrease in haemoglobin in the Intas denosumab treatment arm in the PK/PD-study in healthy men but none in the Xgeva treatment arms. Haematologic adverse events are not listed as adverse drug reaction in the SmPC section 4.8 of Prolia or Xgeva. However, the total number of events were few and the small differences observed between treatment arms are not considered clinically relevant.

The PT nasopharyngitis showed a small increase in Intas denosumab n=6 (2.2%) versus EU-Prolia n=1 (0.4%) and also cough (Intas denosumab n=5 (1.8%) and EU-Prolia n=2 (0.7%)). However, the overall number of reported nasopharyngitis and cough PTs were few, and the small differences between treatment arms are not considered clinically relevant.

Other adverse events considered drug related were few and without differences between treatment arms. In study 0774-19 adverse events of special interest were injection site reactions, hypersensitivity reactions, hypocalcaemia, osteonecrosis of the jaw, atypical femoral fractures and serious infections leading to hospitalisation. These AESI are agreed. Except for hypocalcaemia only 2 AESI were reported in the test arm (gastroenteritis and lower respiratory tract infection). No AESI except hypocalcaemia were reported in the reference arm. Thus, no injection site reactions or hypersensitivity reactions were reported in either of the treatment arms. At least the fact that there were no injection site reactions could be considered an unexpected finding, but it is also acknowledged that there were only a few injection site reactions in the pivotal study with Prolia.

No deaths occurred in the test arm but there was one death in a patient receiving Prolia in the main treatment period. This death was considered unrelated to treatment. There were 4 SAEs during the main treatment period of which 2 were reported in subjects administered the test drug. These SAEs consisted of the AESI gastroenteritis and lower tract infection as previously described. No SAEs were considered related to study treatment, and this is agreed based on the provided case narratives. During the main treatment period of the study, none of the patients discontinued due to AEs. However, 3 patients were withdrawn from the study due to the SAEs and 1 patient was withdrawn from the study due to death.

In the transition- extension period of study 0774-19 40.3% in the Intas denosumab treatment arm experienced at least one TEAE, a frequency similar to that observed in the Prolia arm (40.7%). There were no moderate TEAEs in neither of the treatment arms. The number of participants experiencing TEAEs possibly or probably related to treatment was also similar between treatment arms.

Hypocalcaemia was by far the most common TEAE in both treatment arms (Intas denosumab 29% of subjects; Prolia 32.8% of subjects) and also the most common TEAE reported as related to study treatment. In the transition-extension phase of the study hypocalcaemia was the only reported AESI.

Other TEAEs were in line with the known safety profile with Prolia, for example musculoskeletal pain and asthenia. The switch from Prolia to Intas denosumab in the transition-extension period did not result in an increase of TEAEs or TEAEs of different character. No injection site reactions or hypersensitivity reactions were reported which should be discussed by the applicant as previously described, please also see List of questions. Such reactions are of particular interest in relation to immunogenicity.

In total there were only two fractures during the main treatment period and transition- extension period of study 0774-19 (one hand fracture and one upper limb fracture) which is rather low for a study population of postmenopausal women with osteoporosis and given the length of the study. According to Prolia SmPC 7.2% of women experienced fractures during 3 years of clinical trials. The incidence of vertebral fractures according to the Prolia SmPC was 1.4% over 0-2 years in clinical studies. Fracture data are also presented in section 2.3.4 Clinical efficacy.

In summary, the overall percentage of subjects with AEs was similar across treatment groups in both the phase I study and the phase III study. Also on SOC level, comparable incidences were observed between the test products and the reference products. The overall incidence of AEs suspected to be related to study drug was similar across treatment groups and foremost concerned cases of hypocalcaemia. The overall incidence of SAEs was low and balanced between treatment groups.

2.6.10. Conclusions on the clinical safety

Based on the provided data, no unexpected safety concerns were detected across the clinical studies and the observed safety findings correspond to the known safety profile of the reference product.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 48. Summary of safety concerns

Important identified risks	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcemia in paediatric patients receiving denosumab and after treatment discontinuation
Important potential risks	• Fracture healing complications. • Infection • Cardiovascular events • Malignancy
Missing information	• None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 49. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Hypocalcaemia	Routine risk minimisation measures: • SmPC Section 4.2, 4.3, 4.4 and 4.8 • PL Section 2 and 4 • Recommendation for correction of hypocalcaemia prior to initiating treatment with Osvyrti and clinical monitoring of calcium levels during treatment with Osvyrti is included in SmPC Section 4.4. • The prescription only status of the product. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypocalcaemia Additional pharmacovigilance activities: • None
Skin infection leading to hospitalisation	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 • The prescription only status of the product. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for Infection Additional pharmacovigilance activities: • None
Osteonecrosis of the Jaw	Routine risk minimisation measures*:* • SmPC Section 4.8 • PL Section 2 and 4 • Recommendation for oral examination, maintenance of good oral hygiene during treatment,	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for Osteonecrosis of the Jaw

	management of patients with unavoidable invasive dental procedures, and temporary interruption of treatment if ONJ occurs is included in SmPC Section 4.4. • The prescription only status of the product. <u>Additional risk minimisation measures:</u> • Patient reminder card	<u>Additional pharmacovigilance activities:</u> • None
Hypersensitivity reactions	<u>Routine risk minimisation measures:</u> • SmPC Section 4.3 and 4.8 • PL Section 4 • The prescription-only status of the product. <u>Additional risk minimisation measures:</u> • None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • Follow-up questionnaire for Hypersensitivity <u>Additional pharmacovigilance activities:</u> • None
Atypical femoral fracture	<u>Routine risk minimisation measures:</u> • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 • Recommendation for reporting new or unusual thigh, hip, or groin pain is included in SmPC Section 4.4. • The prescription only status of the product. <u>Additional risk minimisation measures:</u> • None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • Follow-up questionnaire for Atypical femoral fracture <u>Additional pharmacovigilance activities:</u> • None
Hypercalcemia in paediatric patients receiving denosumab and after treatment	<u>Routine risk minimisation measures:</u> • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u>

discontinuation	• The prescription only status of the product. Additional risk minimisation measures: • None	• None Additional pharmacovigilance activities: • None
Important Potential Risks		
Fracture healing complications	Routine risk minimisation measures: • SmPC Section 5.3 • The prescription only status of the product. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for fracture healing complications Additional pharmacovigilance activities: • None
Infection	Routine risk minimisation measures: • SmPC Section 4.8 • PL Section 4 • The prescription only status of the product Additional risk minimisation measures: • None	*Routine pharmacovigilance* activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection *A*dditional pharmacovigilance activities: • None
Cardiovascular events	Routine risk minimisation measures: • The prescription only status of the product additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Malignancy	<u>Routine risk minimisation measures:</u> • The prescription only status of the product <u>Additional risk minimisation measures:</u> • None	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> • Follow-up questionnaire for malignancy <u>Additional pharmacovigilance activities:</u> • None
Missing Information		
None		

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

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

2.9. Product information

2.9.1. User consultation

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Osvyrti was developed as a biosimilar product to Prolia (INN: denosumab), marketed by Amgen and was developed with the same strength and presentation (Prolia: 60 mg/mL PFS). Prolia is indicated for:

- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.
- Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

For this MAA, the applicant intends to claim all of the indications of the reference product.

Quality

INTP23.1 60 mg/mL pre-filled syringe (PFS) is developed as a proposed biosimilar product to EU approved Prolia®. In parallel, INTP23.1 120 mg/1.7 mL vial is developed as a proposed biosimilar product to EU approved Xgeva®. The analytical similarity exercise was designed to integrate the characterisation of both formulations of INTP23.1 to demonstrate overall biosimilarity of INTP23.1 to the RMPs.

The applicant has performed an extensive biosimilarity exercise, evaluating relevant quality attributes by a panel of state-of-the-art analytical methods. The overall approach to assess analytical similarity is found acceptable.

The batches included in the biosimilarity study are found acceptable, both with respect to INTP23.1 vial and PFS, the EU approved Xgeva® and Prolia® (RMP) and US licensed Xgeva® and Prolia®. The analytical similarity assessment has been performed with a combination of methods assessing the primary and higher order structures, post-translational modifications, purity and impurities and product variants. In addition, biological activities related to Fab binding and Fc related functions have been evaluated. A comparative forced degradation stability study is also presented.

Overall, the provided data indicates a high degree of similarity between INTP23.1 and the RMP. Some minor differences are noted, for instance, in cysteinylation, glycation, C-terminal lysine, the N-glycan profile, charged forms and high molecular weight species. The applicant justifies most differences and provides arguments related to denosumab mode of action, results from biological characterisation, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful. EU-approved Xgeva®/Prolia® and US-licensed Xgeva®/Prolia® are also considered comparable.

Clinical

Clinical development programme included phase I study 0568-19 in healthy male subjects to compare PK, PD, immunogenicity and safety of Intas Denosumab with Xgeva (US) and Xgeva (EU).

In addition, phase III study 0774-19 compared the efficacy, safety, PK, PD and immunogenicity of Intas Denosumab with Prolia was conducted in postmenopausal women with osteoporosis. The overall study design, including study population and primary/secondary endpoints was discussed and agreed with the EMA via Scientific Advice.

The applicant reported that 4 sites in in India in the phase III study were terminated because DXA scans had been falsified and patient eligibility criteria had been violated. The provided a detailed account of how the falsification of data was discovered and handled, including the measures taken to ensure that no GCP issues occurred at other sites. The applicant also submitted monitoring reports for the sites in question.

In addition to the applicant's information, the CHMP triggered a GCP inspection to verify the corrective and preventive measures taken and the conduct of the trial in other sites. The inspectors found some departures from GCP, but concluded that the trial was ethically conducted and that the data were of sufficient quality to be evaluated in a Marketing Authorisation Application.

The robustness of the primary efficacy results was initially questioned because the supportive mITT analyses included patients from sites that falsified DXA scans but excluded patients who lacked follow-up data (it is preferable to impute missing data). A reanalysis failed to show therapeutic equivalence when all randomised patients were included in the analysis, but it succeeded in showing therapeutic equivalence after exclusion of the 30 patients from sites that falsified data.

The frequency of hypocalcaemia in study 0774-19 was generally higher than expected no injection site reactions were reported in study 0568-19 and study 0774-19. However, there were no significant differences in the safety profile between the test product and reference products.

3.2. Results supporting biosimilarity

Quality

The applicant has performed an extensive biosimilarity exercise, evaluating relevant quality attributes by a panel of state-of-the-art analytical methods. The overall approach to assess analytical similarity is found acceptable.

Overall, the provided data indicates a high degree of similarity between INTP23.1 and the RMP. Some minor differences are noted, for instance, in cysteinylation, glycation, C-terminal lysine, the N-glycan profile, charged forms and high molecular weight species. The applicant justifies most differences and provides arguments related to denosumab mode of action, results from biological characterisation, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful.

Pharmacokinetics

PK similarity between Intas Denosumab and the reference products (Xgeva and Prolia) was demonstrated in study 0568-19 and study 0774-19, as the 90% CI for the geometric means ratios of $AUC_{0\text{-}inf}$ and C_{max} parameters were fully contained within the predefined bioequivalence limits of 80.00-125.00%.

From a pharmacokinetic perspective, pharmacokinetic similarity is considered sufficiently demonstrated between Intas Denosumab and the reference products (Xgeva and Prolia).

The immunogenicity results were comparable between Intas Denosumab (biosimilar) and the reference products and the results indicate that there is no impact of ADAs on the PK.

Clinical

PD

Tmax, Emax and AUEC0-t% of bone biomarker serum CTX were secondary efficacy evaluation parameters of the phase I study and Co-primary parameters in phase III study.

In the phase I study in heathy volunteers, the 95% CIs of the geometric LSM ratios, derived from the analysis on the ln transformed serum CTX Emax (99% to 103%) and serum CTX AUEC0-t (96% to 115%) of Intas Denosumab relative to US-Xgeva and EU-Xgeva were well within the acceptance range of 80.00% to 125.00%.

Similarly, in the phase III study in osteoporosis patients, the 95% CIs of the geometric LSM ratios, derived from the analysis on the ln transformed serum CTX Emax (95% to 99%) and serum CTX AUEC0-t (96% to 104%) of Intas Denosumab relative to US-Xgeva and EU-Xgeva were well within the acceptance range of 80.00% to 125.00%.

Efficacy

The primary efficacy endpoint in the phase III study was mean percentage change in BMD of lumbar spine from baseline to 12 months. The % change from baseline in BMD of lumbar spine at 12 months in PP set was 6.25 for test and 6.36 for reference. The mean difference was -0.20 and the 95%

confidence interval for the percentage change in BMD from baseline to 12 months [-1.42 to 1.03] is within acceptance range [-1.45 to 1.45] for PP set.

When the analysis included all randomised patients, except those from sites that falsified data, and missing data were handled using the last-observation-carried-forward method, the % change from baseline in BMD of lumbar spine at 12 months was 5.62 for test and 5.69 for reference. The mean difference was -0.13 and the 95% confidence interval was [-1.27 to 1.01], which is within the acceptance range [-1.45 to 1.45]. Similarly, when missing data were instead handled under a missing at random assumption, the % change from baseline in BMD of lumbar spine at 12 months was 6.25 for test and 6.37 for reference. The mean difference was -0.15 and the 95% confidence interval was [-1.37 to 1.06], which is within the acceptance range [-1.45 to 1.45].

Safety

The adverse events most frequently reported in both studies are known adverse drug reactions with Prolia and Xgeva, for example hypocalcaemia, headache, asthenia and musculoskeletal pain. The incidence of severe (grade 3 or 4) AEs as well as of SAEs was generally low. The frequency and character of adverse events was similar between treatment arms in both studies.

3.3. Uncertainties and limitations about biosimilarity

Quality

The overall approach to assess analytical similarity is found acceptable. Some minor differences are noted, for instance, in cysteinylation, glycation, C-terminal lysine, the N-glycan profile, charged forms and high molecular weight species. The applicant justifies most differences and provides arguments related to denosumab mode of action, results from biological characterisation, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful.

Efficacy

Using a per-protocol set is acceptable in the primary efficacy analysis, but an analysis in an intention-to-treat/full analysis set is considered equally important for decision making. A relatively large number of patients did not complete the main phase of the trial (n=88/552, 16%), and two analyses in a modified in a modified intention-to-treat (mITT) set presented by the applicant showed inconsistent results.

In addition, the modified intention-to-treat (mITT) set used by the applicant is inappropriate because it included patients from sites that falsified data (these data are not trustworthy) but included patients who lacked follow-up data (it is preferable to impute missing data).

A reanalysis was requested, which failed to show significant therapeutic equivalence in all randomised patients, regardless of whether LOCF or MMRM was used. However, significant therapeutic equivalence was found with both methods after exclusion of the 30 patients from sites that falsified DXA data.

Since the results varied depending on the analysis set used and, in the mITT set, how missing data were handled, the results of this trial are not easy to interpret. On the one hand, it is reassuring that therapeutic equivalence was shown in the most appropriate analysis set (that is, the set of all

randomised patients except those from sites that falsified data). On the other hand, it is unclear why the results vary.

3.4. Discussion on biosimilarity

Quality

From a quality perspective, the applicant has performed an extensive biosimilarity exercise, evaluating relevant quality attributes by a panel of state-of-the-art analytical methods. The overall approach to assess analytical similarity is found acceptable.

Overall, the provided data indicates a high degree of similarity between INTP23.1 and the RMP. Some minor differences are noted, for instance, in cysteinylation, glycation, C-terminal lysine, the N-glycan profile, charged forms and high molecular weight species. The applicant justifies most differences and provides arguments related to denosumab mode of action, results from biological characterisation, information in the literature as well as results obtained in non-clinical and clinical studies, implying that these differences are not clinically meaningful. EU-approved Xgeva®/Prolia® and US-licensed Xgeva®/Prolia® are also considered comparable.

Pharmacokinetics

Pharmacokinetic similarity is considered sufficiently demonstrated between Intas Denosumab and the reference products (Xgeva and Prolia).

Clinical

Efficacy

Therapeutic equivalence was not demonstrated in the population of all randomised patients. However, the exclusion of patients from the 4 sites in India that had falsified DXA data brought the difference between the test and reference arms within the pre-specified acceptance range. Overall based on these latter analyses, the CHMP concluded that the phase III study demonstrated the therapeutical equivalence between Intas Denosumab and Prolia, acknowledging the multiplicity issue arising from the various analyses performed.

While this could be considered as being supportive of the premise that the test and reference products are equivalent, the fact that equivalence was not shown with MMRM-MAR or ANCOVA-LOCF in the whole randomised population was considered as a weakness of the application.

Safety

The frequency and character of AEs, ADRs, AESI and SAEs were similar between treatment arms in both study 0568-19 and study 0774-19. The AEs were in general in line with the known safety profile with denosumab. However, the frequency of hypocalcaemia was unexpectedly high in study 0774-19. The reporting of injection site reactions was lower than expected in both studies. In summary, the adverse events were similar in frequency and character between treatment arms in both studies which could support similarity.

3.5. Extrapolation of safety and efficacy

The product was developed as a biosimilar product to Prolia and Xgeva. The mechanism of action is identical to the reference products. The monoclonal antibody denosumab targets and binds to RANKL, thus preventing interaction of RANKL with RANK. Block of interaction of RANKL with RANK leads to

reduced osteoclast formation and function. Thus, bone resorption and cancer induced bone destruction is decreased.

The mechanism of action is identical across all indications, i.e. binding to RANKL and thus preventing activation of its receptor RANK. The desired pharmacological action of denosumab occurs invariably in the bony tissue, through prevention of generalised bone resorption in primary or secondary osteoporosis, or local bone resorption and destruction around bone metastases. Thus, based on the same mechanism of action, extrapolation to all indications might be allowed depending on the totality of data, meaning similarity is shown on quality and extended functional characterisation and clinical data show comparability in terms of PK, PD, efficacy and safety.

Furthermore, the clinical data were derived from healthy male volunteers and female osteoporosis patients. These are regarded sensitive populations in terms of evaluating biosimilarity of INTP23.1 and the reference products.

3.6. Additional considerations

Not applicable.

3.7. Conclusions on biosimilarity and benefit risk balance

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

4. Recommendations

Outcome

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

Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.

Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (see section 5.1). In men with prostate cancer receiving hormone ablation, denosumab significantly reduces the risk of vertebral fractures.

Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see section 5.1).

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set

out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.